AN ABSTRACT OF THE DISSERTATION OF

Chien Ngoc Nguyen for the degree of Doctor of Philosophy in Pharmacy presented on November 3, 2006.

Title: 1) Development of Hot-melt Pan-coating, Application to Sustained-release Capsules and Tamper Resistant-coating. 2) Formulation of Verapamil HCl and Diltiazem HCl Semisolid Matrix Capsules. 3) Novel Sustained Release Tablet of Glipizide: Compression of Coated Drug Beads, Formulation, Dissolution, and Convolution. 4) Verapamil Sustained Release: New Formulation and Convolution.

Abstract approved:

James W. Ayres   J. Mark Christensen

Hot-melt pan-coating, which is a novel coating method and takes 2-3 hours for 300 mg coating weight gain per capsule and tamper-resistant coating, which takes 30 minutes, is much faster than tedious sugar coating and allows greater coating weight gains in shorter times than spray-melt coating. Although hot-melt pan coating is promising, it needs modification for industrial scale-up and to provide more elegant formulations.

Hot-melt capsule filling is an especially appealing and simple way to make sustained release formulations.

A novel formulation of glipizide developed comprising compression of four-layer coated beads into tablets has advantages of keeping sustained-release characteristics following a lag time, providing approximately zero-order release, and releases drug nearly independent of paddle speeds 50 and 100 rpm. The amount of binding and disintegration ingredients can be adjusted to produce appropriate disintegration times for tablets and to release individually coated particulates. Formulation CH20 tablet, matched the dissolution pattern of Glucotrol-XL osmotic pump tablets in two pH media at 100 rpm paddle, and dissolution patterns of Glucotrol XL and CH20 tablet were close to each other at 50, 150 and 200 rpm paddle. This formulation is predicted by convolution simulation to be bioequivalent to Glucotrol-XL in-vivo.

A novel bead formulation of verapamil was developed comprising a combination of extrusion and spheronization to produce a relatively high drug load, followed by coating with an insoluble polymer (ethylcellulose) that contains a water soluble channeling agent (lactose), thus allowing a sufficiently thick coating to be uniform and robust without "shutting down" release of the relatively insoluble drug. Formulation OSU2, provided the unexpected benefit where by adjusting the coating thickness and ethylcellulose/lactose ratio, it is possible to obtain essentially non-agitation sensitive and zero-order drug release up to 14 hours in either KCl or two different pH media at stirring speeds of either 75 or 200 rpm with the USP basket or paddle stirring method. This formulation matched the dissolution pattern of Verelan-PM capsules with basket method and paddle method in KCl medium, and two pH medium methods at different speeds and is predicted by convolution simulation to be bioequivalent to Verelan-PM in-vivo.

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by
Chien Ngoc Nguyen

A DISSERTATION

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CONTRIBUTION OF AUTHORS

Sarah Nigro assisted with the laboratory research on hot-melt pan coating project.

Josh McNeill assisted with the laboratory research on Diltiazem HCl Semisolid matrix capsules project and tamper resistant-coating project.

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CHAPTER 1

GENERAL INTRODUCTION

To administer drugs to patients, drugs can be formulated into injectable, transdermal, nasal, oral, and other dosage forms. Among these dosage forms, oral administration is still preferred and oral sustained release dosage forms are desirable since the oral sustained release dosage forms have numerous benefits over other conventional dosage forms such as convenient use, narrow fluctuation of drug concentrations in plasma, less frequency of administration, less toxicity, and higher patient compliance. In oral sustained release dosage forms, multiple particulate dosage forms are more advantageous than single dosage forms since multi-particulate dosage forms distribute more uniformly in the gastro-intestinal tract, have less bioavailability variability, and avoid dose dumping. Multiple particulate dosage forms, in either pellets or beads, can be filled into capsules or compressed into tablets. Beads-filled into capsules are much easier to produce but are more expensive than beads-compressed into tablets. This thesis describes the development of novel sustained release beads filled into capsules and a novel sustained release beads compressed into tablets, and a novel hot-

melt coating method. Hot melt pan coating, which does not need organic solvents, reduces environmental pollution and production cost, and was initially developed at Oregon State University. Anti-tamper coating based on hot melt pan coating was proposed to produce tamper resistant capsules.

Chapter 2 describes how novel hot-melt pan coating works. Pan coating, similar in its function to the old sugar coating process, was developed to provide a new coating method that eliminates using organic solvents and add a new page to coating techniques. Hot melt-pan coating by modifying the coating pan and using hair dryers can produce in a lab scale a large amount of coating weight gain in a short time. In hot melt coating, waxes were melted and poured into a spinning pan to make a thin wax layer, cooled, and then substrates were poured into the cool rotating pan and capsules were coated when heat was applied to the pan. Tamper-resistant coating was applied by mixing capsules with melted wax in a container for a limited time before separating and smoothing capsules in a heated spinning pan.

Chapter 3 presents a simple method for hot melt filling of capsules to produce sustained release semisolid matrix capsules using cetyl alcohol, stearic acid and Gelucire 50/13. In this method, wax ingredients were melted and mixed well with drug at temperature higher than melting point of waxes. Then the mixture was poured into capsules held up-right until the formulation matrix inside capsules was congealed by cooling. Dissolution of semisolid matrix capsules was studied to investigate the effects of wax amounts and ratio of ingredients on drug release.

Chapter 4 demonstrates beads compressed into tablets. Nonpareil sugar beads were spayed loaded with a model drug, glipizide, using Surelease® (Surelease) as a binder. Drug loaded beads were subsequently spray-coated with a hardening layer, then a controlled release membrane layer with a channeling agent, and then a binder/disintegrant layer. Resulting beads were then compressed into tablets. Effects of amount of Surelease in drug layer, amount of Surelease in controlled release layer, ratio of solids content of Surelease layer to lactose, amount of hardening, and amount of binder/disintegrant layer were investigated. Dissolution profiles of beads compressed into tablets were compared with Glucotrol XL tablets. Convolution was conducted for a formulation that is comparable to Glucotrol XL tablets.

Chapter 5 describes beads filled into capsules. Verapamil hydrochloride was chosen as a model drug. Powder mixture of drug, diluent and dry binder was wet by water, and then extruded through an extrusion machine. Wet, extruded granules were cut into fragments of 3-6 mm and added to 25% of powder mixture to be spheronized in spheronization machine fitted with a 1 mm scored friction plate and was allowed to rotate for 5-7 minutes residence time. Spherical pellets were dried in an oven at 37^0C for 20 hours and sieved to select pellets between sizes 0.833 to 1.41 or 1 to 1.4 mm and used for spray coating. Drug beads were spray-coated with a controlled release membrane layer containing a channeling agent. The resulting beads were then filled into capsules. Effect of ratio of solids content of Surelease layer to lactose in controlled release membrane, and coating weight gain on drug release were studied. Effects of surfactant, tween 80, and disintegrant, Explotab®, were also evaluated. Dissolution profiles of beads filled into

capsules were compared with Verelan PM capsules. Convolution was performed for a test bead capsule formulation with similar dissolution characteristics to Verelan PM capsules.

CHAPTER 2

Development of Hot-Melt Pan-Coating:

Application to Sustained-Release Capsules and Tamper Resistant-Coating

Chien N. Nguyen*, J. Mark Christensen, James W. Ayres

ABSTRACT

Purposes. Hot-melt pan coating, a new method developed in the College of Pharmacy, Oregon State University, can create a variety of drug-release patterns and produce tamper-resistant capsules. The process is particularly useful for researchers who wish to create sustained release or pulse release formulations with limited equipment in a small laboratory. In hot-melt pan-coating, the coating material is applied onto the capsule surface in the soft state employing a coating pan. The purpose of this study was development and evaluation of a hot-melt pan-coating process to produce sustained-release capsules and anti-tamper coated capsules. **Methods.** A pan, which is used for sugar coating, was modified for hot-melt coating. Empty or verapamil HCl, chlorpheniramine maleate, or diltiazem HCl filled capsules were coated with Gelucire® 50/13 (Gelucire 50/13), cetyl alcohol, and polyethylene glycol 300. These capsules were tested in the USP dissolution apparatus II in simulated gastric fluid for 2h and then in pH 7.4 buffer solutions. **Results.** The greater the weight gain, the slower the drug release of chlorpheniramine from coated capsules. Chlorpheniramine coated capsules prolonged drug release profiles for 12 hours. Coated capsules which contained 80 mg of verapamil HCl inside the capsule, then coated with 300 mg of Gelucire 50/13:cetyl alcohol (= 4:1 with 2% polyethylene glycol 300), and then 80 mg of spray-loaded verapamil HCl outside, provided a pulse release pattern, with a lag time of 4 to 6 hours between the two releases of drug. Tamper-resistant coated capsules were slippery, easy to swallow and not easy to open. The tamper-resistant coating also did not affect release of diltiazem HCl from capsules. Hot-melt pan coating, which took 2-3 hours for 300 mg weight gain, and

tamper-resistant coating, which took 30 minutes, are much faster than tedious sugar coating and allows greater coating weight gains in shorter times than spray-melt coating. Although hot-melt pan coating is promising, it needs modification for industrial scale-up to provide more elegant formulations. **Conclusions.** The newly developed method, which is easy to perform in a lab, can make sustained release formulations and tamper-resistant capsules.

INTRODUCTION

The process of coating is one of the oldest pharmaceutical practices (Porter, 2000), and the first reported pill coating dates back to the Greek-Arabic civilization around 850 A.D. (Bauer et al., 1998). Over the years, various coating methods have been developed such as sugar coating, film coating, compression coating (Porter, 2000), dry coating, hot melt spray coating, solid dispersion hot-melt coating, and hot melt direct blending coating. Many coating methods require solvents for solution or dispersion preparation, which involve using polymers and organic or aqueous solvents to produce the desired coatings on a substrate fluidized on a bed or in a column of air. Although still receiving relatively little attention, hot-melt coating systems have become an area in the pharmaceutical industry where more and more research effort has been applied to develop alternatives to organic- or aqueous-based polymer systems.

Dry coating method involves direct feeding of coating polymer powder and simultaneous spraying of plasticizing agent, without either organic solvent or water, using a centrifugal granulator, fluidized bed, or tablet-coating machine (Sakae et al., 1999). For film formation, a curing step is necessary; this involves spraying a small amount (3-8% of core weight) of water or hydroxypropyl methylcellulose (HPMC) solution, followed by heating. The dry coating method to coat beads and tablets requires a higher coating amount of hydroxypropyl methylcellulose acetate succinate for gastric resistance compared with the conventional coating, but the processing time was dramatically reduced. Dry coating still has some obstacles (Sakae et al., 1999). The

surface of the tablets obtained by dry coating was slightly rougher than with conventional coating, even though the surface of the tablets is in the acceptable range, and the core tablets must be coated with HPMC prior to dry coating. Some polymers which are easily softened by heating, and can be well plasticized to form a film in the presence of water can be used in dry coating. HPMC and acrylic resins were not successful in dry coating with aqueous curing (Sakae et al., 1999).

In hot melt spray coating, the coating material is applied onto the substrate surface in the molten state, providing several advantages over current and conventional coating techniques that use dissolved or suspended polymers. No organic or aqueous solvents are needed and processing time may be reduced (Jozwiakowski et al., 1990). A conventional hot melt spray coating process carried out with a fluidized bed may consist of three steps: spraying of molten material onto substrate surface while maintaining constant substrate fluidization with a stream of air, spreading of the molten material around the substrate surface in a fluidized bed, and congealment of the molten material while keeping the substrate fluidized. In order to prevent molten coating material from congealing prior to being delivered to the substrate surface, the coating is normally kept at a temperature of $40\text{-}60^0\text{C}$ above its melting point. To maintain constant temperature, air used for atomization of the coating material must be heated to the same temperature as the molten coating material. Also, the nozzle needle must be insulated to prevent re-melting of the congealed molten coating material and bed temperature must be kept below the melting point of the coating material throughout the coating phase (Jozwiakowski et al., 1990).

Obstacles relating to hot melt spray coating are the requirement for complex equipment to maintain high temperature and the high cost to pay for high energy needed for heating.

Another reported process is solid dispersion hot-melt coating in a fluid bed. The coating agent and substrate are combined in a fluid bed chamber, fluidized, and then heated to melt the coating agent (Kennedy and Niebergall, 1996 and 1998). This system was simpler than hot-melt spray coating with respect to the coating setup by eliminating the need for spraying the molten coating material onto the substrate surface, but has a number of disadvantages. One limitation in these procedures is that coating agents can only be used with melting points and molten viscosities less than 80^0C and 300 centipoise, respectively. It was reported that the maximum feasible hot-melt coating level can only be varied from 2.5 percent to 5.5 percent depending on different substrate sizes. Also, substrates of 10-30 U.S. standard mesh (0.5 to 2.0 mm) can be coated as individual particles, while particle sizes smaller than 40 mesh (0.42 mm) agglomerate. To maintain batch-to-batch reproducibility and overall robustness of the final product, seal coatings or strict substrate porosity specifications are required. For multiple coating, another problem encountered is that melting points of multiple coating agents must differ by 15^0C or more.

Hot melt direct blending coating, as reported herein, involves application of a molten coating material onto beads or capsules in a heated tablet coating pan. In the hot-melt pan coating cetyl alcohol and Gelucire® (Gelucire) 50/13 were used as coating agents. Gelucires® (Gelucires) are a family of vehicles derived from mixtures of mono-,

di-, and triglycerides with polyethylene glycol (PEG) esters of fatty acids. Gelucires are available with a range of properties depending on their Hydrophilic Lipophilic Balance (HLB 1-14) and melting points (33^0C-65^0C) range. The Gelucires containing only PEG esters (Gelucire 55/18) are generally used in preparation of fast release formulations, while Gelucires containing only glycerides or a mixture of glycerides and PEG esters (Gelucire 54/02, 50/13, 43/01) are used in preparation of sustained release formulations (Shimpi et al., 2004). Gelucire 50/13 contains a large proportion of PEG mono- and diesters with palmitic (C16) and stearic (C18) acid, with 20% glycerides and 80% PEG esters (Sutananta et al., 1995). Gelucire 50/13 has a nominal melting point of 50^0C and an HLB value of 13.

The purpose of this study was to produce sustained and pulse release capsules, and to produce tamper resistant coated capsules using a new hot-melt pan coating method. The three drugs used in this study were chlorpheniramine maleate, diltiazem hydrochloride and verapamil hydrochloride.

MATERIALS AND METHODS

Chemicals

Chlorpheniramine maleate, and diltiazem hydrochloride (from Fluka, BioChemika, Switzerland) were purchased from Sigma-Aldrich Co. (St. Louis, MO). Verapamil hydrochloride (HCl) was a gift from Teva Pharmaceuticals (Sellersville, PA). The capsules, shell size 2, and 4, were from Capsugel (Greenwood, SC). The Macrogol glycerol stearate (Gelucire® 50/13) was purchased from Gattefosse (Saint-Priet Cedex, France). Cetyl alcohol, 1-hexadecanol, $C_{16}H_{34}O$, was from Spectrum Chemical Mfg. Corp., (Gardena, CA and New Brunswick, NJ). The Polyethylene glycol 300 (PEG 300) was supplied by Sigma- Aldrich, Inc. (St. Louis, MO). The Eudragit® (Eudragit) L 30 D-55 was from Pharma Polymere, made in Germany. Surelease® (Surelease), formula No.: E-7-19010 with solids content of 25.0%, and Opadry® (Opadry) YS-1-7472 were a gift from Colorcon (West Point, PA). Chlorpheniramine maleate extended release capsules (Huntsville, AL) was from Qualitest Pharmaceuticals (Chlorphen capsules), Inc. and the pulse release Chlor-Trimeton 8 hours and Chlor-Trimeton 12 hours were distributed by Schering-Plough HealthCare Products, Inc. (Memphis, TN).

Equipment:

The equipment used was a French made kitchen aid pan designed by Pascal Brunstein, voted the best French pastry chef in 1993 (http://mycookingstore.com/shopping/customer/product.php?productid=9578&cat=0&pa

ge=1). This is a mini version of similar coating pans used in commercial candy manufacturing. This stainless steel coating pan is round in shape with a 16" diameter, width 9 1/4" and front opening of 9 3/8" (http://mycookingstore.com/shopping/customer/product.php?productid=9578&cat=0&page=1). Any rounded pan that can be turned is anticipated to be adaptable to the process.

Methods

(i) Sustained-release capsules

Hot-melt pan coating

Weight composition of formulations of chlorpheniramine sustained release capsules is shown in Table 2.1. Hot-melt pan coating process is discussed after that.

Table 2.1: Weight composition of formulations of chlorpheniramine sustained release capsules

Formulation	Chlor (mg)	PEG 300 mg (%)	Amount (mg)		Total weight gain (mg)
			Gelucire 50/13 (2)	Cetyl alcohol (1)	
F1	12.0	2.00 (2%)	65.330	32.670	112.0
F2	12.0	2.80 (2%)	91.470	45.730	152.0
F3	12.0	3.20 (2%)	104.530	52.270	172.0
F4	12.0	3.60 (2%)	117.600	58.800	192.0

% of PEG 300 was compared to weight of Gelucire 50/13 and cetyl alcohol, Chlor = chlorpheniramine maleate.

Step 1: Place the mixture of Gelucire 50/13 and cetyl alcohol and PEG 300 for each formulation in Table 2.1 with the drug in a beaker. Place the beaker in the water bath with the temperature approximately 60^0C to melt the materials.

Step 2: Pour the molten material into the coating pan while it is spinning at a rate of 45 RPM. Let the wax cool and harden to make a thin wax layer. Next, melt the wax, using a blow (hair) dryer, and pour the empty or filled capsules into the pan. Turn the blow dryer on cool, and separate the capsules by hand (while the pan is spinning) until the wax has hardened. Then increase the temperature at different sites of capsules in the pan to about 42^0C so the wax softens. Once the wax is softened, separate the capsules by hand while allowing the coating material to spread evenly over the capsules. Turn the blow dryer on cool at different sites if necessary. While the capsules are being coated, the temperature should slowly be reduced to room temperature. Repeat the process until the desired coating weight gain (coating weight gain is the percent increase in capsule weight provided by outside coating) is reached.

Step 3: After the capsules are coated, they are smoothed by spraying DI water for five seconds while the pan is rotating. Separate and smooth the capsules for 10 minutes by hand until the capsules dry. Once the capsules are dry, repeat the process until the capsules reach the desired smoothness. The entire hot-melt pan coating process takes about two hours. Approximately one and a half hours is required to completely coat the capsules and about a half hour for smoothing.

Hot-melt pan coating process is described in Figure 2.1.

Step 1a: Melt wax with drug and pour molten wax into a spinning pan.

Step 1b: Then make a thin wax layer
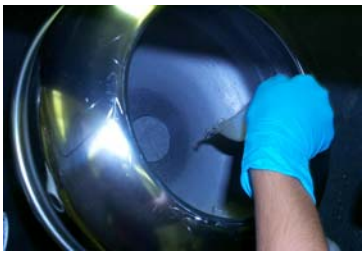
Step 2a: Pour capsules into the rotating pan and separate capsules by hand

Step 2b: Build coating layer
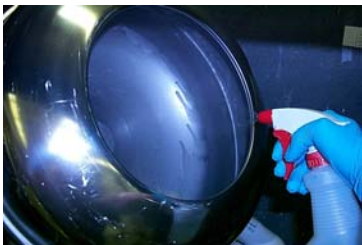
Step 3: Smooth coated capsules

Figure 2.1: Process of hot-melt pan coating

Figure 2.2 shows the cross surface of chlorpheniramine maleate sustained release capsules with two layers. The first layer is an empty size 4 capsule. The second layer is the wax layer containing drug. The wax-drug layer was coated outside of capsules by hot-melt pan-coating method.
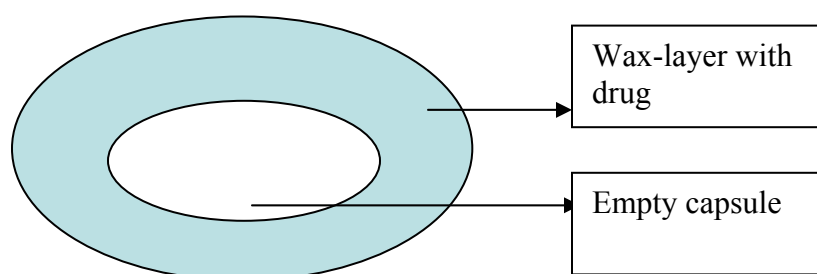
Figure 2.2: Cross surface of chlorpheniramine maleate hot-melt coated capsules

Chlorpheniramine Assay

Standard Curves of Chlorpheniramine maleate

An exact amount (50.0 mg) of chlorpheniramine maleate was weighed and transferred to the 1000-ml volumetric flask. The sample was dissolved in either simulated gastric fluid (pH 1.4 ± 0.1) without pepsin or pH 7.4 buffer solution and adjusted to final volume. This stock solution contained chlorpheniramine maleate at a concentration of 50 μg/ml. A series of standard solutions of chlorpheniramine maleate with concentrations ranging from 1-50 μg/ml were prepared from the stock solutions by dilution. UV absorbance of standard solutions was measured by UV spectrophotometer at 261 nm in pH 7.4 buffer and 264 nm in simulated gastric fluid. Standard curves of observed

absorbance versus chlorpheniramine maleate concentration in pH 7.4 buffer and simulated gastric fluid are seen in Figures 2.3 and 2.4 respectively.

In Vitro Dissolution Testing of Formulations

Dissolution studies were performed according to the USP XXV apparatus 2. Test formulations were placed in dissolution media being stirred at 50 rpm and maintained at $37 \pm 0.5\,^{0}C$, using 475 ml of simulated gastric fluid in first 2 hours, then 150 ml of 0.2 M Na_3PO_4 was added and the pH adjusted to 7.4 with 6 N NaOH or concentrated hydrochloric acid. 4-mL dissolution samples were filtered through flow filters (0.70 µm), and collected via an autosampler at predetermined time intervals for 12h during the dissolution study. Filtered solutions were centrifuged at 3000 rpm for 10 minutes, supernatants were filtered again through 0.45 µm membrane and measured to determine absorbance at 264 nm in simulated gastric fluid, or 261 nm in pH 7.4 buffer. Dissolution drug concentrations were determined via standard curves (Figures 2.3 and 2.4) in each medium and converted to percentage drug released.

Average percentage of drug release versus time with their standard deviations was calculated from three replications of dissolution trials in all dissolution experiments. Chlorpheniramine maleate dissolution profiles are presented as percent drug release versus time curves.
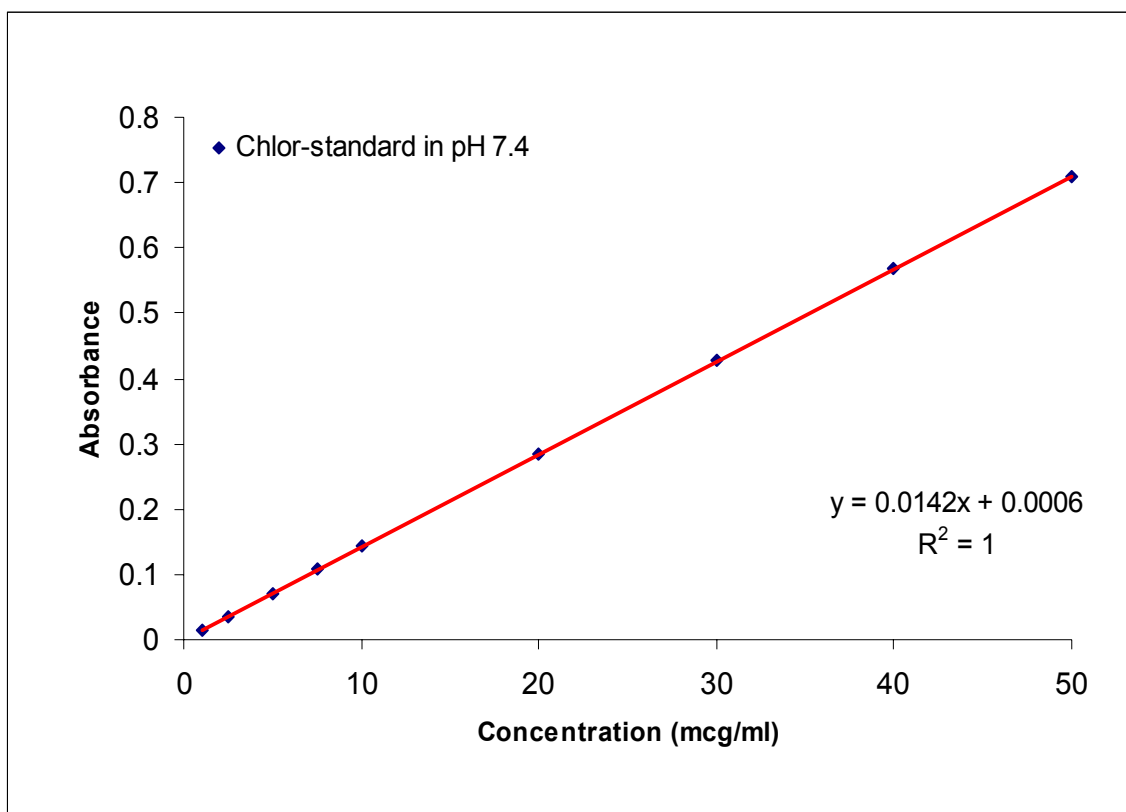
Figure 2.3: Standard curve of chlorpheniramine maleate in pH 7.4 buffer (UV wavelength at 261 nm)
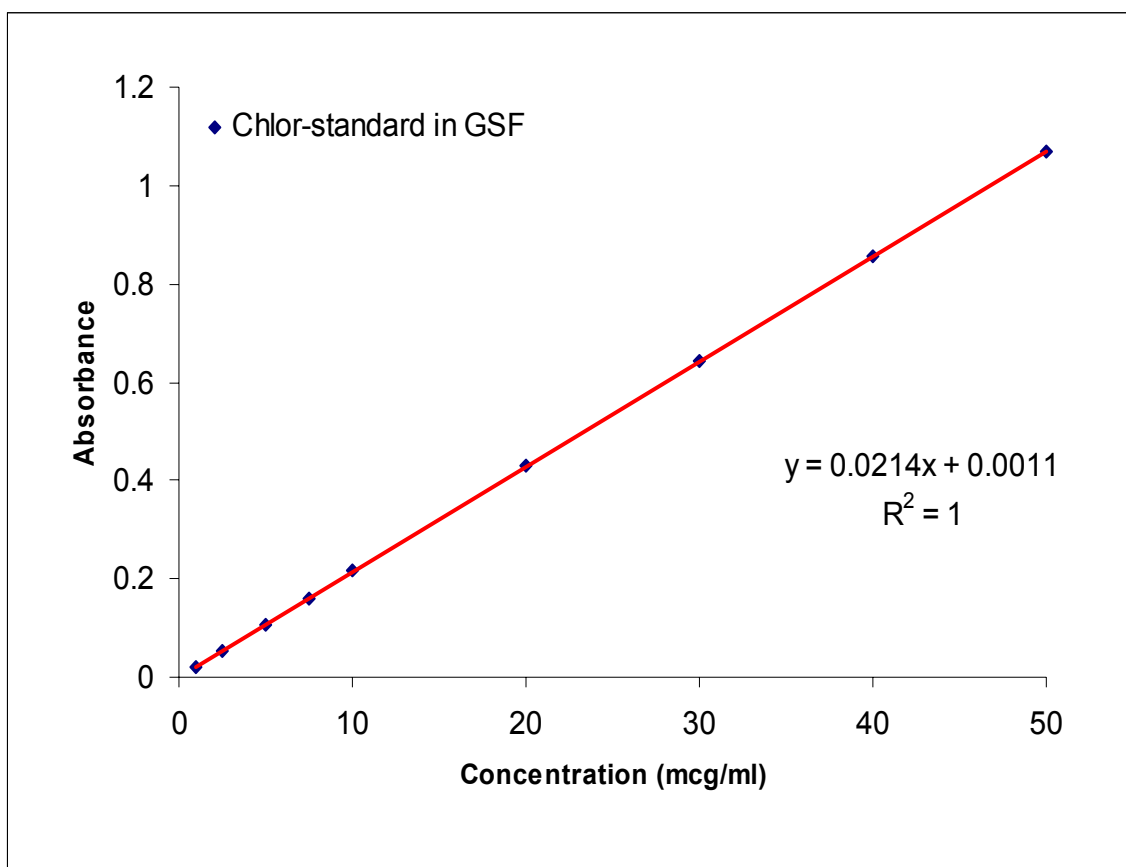
Figure 2.4: Standard curve of chlorpheniramine maleate in simulated gastric fluid (UV wavelength at 264 nm)

(ii) Pulse release capsules

Chlorpheniramine maleate pulse-release capsules

Table 2.2 shows pulse release formulations of chlorpheniramine maleate capsules. Cross surface of pulse-release chlorpheniramine maleate capsules is seen in Figure 2.5.

Table 2.2: Pulse release formulations of chlorpheniramine maleate capsules

Formulation	F5	F6	F7
First layer: Chlor (mg) inside size 4 capsules	6.0	6.0	4.0
Second layer: (wax, mg): 4 Ge: 1Ce, 2% PEG 300	250.0	250.0	175.0
Third layer: Eudragit L 30 D-55 (mg)	50.0	50.0	50.0
Fourth layer: Surelease and Chlor			
Ratio of Surelease:Chlor	4:1 (6)	2:1 (6)	4:1 (4)
Chlor (mg)			

Ge = Gelucire 50/13, Ce = cetyl alcohol, 2 % of PEG 300 was compared to total weight of Gelucire 50/13 and cetyl alcohol. Chlor = chlorpheniramine maleate.

Pulse-release chlorpheniramine maleate capsules consist of four layers with compositions of each formulation presented in Table 2.2. The first layer is a capsule containing half of chlorpheniramine maleate content. The second layer is a delay layer with various amounts of Gelucire 50/13 and cetyl alcohol, at a ratio of 4 to 1. The third layer is EudragitL-30-D55. Then the last layer is Surelease (ethylcellulose) containing the

second half of chlorpheniramine maleate being sprayed on the outside utilizing the spray
coater (Figure 2.5).

50 % of chlorpheniramine maleate

Wax layer

Eudragit L 30 D-55

Surelease with 50 % of chlorpheniramine maleate
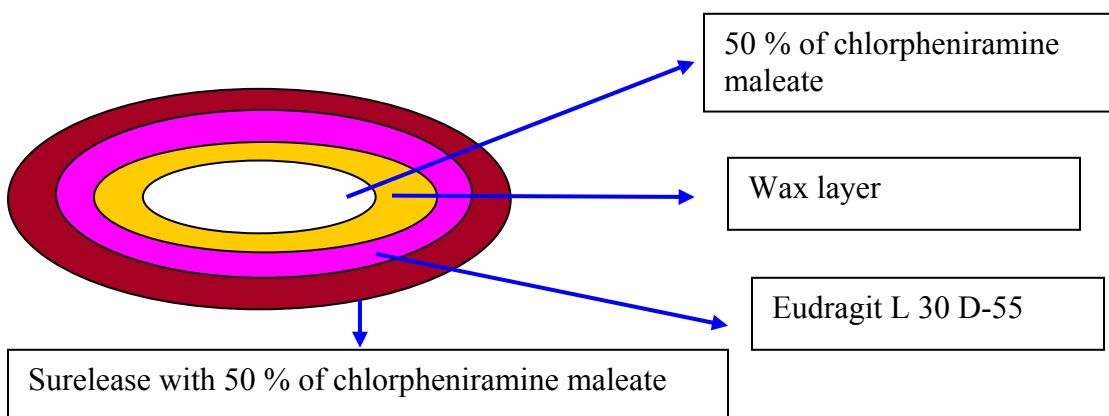
Figure 2.5: Cross surface of pulse-release chlorpheniramine maleate capsules

Chlorpheniramine maleate capsule filling preparation:

Composition of the first layer of each chlorpheniramine maleate 4 mg and 6 mg
capsule is seen in Table 2.3.

Table 2.3: Composition of each chlorpheniramine maleate 4 mg and 6 mg capsule

Ingredient (powder)	6 mg content	4 mg content
	Quantity	Quantity
Chlorpheniramine maleate	6.0 mg	4.0 mg
Lactose monohydrate	74.0 mg	76.0 mg

The preparation of filling capsules is described as follows.

1. Accurately weigh each ingredient and mix all ingredients of each formulation in Table 2.3 in a mortar for 10 minutes.

2. Sieve the above mixture through a screen of mesh size 25.

3. Repeat step 2 and mix well.

4. Fill each size 4 capsule with an amount of powder that is equivalent to 4 or 6 mg of chlorpheniramine maleate.

Wax coating

The weight composition of the second layer, or the delayed layer, of pulse-release chlorpheniramine maleate capsules is shown in Table 2.4. Wax coating was performed using hot-melt pan coating described as above for sustained-release chlorpheniramine maleate capsules except that chlorpheniramine maleate was not added in the first step.

Table 2.4: Weight composition of wax layer for test formulations

250 mg weight gain			175 mg weight gain		
Gelucire 50/13	Cetyl alcohol	PEG 300	Gelucire 50/13	Cetyl alcohol	PEG 300
196.0 mg	49.0 mg	5.0 mg	137.2 mg	34.3 mg	3.5 mg

Eudragit L 30 D-55 coating

Compositions and preparations of polymer coating solution/dispersions are described as follows. Spray coating conditions are presented in Table 2.6.

Eudragit L-30-D 55   30 ml

Triethyl citrate   0.9 g

DI water   30 ml

Eudragit® L30D-55 (dispersion 30%) is accurately measured in a cylinder and poured into a beaker. Triethyl citrate is weighed and added to Eudragit® suspension and gently mixed. Finally deionized water is used to rinse the cylinder, and the rinse is added into Eudragit® mixture and gently mixed. This mixture is gently stirring. This dispersion was used for 100 capsules.

Surelease – Chlorpheniramine maleate loading dispersion

Weight composition of formulations of the last layer of pulse-release chlorpheniramine maleate capsules is seen in Table 2.5.

Table 2.5: Formulations of Surelease drug layer

	Surelease	Chlor	Talc	DI water
Surelease: Chlor = 4:1	10 ml (equivalent to 2.50 g of solid)	0.625 g	0.250 g	10 ml
Surelease: Chlo = 2:1	10 ml (equivalent to 2.50 g of solid)	1.250 g	0.500 g	10 ml

Chlor = chlorpheniramine maleate.

Preparation of drug and Surelease dispersions is described as follows. Surelease of each formulation (see Table 2.5) was accurately measured in a cylinder and poured into a beaker. Then the beaker is rinsed with 2.5 ml of de-ionized (DI) water, and the rinse is added to Surelease. Weighed talc and chlorpheniramine maleate in each

respective formulation (see Table 2.5) were dispersed in 7.5 ml of deionized water. The drug dispersion was then added into Surelease mixture and gently mixed. This mixture was gently stirring.

In vitro dissolution testing of pulse release formulations of chlorpheniramine maleate capsules was performed the same as *in vitro* dissolution testing of formulations of sustained release chlorpheniramine maleate capsules.

Verapamil pulse release capsules

The following figure (Figure 2.6) is for verapamil HCl pulse-release capsules.

| 80 mg of verapamil HCl inside |
| 300 mg of wax |
| 80 mg of verapamil HCl outside |
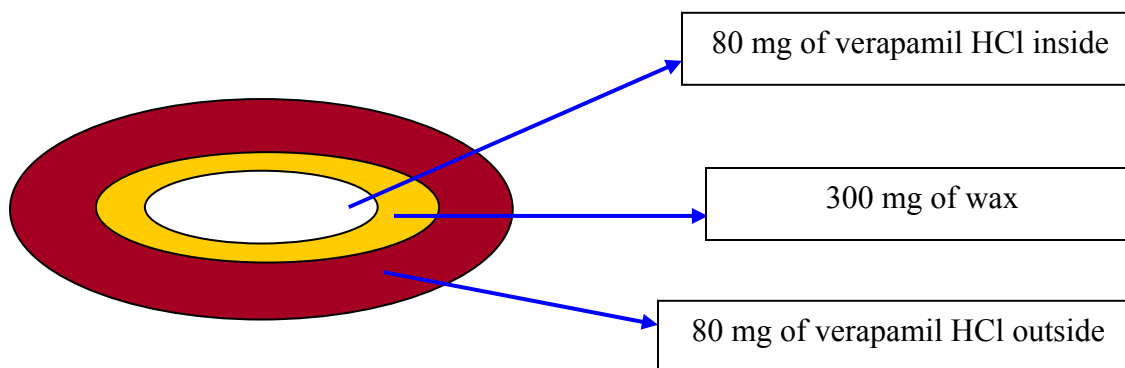
Figure 2.6: Cross surface of pulse-release verapamil HCl capsules

Pulse-release verapamil HCl capsules consist of three layers. The first layer is a capsule containing 80 mg of verapamil HCl. The second layer was a delay layer with 300 mg of Gelucire 50/13 and cetyl alcohol, at a ratio of 4 to 1, and 2% PEG 300. The outside layer is 80 mg of verapamil HCl sprayed on the outside of capsule utilizing Opadry (HPMC) as a binder (Figure 2.6).

Verapamil HCl capsule filling preparation:

Composition of the first layer in each capsule and filling preparation are as follows.

      Verapamil HCl   80.0 mg

      Lactose monohydrate   60.0 mg

1. Accurately weigh each ingredient and mix all ingredients in a mortar for 10 minutes.
2. Sieve the above mixture through a screen of mesh size of 20.
3. Repeat step 2 and mix well.
4. Fill each size 4 capsule with an amount powder that has the equivalence of 80 mg verapamil HCl.

Wax coating

      Composition of the second layer, the wax layer, of 300 mg coating weight gain is as follows.

      Gelucire 50/13   228.0 mg

      Cetyl alcohol   57.0 mg

      PEG 300   15.0 mg

      Wax coating was applied using hot-melt pan coating described as aforementioned for the sustained-release capsules except that verapamil HCl was not added in the first step.

Verapamil HCl loaded coating

The last layer contains 50% of verapamil HCl outside capsules. The composition and preparations of drug loading solution are described as follows.

Verapamil HCl – Opadry solution for 100 capsules

Opadry (clear) YS-1-7472	3.0 g
Verapamil HCl	8.0 g
DI water	80 ml
Ethanol	20 ml

Accurately weighed Opadry is dissolved in a mixture of measured water and ethanol. Accurately weighed verapamil HCl was added in the above solution and mixed until solution was clear. This solution is gently stirring.

Verapamil HCl assay

Standard Curves of Verapamil HCl

An exact amount (250.0 mg) of verapamil hydrochloride was weighed and transferred to a 1000-ml volumetric flask. The sample was dissolved in either simulated gastric fluid (pH 1.4 ± 0.1) without pepsin or pH 7.4 buffer solution, and adjusted to final volume. This stock solution contained verapamil hydrochloride concentration of 250µg/ml. A series of standard solutions in either simulated gastric fluid (pH 1.4 ± 0.1) without pepsin or pH 7.4 buffer solution was prepared with a concentration range of 4-

250 μg/ml from the stock solutions by dilution. UV absorbance of the standard solutions was measured by UV spectrophotometer at 277 nm in pH 7.4 buffer and simulated gastric fluid. Standard curves were performed in triplicate in each medium to obtain an average value. Standard curves of observed absorbance versus verapamil hydrochloride concentration in simulated gastric fluid and pH 7.4 buffer are seen in Figures 2.7 and 2.8, respectively.

In Vitro Dissolution Testing of Verapamil HCl Formulations

Dissolution studies were performed according to the USP XXV apparatus 2. The dissolution vessel was maintained at 37 ± 0.5^0C with 750 ml of simulated gastric fluid being stirred at 50 rpm during the first 2 hours, then 242 ml of 0.2 M Na_3PO_4 was added, and adjusted to pH 7.4 by 6 N NaOH or concentrated hydrochloric acid. Samples were filtered through flow filters (0.70 μm), and collected via an autosampler at predetermined time intervals for 24 h dissolution studies. Filtered solutions were centrifuged at 3000 rpm for 10 minutes, supernatants were filtered again through 0.45 μm membrane and measured to determine absorbance at 277 nm for verapamil hydrochloride. Dissolution drug concentrations were determined via standard curves (Figures 2.7 and 2.8) in each medium and converted to percentage drug released.

Average drug released and their standard deviations were calculated from three replications in all dissolution experiments. Verapamil HCl dissolution profiles are presented as percent drug release versus time curves.

Spray Coating Parameters

An aeromatic fluid bed spray coater (NIRO-AEROMATIC) with a Wurster column insert was used to coat the capsules. Coating conditions for pulse release formulations are listed in Table 2.6.

Simulated gastric fluid preparation.

Add 8 grams of sodium chloride and 20 ml of concentrated hydrochloric acid to 1000 ml of DI water and mix well. Add 2950 ml of DI water and mix well. Adjust to pH 1.4 ± 0.1 with concentrated hydrochloric acid. Add DI water up to 4000 ml.

Table 2.6: Coating conditions for pulse release formulations

Coating layer	Eudragit	Surelease-drug	Opadry-drug
Approximate batch size (number capsules)	100	100	100
Drying Air Temperature (^{0}C)	29	29	31
Nozzle Diameter (mm)	0.8	0.8	0.8
Atomizing Air Pressure (psi)	5-10	5-10	15-20
Fluid Application Rate (ml/min)	0.6	0.7	0.4

Eudragit = Eudragit L-30-D 55 and Triethyl citrate; Surelease-drug = Surelease – chlorpheniramine maleate layer; Opadry-drug = Verapamil HCl – Opadry layer.
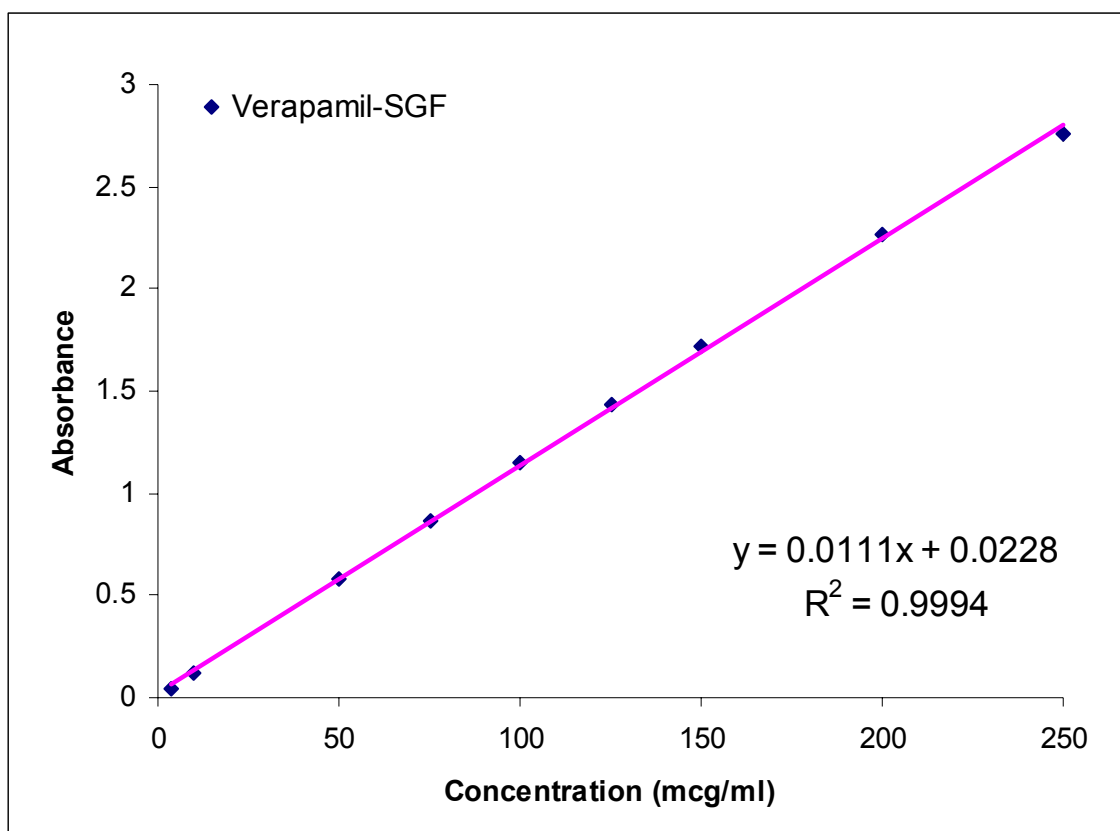
Figure 2.7: Standard curve of verapamil hydrochloride in simulated gastric fluid (UV wavelength at 277 nm)
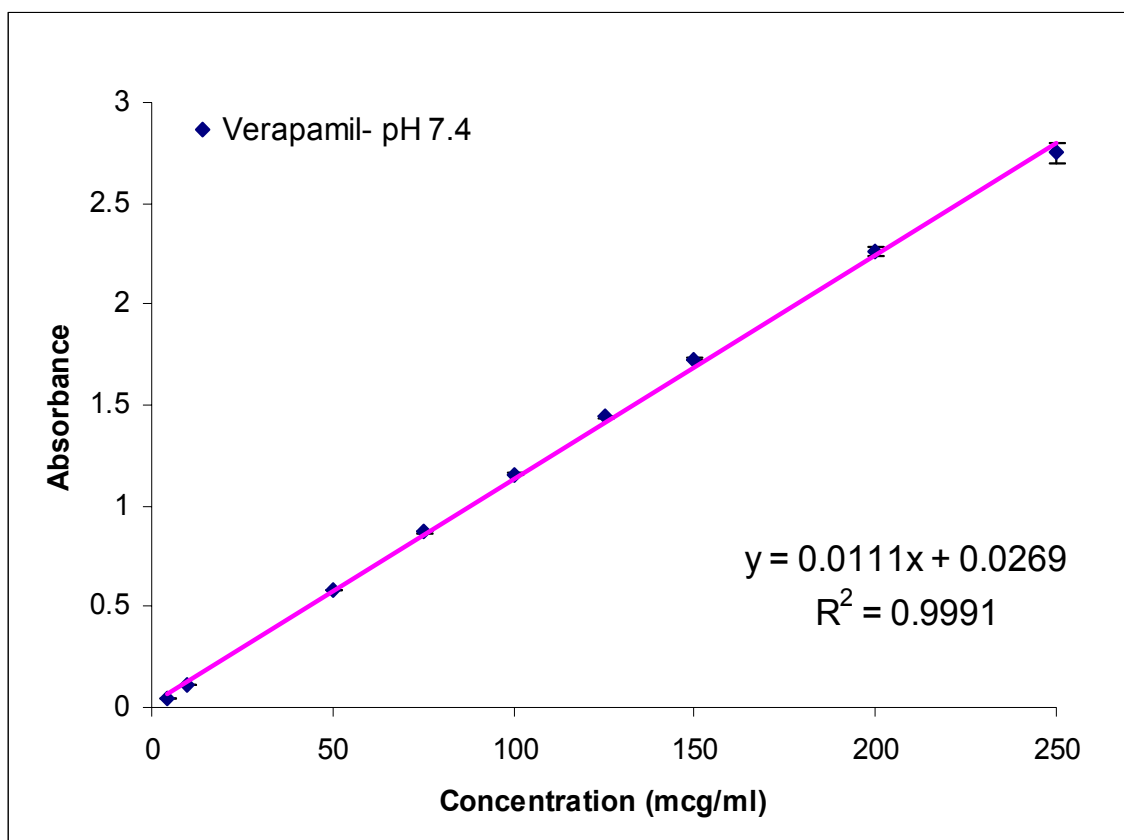
Figure 2.8: Standard curve of verapamil hydrochloride in pH 7.4 buffer (UV wavelength at 277 nm)

(iii) Anti-Tampering Coating

Hot-melt filled diltiazem HCl capsules were used to evaluate the effect of tamper proof coating layer. Hot-melt filled diltiazem HCl capsules were prepared as follows: Melt 240 mg of 1.5 parts of Gelucire 50/13: 1 part of cetyl alcohol in a beaker at 60^0C in a water bath. After complete melting, 120 mg of diltiazem hydrochloride (formulation F8) was added and mixed well in the beaker while maintaining temperature of the molten system at 55-60^0C throughout to prevent premature hot-melt congealment from occurring. At the end of blending, the beaker was removed from the heated water bath, and the molten mixture was poured into size 2 capsules kept upright, and congealing was allowed to occur inside capsules at room temperature to produce semisolid matrix inside capsules.

Anti-tampering coating is described in Figure 2.9 with tamper proof coating formulation below.

1. Melt a mixture of Gelucire 50/13, cetyl alcohol, PEG 300 and color– Brilliant red in a beaker at 60^0C. Pour hot-melt filled diltiazem HCl capsules into the beaker

2. Mix hot-melt filled diltiazem HCl capsules with molten wax in the beaker for 2 minutes.

3. Separately heat coating pan to 40-45^{0}C.

4. Pour capsules into heated spinning pan.

5. Use hand to smooth and separate the capsules

Figure 2.9: Process of tamper proof coating using hot-melt pan coating

Composition of tamper proof hot-melt pan coating

Composition of 30 mg of wax layer in tamper proof coated capsules is as follows (TP formulation).

Gelucire 50/13	23.52 mg
Cetyl alcohol	5.88 mg
PEG 300	0.60 mg
Color #3013 – Brilliant Red	0.01 mg

Wax coating was applied using hot-melt pan coating described in Figure 2.9.

Diltiazem HCl Assay

Standard Curves of Diltiazem HCl

An exact amount (50.0 mg) of diltiazem hydrochloride was weighed and transferred to a 1000-ml volumetric flask. The sample was dissolved in either simulated gastric fluid (pH 1.4 ± 0.1) without pepsin or pH 7.4 buffer solution and adjusted to final volume. This stock solution contained diltiazem hydrochloride of concentration of 50 μg/ml. A series of standard solutions with a concentration range of 0.5-50 μg/ml was prepared from the stock solutions of either simulated gastric fluid (pH 1.4 ± 0.1) without pepsin or pH 7.4 buffer solution by dilution. UV absorbance of standard solutions was measured by UV spectrophotometer at 236 nm in pH 7.4 buffer and simulated gastric fluid. Standard curves of diltiazem hydrochloride standard solutions in both media were identical. Average curve was calculated for both media. Standard curves of observed

absorbance versus diltiazem hydrochloride concentration in pH 7.4 buffer and simulated gastric fluid are seen in Figures 2.10 and 2.11 respectively.

In Vitro Dissolution Testing of Formulations

Dissolution studies were performed according to the USP XXV apparatus 2. The dissolution vessel was maintained at 37 ± 0.5^0C with 750 ml of gastric fluid being stirred at 50 rpm during the first 2 hours, then 242 ml of 0.2 M Na_3PO_4 was added, and adjusted to pH 7.4 by 6 N NaOH or concentrated hydrochloric acid. 4-mL dissolution samples were filtered through flow filters (0.70 μm), and collected via an autosampler at predetermined time intervals for 24 h dissolution studies. Filtered solutions were centrifuged at 3000 rpm for 10 minutes, supernatants from 2 h to 24 h were diluted to appropriate concentrations and absorbance measured at 236 nm to determine diltiazem hydrochloride concentrations. Dissolution drug concentrations were determined via standard curves (Figures 2.10 and 2.11) in each medium and converted to percentage drug released.

Average percent drug released with standard deviation were calculated from three replications in all dissolution experiments. Diltiazem HCl dissolution profiles are presented as percent drug release versus time curves.

pH 7.4 buffer preparation

Add 400 ml of simulated gastric fluid to 100 ml of 0.2M Na_3PO_4, mix well and adjust to pH 7.4 ± 0.1 by 6 N NaOH or concentrated hydrochloric acid.
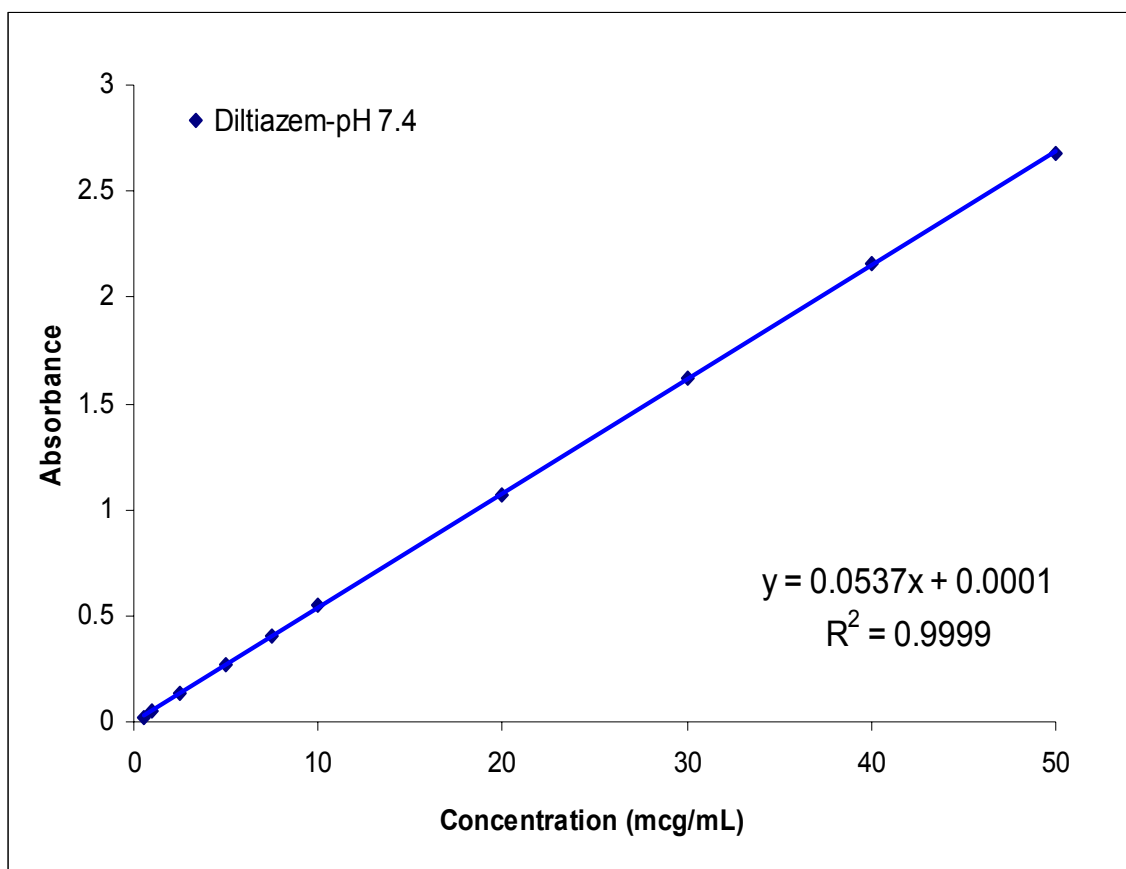
Figure 2.10: Standard curve of diltiazem hydrochloride in pH 7.4 buffer (UV wavelength at 236 nm)
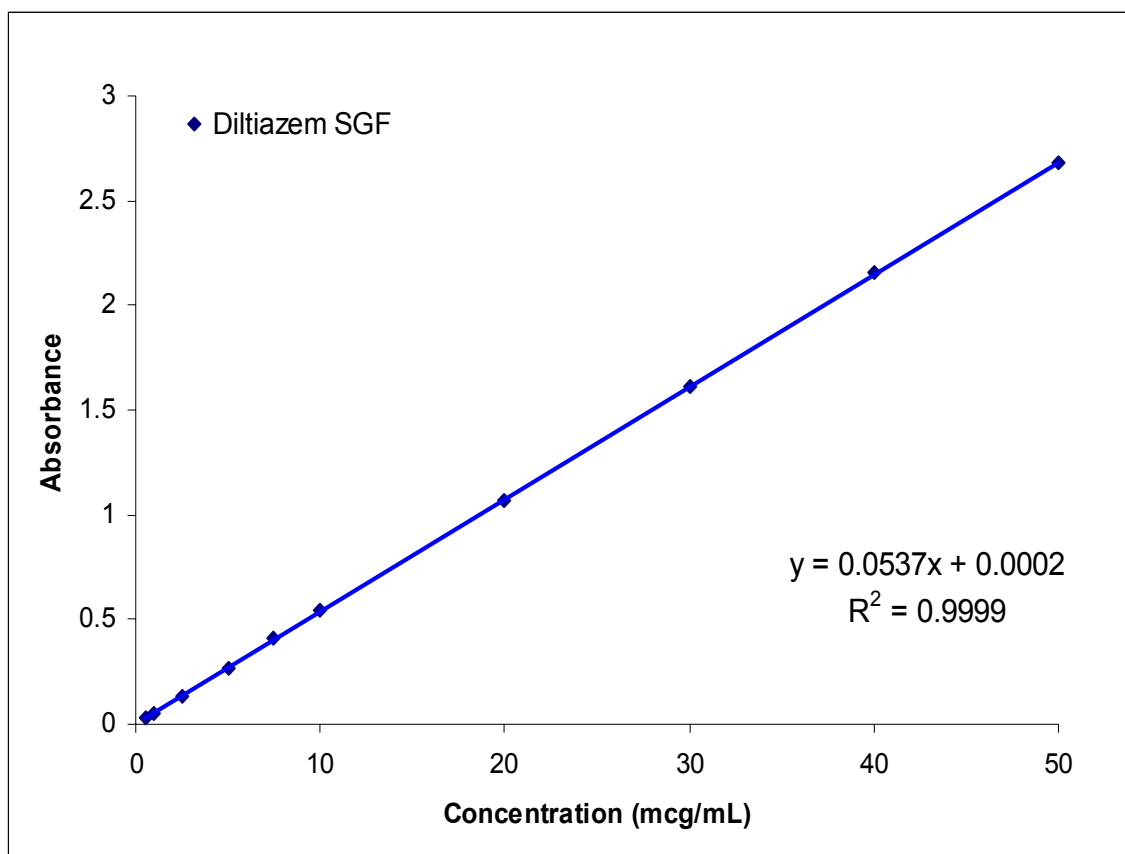
Figure 2.11: Standard curve of diltiazem hydrochloride in simulated gastric fluid (UV wavelength at 236 nm)

RESULTS AND DISCUSSION

The coating method worked well in the lab when either the drug was included in the coating mixture or when there was no drug in the coating mixture. Figure 2.12 shows three pictures of the hot-melt pan coated capsules

275 mg weight gain of wax
(4 parts Gelucire 50/13:1 part cetyl alcohol containing 2% PEG 300)

300 mg weight gain of wax
(4 parts Gelucire 50/13:1 part cetyl alcohol containing 2% PEG 300)

Anti-tampering coated capsules of 30 mg weight gain

Figure 2.12: Pictures of hot-melt pan coated capsules

Sustained Release Chlorpheniramine Results and Discussion

Table 2.7: Average weight with variance and CV of chlorpheniramine maleate in hot-melt coated capsules (n = 20), initial capsule weight 50 mg

Formulation	F1 (112mg desired weight gain)	F2 (152mg desired weight gain)	F3 (172mg desired weight gain)	F4 (192mg desired weight gain)
Average	157.525	234.070	240.765	258.095
Standard deviation	11.793	28.213	16.152	28.203
CV (coefficient of variation)	7.486	12.053	6.709	10.927

Table 2.7 shows that coefficient of variation for hot-melt coating weight gain on empty capsules ranged from 6.7% to 12.1%. Amount of variation depended on the skill and experience of the person doing coating. Individual weights of chlorpheniramine hot-melt coated capsules are seen in Table A.1. The surfaces of coated capsules were somewhat rough, and coating at ends of capsules was a little thicker than at the middle of capsules. This may be because the capsule ends contact the pan containing a thin wax layer more frequently than the body of capsules when capsules tumbled over each other. Note that whenever capsules contact the soft thin wax layer they were coated. The PEG 300, 2%, was added to the mixture of Gelucire 50/13 and cetyl alcohol in all formulations to assist in making the coat even and smooth.

When the amount of wax coating increases, the drug release rate decreases as seen in Figure 2.13. The weight of capsule shell is about 50 mg. The limit for the difference between individual capsule weight and average weight of capsule is usually set at less

than 10%. The net average coated weights of F1 to F4 after deducting 50 mg of the capsule shell range from about 107 to 208 mg (Table 2.7). 10% of these net average weights range from about 12 to 21 mg. Thus, the weight gain between formulations was chosen to be at least 20 mg. Physical observation during dissolution testing revealed that drug was released as coating eroded and broke away. The capsules initially floated in the medium, but began sinking after 2 h and floated up and down being broken into parts when hitting the paddle. Figure 2.13 shows that hot-melt pan coating worked with these formulations to produce sustained-drug release with the greater the outer coating weight gain, the slower the drug release. Formulations F1 (112 mg weight gain) and F2 (152 mg weight gain) sustained the drug release for 8 hours. Formulations F3 (172 mg weight gain) and F4 (192 mg weight gain) sustained the drug release for 12 hours.

Simulated plasma concentrations of new chlorpheniramine maleate sustained release capsules were performed by convolution and are shown in Figure 2.14. Intravenous data from Huang's paper (1982, subject A) was used in the convolution simulation. The assumption of bioavailability of chlorpheniramine maleate sustained release capsules is 0.4 (based on Huang's data, 1982). As expected, simulated plasma concentrations time curves of hot-melt pan coated formulations and chlorpheniramine maleate extended-release capsules were sustained as shown in Figure 2.14. Simulated maximum concentrations were 17.6, 16.0, 15.6, and 19.3 mcg/l for Chlorpheniramine maleate extended-release capsules, and 172, 192, and 152-mg weight gain formulations, respectively.
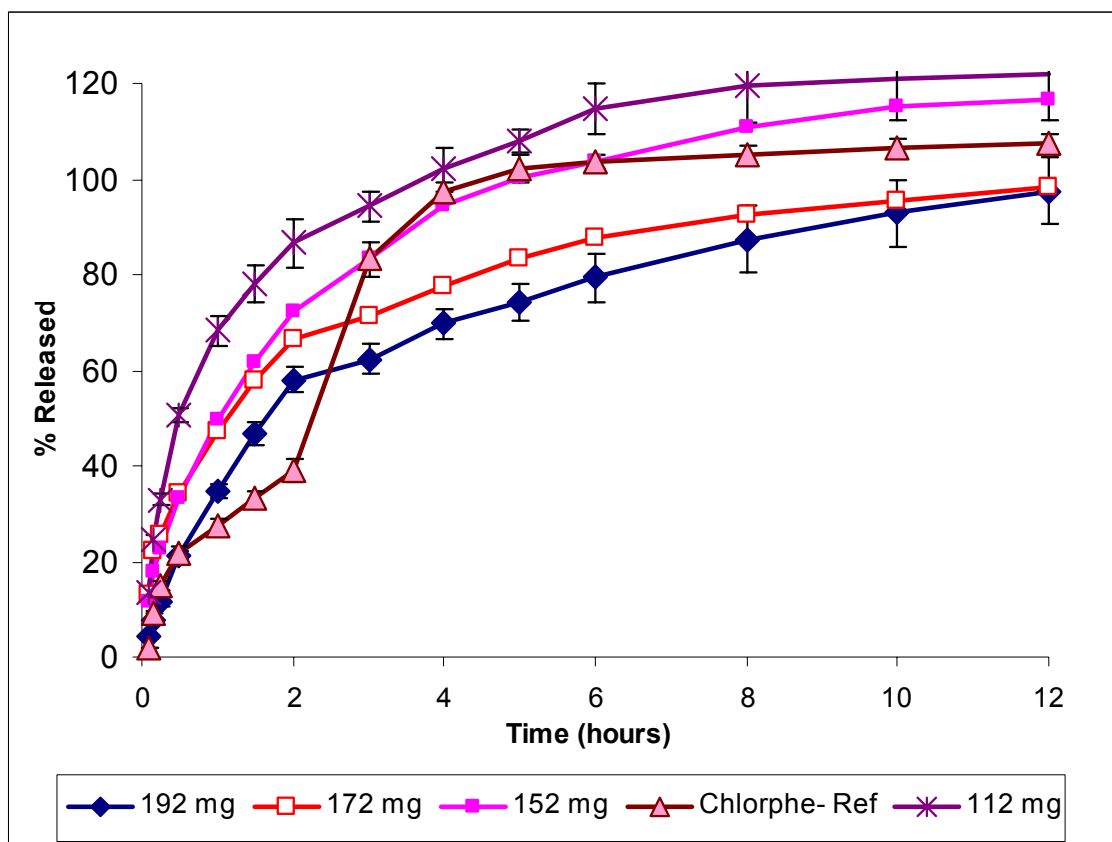
Figure 2.13: Dissolution profiles of sustained-release chlorpheniramine maleate capsules

192 mg = F4 formulation.

172 mg = F3 formulation.

152 mg = F2 formulation.

Chlorphe- Ref = Chlorpheniramine maleate extended-release capsules

112 mg = F1 formulation.
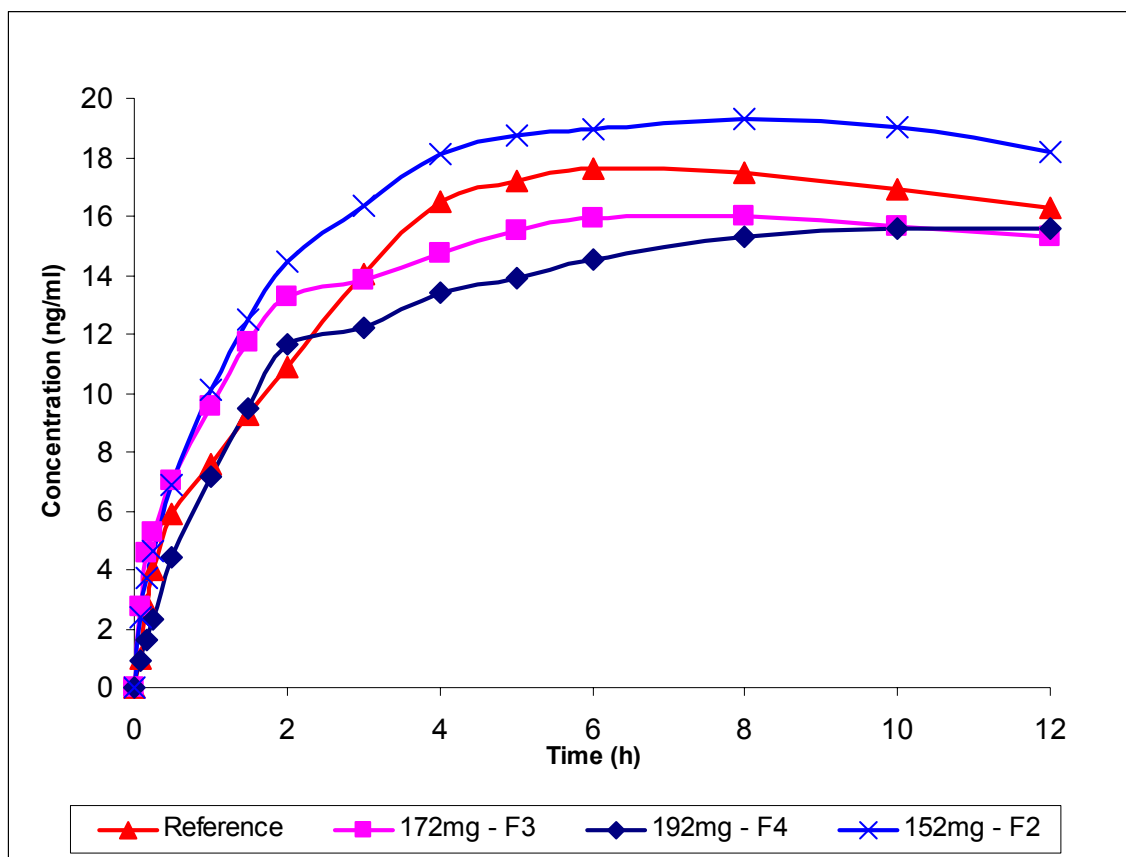
Figure 2.14: Simulated plasma concentrations performed by convolution of chlorpheniramine maleate sustained-release capsules

Reference = Chlorpheniramine maleate extended pulse-release capsules.

172mg - F3 = F3 formulation.

192mg - F4 = F4 formulation

152mg - F2 = F2 formulation.

Pulse Release Results and Discussion

A pulse release formulation for chlorpheniramine maleate that produces another type of drug concentration profile was also created using hot-melt pan coating, followed by a standard spray coating. In order to create the pulse-release profile, half the drug content was filled as a powder in lactose inside the capsules, and the other half of the drug was coated on the outside after hot-melt coating the capsules. The filled capsules were coated with various amounts of Gelucire 50/13 and cetyl alcohol, at a ratio of 4 to 1, using the hot-melt pan coater to make a delay layer. After the capsules were coated with the wax, the product was coated with Eudragit L-30-D55 enteric coating, and then Surelease with chlorpheniramine maleate was sprayed on the outside utilizing the spray coater (see Figure 2.5). This outer "immediate release" layer could also be applied using a quick-release melt coating if desired.

The outermost layer contained Surelease, which is insoluble and helps delay water penetration into the wax, but the wax is the primary delaying layer in the intestine. Underneath the Surelease layer, the capsules were coated with Eudragit L-30-D 55 (Eudragit), an enteric coating material, which is only soluble once it reaches the intestine. After the capsules enter the intestine, the Eudragit dissolves, which enables the fluid to reach the wax layer and the center of the capsule where the second half of the drug is located. Next, pressure builds up inside the capsules over time, causing the capsule to rupture at about 6 to 8 hours and release the remainder of the drug inside capsules. The spray coating after hot-melt coating was implemented under low temperature. The best

temperature was below 32^0C degree; otherwise the wax layer softened, and wax layer deformed or melted. Since the temperature was kept low, the rate the fluid flowed through the nozzle for spraying the coating on to the capsules was also kept low to allow drying and insure coating efficiency.

Table 2.8 shows weight with variance of chlorpheniramine maleate hot-melt coated capsules with wax only in the coating layer.

Table 2.8: Average weight, variance and CV of chlorpheniramine maleate hot-melt coated capsules with wax only

Chlorpheniramine maleate inside capsule	Average	Standard deviation	CV (coefficient of variation)
200 mg weight gain (n = 20)	324.895	21.570	6.639
275 mg weight gain (n = 20)	393.040	26.098	6.640
300 mg weight gain (n = 10)	431.850	12.676	2.935

From experience, wax coating without the drug was much easier to apply than with the drug in molten materials. The surfaces of capsules coated with only wax were smoother and more uniform. Coefficient of variation of the weight of coated capsules without drug were smaller than that with drug as seen in Tables 2.7, and 2.8. The reason for smooth and uniform capsules is that the wax without the drug was more uniformly distributed inside the pan than the wax with the drug. It also was easy to separate coated capsules coated with wax only during coating and smoothing processes. Thus, the capsules coated with wax only were smoother and more uniform. The reason the CV of

300 mg coating weight gain is so small is not clear. It is believed the variance is related to the skill and experience of the different operators who coated the respective capsules.

Figures 2.15 and 2.16 show two-stage release of drug from the pulse release chlorpheniramine. The pulse release chlorpheniramine maleate 12 mg capsules only released about 80 to 90% of drug after 12 hours (Figure 2.15). This is thought due to ethylcellulose prolonging drug release. Thus, other more soluble or easily dispersible materials are recommended. Formulations 5 (Surelease:drug = 4:1) and 6 (Surelease:drug = 2:1) drug dissolution profiles are almost parallel to the reference. The reason(s) a ratio of Surelease:drug = 4:1 and Surelease:drug = 2:1 had similar drug release patterns is unclear. It is postulated that the amount of Surelease in the outside layer is so small that the effect of these amounts of Surelease on drug release is negligible.

In the Figure 2.16, dissolution from formulation F7 (the brown curve) was close to the reference. In this formulation, the drug was loaded to 110% of what is expected in the reference product. Note also that the drug was not released completely from the pulse release chlorpheniramine maleate 8 mg capsules after 8 h since less than 110% of reference product labeled drug was released after 8 h.

A pulse release capsule for verapamil HCl was also produced using hot-melt pan coating, followed by a standard spray coating. For verapamil HCl pulse release capsules, half the drug content was filled as a powder in lactose inside the capsules, and the other half of the drug was coated on the outside after hot-melt coating the capsules. The filled capsules were coated with 300 mg of Gelucire 50/13 and cetyl alcohol, at a ratio of 4 to 1,

using the hot-melt pan coater to make a delay layer. After the capsules were coated with the wax, the other 50% of drug was loaded with Opadry as binder utilizing the spray coater. Note that no enteric coating layer was utilized in this formulation.

Table 2.9 presents the average weight with variance of verapamil HCl pulse release capsules coated with wax only.

Table 2.9: Average weight with variance of hot-melt coated capsules without drug in coating layer and verapamil HCl inside capsule

Verapamil HCl inside capsules	Average	Standard deviation	CV (coefficient of variation)
200 mg weight gain (n = 10)	395.600	9.198	2.325
400 mg weight gain (n = 10)	602.210	19.842	3.295

Since Opadry is soluble in both gastric fluid and intestinal fluid, the primary factor delaying drug release in both gastric fluid and intestinal fluid is the wax. When the capsules were put in the dissolution medium, the outer layer dissolved and released 50% of the drug in 30 minutes, which enabled the medium to reach the wax layer. Once the dissolution medium penetrated the wax layer, this medium entered the center of the capsule where the second half of the drug was located. Next, pressure built up inside the capsules over time, causing the capsule to rupture about 4 hours later and release the remainder of the drug from inside the capsules (the light blue curve in Figure 2.16). Figure 2.16 shows that verapamil HCl loaded capsules coated with wax, followed by adding an immediate release layer overcoat of verapamil HCl produced excellent pulse-release capsules.
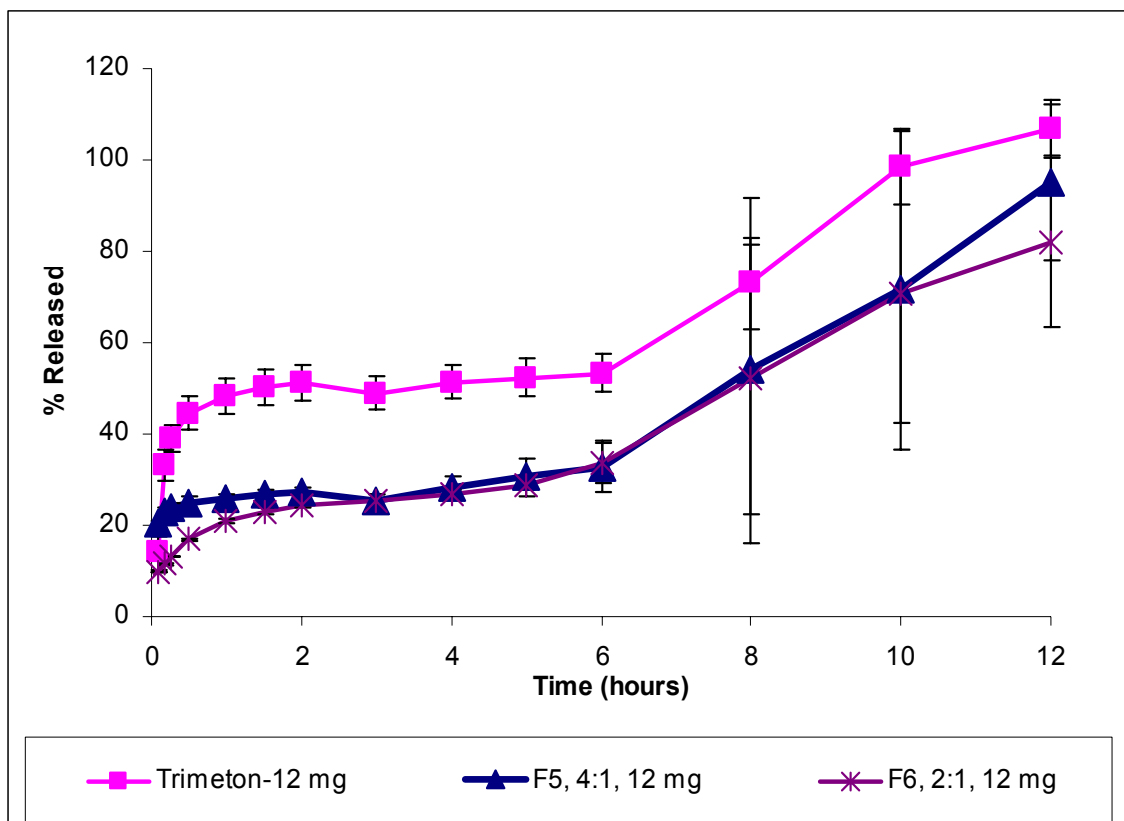
Figure 2.15: Dissolution profiles of pulse release chlorpheniramine maleate capsule 12 mg

Trimeton 12 mg = Chlor-Trimeton 12 hours.

F5, 4:1, 12 mg = F5 formulation.

F6, 2:1, 12 mg = F6 formulation.
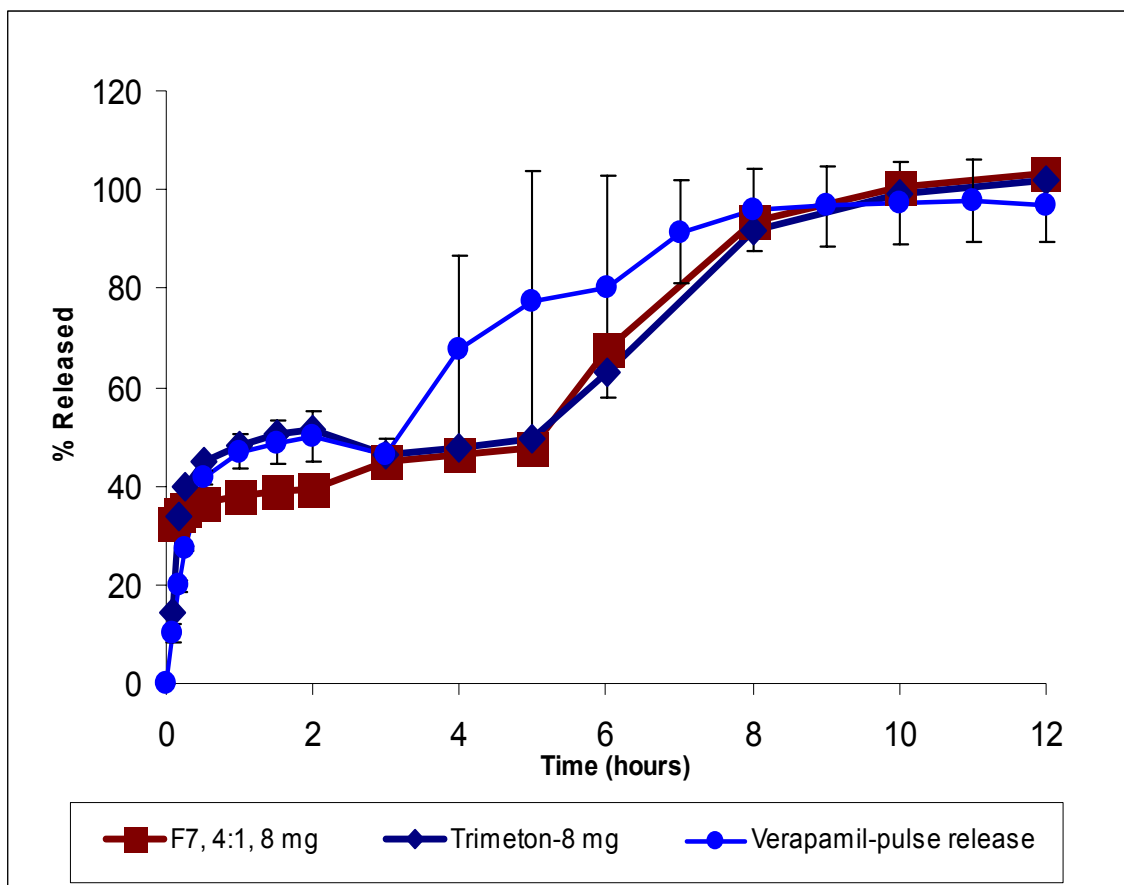
Figure 2.16: Dissolution profiles of verapamil HCl pulse release capsules (160 mg) and chlorpheniramine maleate pulse release capsules (8 mg) compared to Chlor-Trimeton 8 (reference)

F7, 4:1, 8 mg = F7 formulation.

Trimeton-8 mg = Chlor-Trimeton 8 hours.

Verapamil-pulse release = Verapamil HCl pulse release capsules 160 mg.

In the chlorpheniramine maleate pulse release capsules, the time for delayed-release of drug is dependent on the amount and type of wax used, Eudragit, and Surelease. A lag time of up to 6 hours occurred for formulations tested. In the verapamil HCl formulation, the 300 mg mixture of Gelucire 50/13 and cetyl alcohol itself is a delaying layer, and can delay drug release up to 4 h. By adjusting the wax layer or the wax layer over coated with Surelease, a desirable lag time can be produced.

Anti-tamper coating

In order to make tamper proof coating for capsules, capsules were put in molten materials for exactly 2 minutes. During that time, molten wax entered the gap between the two ends of capsules, and stayed there. This wax layer acts like a glue and helps hold the two parts of the capsule together. With mixing times of two minutes, wax penetrates into the space between capsules in sufficient amounts, but with longer mixing times, the wax could penetrate into the capsule contents.

Tamper resistant coated capsules were smooth, uniform, and harder to open compared with uncoated interlocking capsules, and were considered to be easier to swallow because the surface is "slippery", especially when wet with mucosal fluid. To check the tamper proof coating affect on drug release, dissolution of diltiazem HCl hot-melt filled capsules were evaluated with and without a tamper resistant wax coating layer. Coating of capsules with tamper resistant wax layer did not affect diltiazem HCl release from hot-melt filled capsules, except at 20, 24 and 28 hours (Figure 2.17). For the first 20 hours, all capsules sank and remained on the bottom. At 20 h for the uncoated capsules

and at 26 h for wax coated tamper resistant capsules floated up and down, and were hit by the stirring paddle. From 20 h to 26 h, when hit by the stirring paddle, semisolid matrix inside uncoated capsules was broken. The broken semisolid matrix inside uncoated capsules released drug faster than coated capsules from 20 to 28 h which produced differences in dissolution profiles between with and without anti-tampering wax coated capsules from 20 to 28 h. Note that the semisolid matrix inside coated capsules was broken after being hit by the stirring paddle at 26 h.

The data also showed that very simple formulations of hot-melt filled capsules provide good sustained release of drug. Hot-melt filling is the most simple way identified in this laboratory to make sustained release products on a small scale.
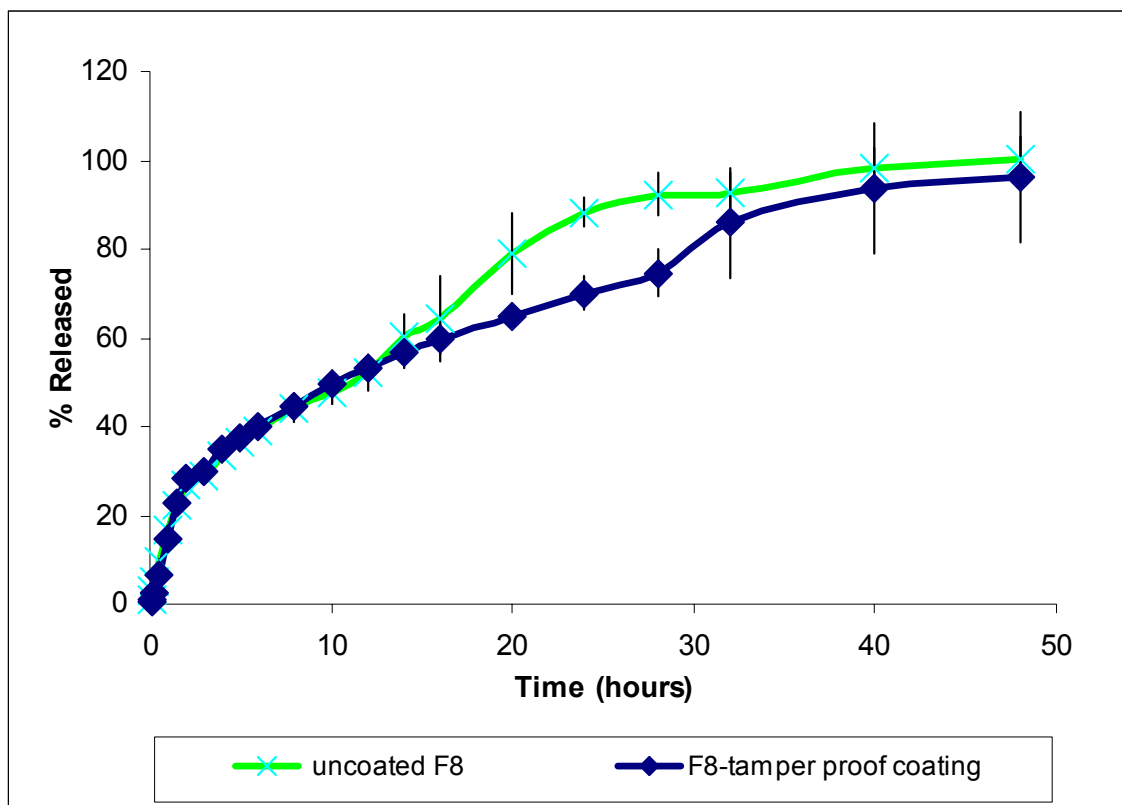
Figure 2.17: Dissolution profiles of diltiazem HCl from hot-melt filled capsules with and without anti-tamper wax coating

uncoated F8 = F8 uncoated capsule formulation (see page 29)

F8-tamper proof coating = F8 coated with tamper proof coating (see page 29 and 31).

CONCLUSIONS

Hot-melt pan coating, which took 2-3 hours for 300 mg coating weight gain on capsules, and tamper-resistant coating, which took 30 minutes, are much faster than tedious sugar coating and allow greater coating weight gains in shorter times than spray-melt coating. Although hot-melt pan coating is promising, it needs modification for industrial scale-up and to provide more elegant formulations. Temperature jacketed ointment vats with side scrapers and mixing blades may be considered for larger scale production. Hot-melt capsule filling is an especially appealing and simple way to make sustained release formulations in the lab.

In summary, methods described herein are easy to perform in a lab, can make both sustained release formulations, and pulse-release formulations, and tamper-resistant capsules. These approaches are recommended for researchers who want to quickly develop and test sustained release or pulse-release dosage forms. Industrial scale-up has not yet been undertaken.

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CHAPTER 3

Formulation of Verapamil HCl and Diltiazem HCl Semisolid Matrix Capsules

Chien N. Nguyen, J. Mark Christensen, James W. Ayres

ABSTRACT

Semisolid matrix capsule formulations prepared by hot-melt capsule filling is found to be an especially appealing and simple way to make sustained release formulations. Semisolid matrix capsules of verapamil HCl and diltiazem HCl were investigated. Both verapamil HCl and diltiazem HCl semisolid matrix capsules eroded and disintegrated at various times depending on combination of waxes. For Gelucire 50/13 and stearic acid combination, the matrix disintegrated faster than Gelucire 50/13 and cetyl alcohol combination. Gelucire 50/13 only matrix or stearic acid only matrix floated more than 8 h, then disintegrated after 12 h. Stearic acid retarded drug release too much and was not appropriate to use alone in forming semisolid matrix capsules for the drugs studied. A combination of Gelucire 50/13 with cetyl alcohol is more effective than stearic acid in appropriately extending verapamil HCl release from semisolid matrix capsules. Semisolid matrix formulations studied are sensitive to stirring speeds.

INTRODUCTION

Filling hard gelatin capsules with semi-solid matrices (SSM) is a simple technique that has been used to extend the release of many drugs and obviates the need for additional excipients, granulation and compression steps (Galal et al., 2004). Additionally, it offers many advantages including improvement in chemical stability, excellent homogeneity and content uniformity, easier formulation of oily drugs and preparation of oral sustained release formulations (Wu et al., 2002). Lipid matrices also cost relatively little to produce, and, in some cases, it is possible to minimize the influence of physiological variables on drug release (Esquisabel et al., 1996).

The Gelucires are a family of lipid-based excipients comprising mono-, di- and triglycerides mixed with mono- and diesters of fatty acids and polyethyelene glycol (PEG) (Sutananta[10,11] et al., 1995; Choy et al., 2005; Wu et al., 2002, Khan et al., 2003; Esquisabel et al., 1996). Molecular weight of PEGs is between 200 and 2000 (Esquisabel et al., 1996). Gelucires may contain pure glycerides, mixtures of glycerides and fatty acid esters of PEG in varying proportion or, in the case of Gelucire 55/18, pure PEG esters with no glycerides present (Galal et al., 2004). The presence of the hydrophilic PEG esters confers an element of water miscibility to the lipid bases, thereby removing the necessity of incorporating surfactants or related molecules to allow drug release to occur over a relevant time scale (Khan et al., 2003). Gelucires have been used pharmaceutically for a number of years, notably as suppository bases and solvents (Sutananta[10] et al., 1995). Each Gelucire is characterized by two numbers (Khan et al., 2003; Vippagunta et

al., 2002; Choy et al., 2005); the first corresponding to the melting point of the material, ranging from 33 to 65^0C (Esquisabel et al., 1996) and the second to the hydrophilic–lipophilic balance (HLB), ranging from 1 to 14 (Esquisabel et al., 1996). HLB number reflects the proportion of water soluble to lipid soluble moieties in each material (Khan et al., 2003). The various grades of Gelucires characterized by two numbers aforementioned lead to a specific behavior when placed in gastrointestinal fluids in respect to hydrodispersibility, melting and floatability (Galal et al., 2004; Wu et al., 2002). Gelucire lipid matrix capsules are new dosage forms which can modulate drug release in relation to the melting point and the hydrophilic-lipophilic balance of the saturated polyglycolysed glycerides used (Ratsimbazafy et al., 1999).

In general, Gelucires with the higher melting bases and a bigger proportion of lipophilic components are used as matrix agents for sustained release formulations, while Gelucires with more hydrophilic components are suitable as bioavailability enhancers. Wu et al. (2002) found that the melting point of Gelucire was the most influential factor on the release of potassium chloride, with the higher the melting point of the Gelucires, the slower the release rate of potassium chloride. Esquisabel et al. (1996) investigated salbutamol sulfate sustained release formulations based on Gelucires. They found Gelucires 48/09, 50/13 and 53/10, were sustained-release agents. All of them have melting points above 48^0C and hydrophilic/lipophilic balance values above 9. Gelucires 33/01, 35/10, 37/02, 42/12 and 44/14 were fast drug release agents, and Gelucires 46/07 and 50/02 exhibited slow release characteristics (Esquisabel et al., 1996). Galal et al. (2004) in an *in vitro* study determined release characteristics of carbamazepine from

semisolid matrix filled capsules. They observed drug release with respect to the excipients melting point and/or HLB values and indicated that different grades of Gelucires bases (Gelucires 50/13, 53/10 and 33/01) could be successfully used to prepare extended release carbamazepine capsules by application of semisolid matrix filling capsule technology.

Gelucires are also used as bioavalability enhancers in solid dispersion. Gelucire 44/14 and 50/13 in a solid dispersion of carbamazepine improved the *in vitro* release rate of the drug, even with a small percentage of the carrier into the formulation (Perissutti et al., 2000). Pluronic F68 and Gelucire 50/13 (1:1) improved the dissolution of nifedipine in solid dispersion (Vippagunta et al., 2002).

In Gelucires family, Gelucire 50/13 is often used as a sustained-release agent. Gelucire 50/13 contains a large proportion of PEG mono- and diesters with palmitic (C16) and stearic (C18) acid, with 20% glycerides and 80% PEG esters (Sutananta[10] et al., 1995); hence Gelucire 50/13 contains both hydrophobic and hydrophilic components.

Gelucire 50/13 appears to be stable. There is no evidence of degradation of Gelucire 50/13 upon heating to 75^0C (Sutananta[11] et al., 1995). However sustained release characteristics from Gelucire 50/13 formulations may not be stable. A number of studies have demonstrated that Gelucire formulations may exhibit a change in drug release characteristics during storage. A remarkable increase in the carbamazepine release rate from Gelucire 50/13 occurred upon storage (Galal et al., 2004). Sutananta[11] et al. (1995) found theophylline release from both Gelucire 50/13 and 55/18 bases increased

on aging for up to 180 days in ambiently cooled systems. The more rapid release from aged Gelucire 50/13 matrices is likely to be attributable to changes in the physical structure of the base (Sutananta[11] et al., 1995). Choy et al. (2005) studied the significance of Gelucire 50/13 matrix aging on *in vitro* paracetamol (acetaminophen) release and *in vivo* bioavailability. They concluded that the increase in the rate of drug release from aged samples could be correlated to the alterations to the supramolecular structure of the Gelucire. Accelerated paracetamol (acetaminophen) release from aged samples could also be seen during *in vivo* studies using healthy human volunteers, although the extent of absorption was not affected (Choy et al., 2005). In contrast for other Gelucires, it has been reported that upon aging, a decrease in the release rate of nifedipine, and salbutamol occurred from sustained release formulations based on Gelucire 50/10, and Gelucire 35/10 respectively (Galal et al., 2004). Semisolid matrix based on Gelucire 53/10 showed high dissolution stability during one year of shelf aging (Galal et al., 2004).

Gelucires may release incorporated drugs by a number of mechanisms depending on their chemical composition. Sutananta[10] et al. (1995) investigated the mechanisms of drug release from Gelucire bases. They showed Gelucire 43/01 and 54/02 systems released the drug by a simple diffusion mechanism, with no evidence for erosion or swelling being noted, while Gelucire 55/18 matrix exhibited a more complex mechanism involving both diffusion and erosion. Drug release from Gelucire 50/13 matrices was principally by erosion, although the process was dominated by swelling and subsequent disintegration of the matrix (Sutananta[10] et al., 1995). Gelucire 50/13 matrix was also shown to swell (Kopcha et al., 1992; Galal et al., 2004; Khan et al., 2003) and exhibit

surface erosion. Galal et al. (2004) observed the erosion occurred through the disintegration of the masses at the surface of the Gelucire 50/13 matrix. Ratsimbazafy et al. (1999) studied proxyphylline release from hard gelatin matrix capsules based on mixtures of Gelucire 50/02 and 50/13. They indicated that drug release increased with Gelucire having a mixture of HLB owing to higher erosion. Modeling of dissolution kinetics has generally shown the predominance of surface erosion of the plugs relative to drug diffusion inside the matrix (Ratsimbazafy et al., 1999). Khan et al. (2003) showed a high initial water uptake for Gelucire 50/13 matrix alone as the water penetrated the outer layer of the dry matrix, followed by a slower uptake process.

The release model of drug from Gelucires semisolid matrices resembles a diffusion controlled model. Using the model based on the Higuchi equations for diffusion controlled release is appropriate for the majority of drugs incorporated in Gelucires with a low HLB (<7). Release rates of drug from bases with high HLB values are faster and are thought to involve both diffusion and erosion mechanism (Sutananta[10] et al., 1995). Wu et al. (2002) found the Higuchi model fit best to potassium chloride release from a Gelucire 50/13 semisolid matrix. Galal et al. (2004) showed zero-order release profiles of carbamazepine were obtained from semisolid matrix based on Gelucire 50/13, Gelucire 53/10 and their blends in ratios higher than 1:1, and Gelucire 53/10 containing croscarmellose sodium (Galal et al., 2004).

The presence of incorporated drugs may affect the structure and behavior of Gelucire matrices. Khan et al. (2003) investigated the effect of incorporating caffeine and

paracetamol (acetominophen) on the structure and behavior of Gelucire 50/13 matrix. They indicated that the presence of incorporated drugs may have a profound influence on the structure and behaviour of Gelucire 50/13 matrices. The presence of paracetamol increased the proportion of the wax material in the lower melting form which results in greater resistance of the surface to disintegration. Consequently, both the erosion process itself and the decrease in diameter caused by erosion may be expected to be less marked for these systems (Khan et al., 2003). Sutananta[11] et al. (1995) also showed that the presence of a larger proportion of drug resulted in disruption to the matrix structure, leading to a predominance of the erosion mechanism.

So far these studies of extended-release semisolid matrices often focus on using Gelucires only. The combination between Gelucires and other waxes has not been mentioned. In this study, the incorporation of cetyl alcohol and stearic acid into Gelucire 50/13 matrix was investigated. Cetyl alcohol, hexadecan-1-ol, is used in pharmaceutical formulations as a coating agent, emulsifying agent, and stiffening agent (Wade and Weller, 1994). Stearic acid, octadecanoic acid, is used as an emulsifying agent, solubilizing agent, and tablet and capsule lubricant (Wade and Weller, 1994).

Verapamil hydrochloride (HCl) and diltiazem HCl were chosen as model drugs for this study. The purpose of study was to investigate the effect of combinations of Gelucire 50/13, stearic acid, and cetyl alcohol on the release of verapamil HCl and diltiazem HCl from semisolid matrix capsules.

MATERIALS AND METHODS

Chemicals

Verapamil hydrochloride was a gift from Teva Pharmaceuticals (Sellersville, PA). Diltiazem hydrochloride (from Fluka, BioChemika, Switzerland) was purchased from Sigma-Aldrich Co. (St. Louis, MO). The capsules, shell size 1, and 2 were from Capsugel (Greenwood, SC). The Macrogol glycerol stearate (Gelucire 50/13) was purchased from Gattefosse (Saint-Priet Cedex, France). Cetyl alcohol, 1-hexadecanol, $C_{16}H_{34}O$, was bought from Spectrum Chemical Mfg. Corp., (Gardena, CA and New Brunswick, NJ). Stearic acid was supplied from J.T. Baker (Phillipsburg, NJ). Verelan sustained-release capsules, 240 mg, were from Schwarz Pharma, Inc. (Milwaukee, WI) and purchased from the Oregon State University (OSU) campus pharmacy. Dilacor XR capsules were from Watson Pharma (Corona, CA) and purchased from the OSU campus pharmacy.

Methods

Verapamil HCl semisolid matrix capsules

Verapamil HCl semisolid matrix capsule preparation

Weight composition of verapamil HCl semisolid matrix capsule formulations is shown in Table 3.1. Semisolid matrix capsule preparation is described as follows.

Table 3.1: Weight composition of test formulations of 240 mg verapamil HCl semisolid matrix capsules

Formulation		Ge	Stearic acid	Cetyl alcohol	Ge:ste:cet ratio
240 mg wax	F1	160 mg	80 mg	0	2:1:0
and 240 mg of	F2	200 mg	40 mg	0	5:1:0
verapamil HCl	F3	240 mg	0	0	1:0:0
	F4	0	240 mg	0	0:1:0
	F5	192 mg	48 mg	0	4:1:0
	F6	180 mg	60 mg	0	3:1:0
	F7	120 mg	120 mg	0	1:1:0
	F8	192 mg	0	48 mg	4:0:1
	F9	120 mg	0	120 mg	1:0:1
210 mg wax	F10	168 mg	0	42 mg	4:0:1
and 240 mg of	F12	175 mg	0	35 mg	5:0:1
verapamil HCl	F14	168 mg	21 mg	21 mg	4:0.5:0.5
	F15	168 mg	10.5	31.5	4:0.25:0.75

Ge = Gelucire 50/13, ste = stearic acid, cet = cetyl alcohol. Wax includes Gelucire 50/13, stearic acid, and cetyl alcohol.

Wax was melted, including Gelucire 50/13, stearic acid and/or cetyl alcohol with the amount of each ingredient in each formulation seen in Table 3.1, in a beaker at 60^0C. After complete melting, 240 mg of verapamil HCl was added and mixed well in the beaker in the water bath where the temperature of the molten system was maintained at $55-60^0$C throughout to prevent premature hot-melt congealment from occurring. At the

end of blending, the beaker was removed from the water bath and the molten mixture poured into capsules of size 1, and capsules were kept upright until the mixture congealed. Solid matrix capsules were stored at room temperature until testing**.**

Verapamil HCl Assay

<u>Standard Curves of Verapamil HCl</u>

An exact amount (250 mg) of verapamil hydrochloride was weighed and transferred to a 1000-ml volumetric flask. The sample was dissolved in either simulated gastric fluid (pH 1.4 ± 0.1) without pepsin or pH 7.4 buffer solutions, and adjusted to final volume. This stock solution contained a verapamil hydrochloride concentration of 250 µg/ml. A series of standard solutions in either simulated gastric fluid (pH 1.4 ± 0.1) without pepsin or pH 7.4 buffer solution were prepared with concentrations ranging from 4-250 µg/ml from the initial stock solutions, by dilution. UV absorbance of standard solutions was measured by UV spectrophotometer at 277 nm in pH 7.4 buffer and simulated gastric fluid. Standard curves were performed in triplicate in each medium to obtain an average. Standard curves of verapamil hydrochloride in both media turned out identical. Average curve of absorbance versus drug concentration was calculated for both media. Standard curves of observed absorbance versus verapamil hydrochloride concentration in simulated gastric fluid and pH 7.4 buffer are seen in Figures 3.1 and 3.2, respectively.
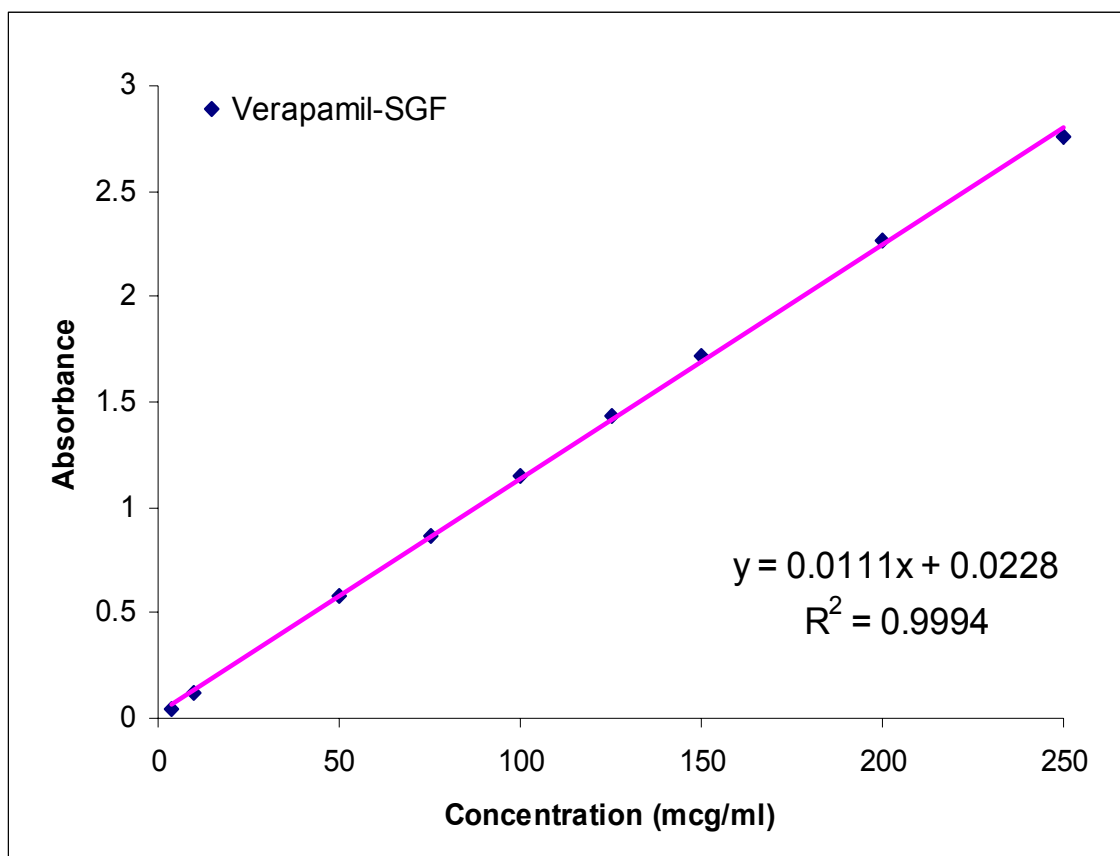
Figure 3.1: Standard curve of observed absorbance versus verapamil hydrochloride concentration in simulated gastric fluid (UV wavelength at 277 nm)
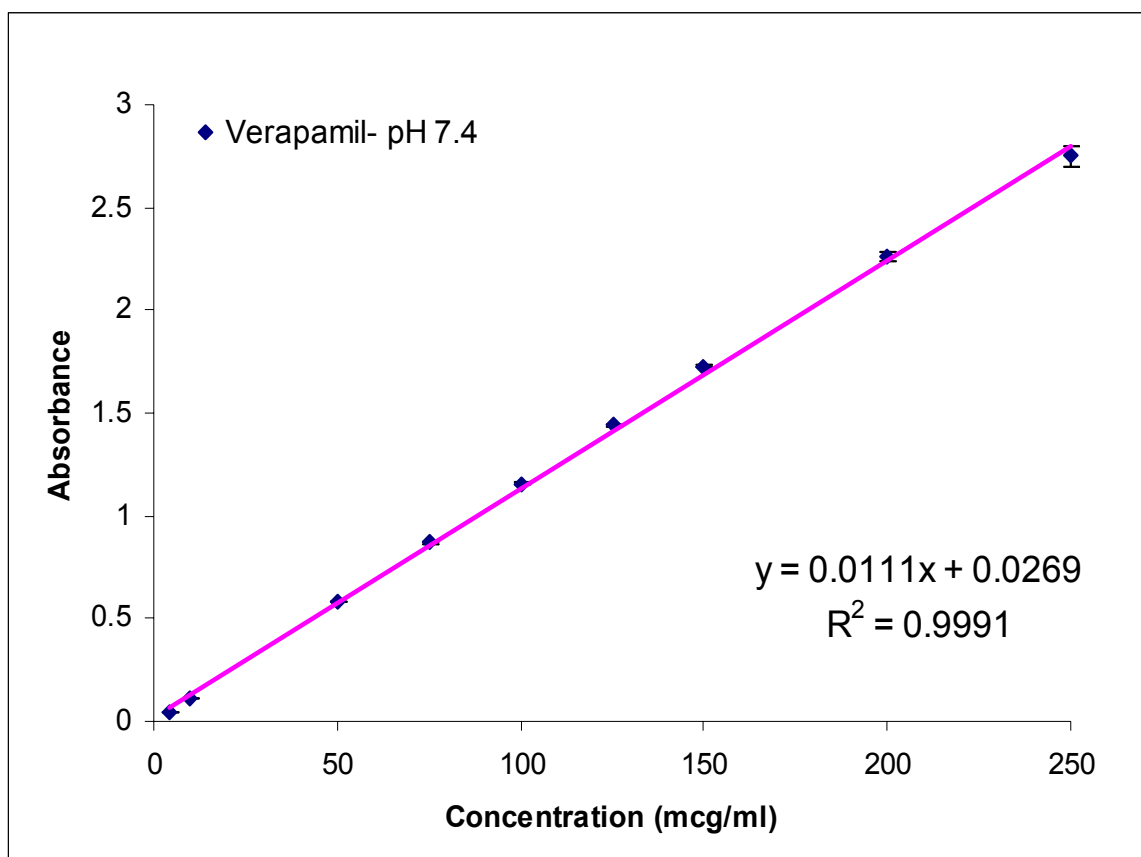
Figure 3.2: Standard curve of observed absorbance versus verapamil hydrochloride concentration in pH 7.4 buffer solution (UV wavelength at 277 nm)

In Vitro Dissolution Testing of Verapamil HCl semisolid matrix capsule

Dissolution studies were performed according to the USP XXV using apparatus 2. Test products were placed first in 750 ml of simulated gastric fluid for the first 2 hours with a stir rate of 50 rpm and maintained at 37 ± 0.5^0C, then 242 ml of 0.2 M Na_3PO_4 was added and the final pH was adjusted to pH 7.4 using 6 N NaOH or concentrated hydrochloric acid. 4 ml dissolution samples were filtered through flow filters (0.70 µm), and collected via an autosampler at predetermined time intervals for 24 h dissolution studies. Filtered solutions were centrifuged at 3000 rpm for 20 minutes, supernatants from 3 h onward to 24 h were filtered again through 0.45 µm membrane and measured to determine absorbance at 277 nm for verapamil hydrochloride. Dissolution drug concentrations were determined via standard curves (Figures 3.1 and 3.2) in each medium and converted to percentage drug released.

Average drug released at various time points and their standard deviations were calculated from three replications in all dissolution experiments. Verapamil HCl dissolution profiles are presented as percent drug release versus time curves.

Diltiazem HCl semisolid matrix capsules

Diltiazem HCl semisolid matrix capsule preparation

Weight composition of diltiazem HCl semisolid matrix capsule formulations is shown in Table 3.2. The preparation of diltiazem HCl semisolid matrix capsule is the

same as verapamil HCl semisolid matrix capsule except that 120 mg of diltiazem HCl was used and the molten mixture was poured into capsules of size 2 for diltiazem HCl.

Table 3.2: Weight composition of test formulations of 120 mg diltiazem HCl semisolid matrix capsules

Formulation		Wax		
		Gelucire 50/13: Cetyl alcohol	Gelucire 50/13	Cetyl alcohol
160 mg wax,	D1	4:1	128 mg (4)	32 mg (1)
and 120 mg of	D2	2:1	106.7 mg (2)	53.35 mg (1)
diltiazem HCl	D3	1:1	80 mg (1)	80 mg (1)
240 mg wax, and	D4	4:1	192 mg (4)	48 mg (1)
120 mg of	D5	2:1	160 mg (2)	80 mg (1)
diltiazem HCl	D6	1:1	120 mg (1)	120 mg (1)
	D7	3:1	180 mg (3)	60 mg (1)
	D8	1.5:1	144 mg (1.5)	96 mg (1)

Diltiazem HCl Assay

Standard Curves of Diltiazem HCl

An exact amount (50 mg) of diltiazem hydrochloride was weighed and transferred to a 1000-ml volumetric flask. The sample was dissolved in either simulated gastric fluid (pH 1.4 ± 0.1) without pepsin or pH 7.4 buffer solutions and adjusted to final volume. This stock solution contained a diltiazem hydrochloride concentration of 50 μg/ml. A series of standard solutions with concentrations ranging from 0.5-50 μg/ml were prepared

from the initial stock solutions in either simulated gastric fluid (pH 1.4 ± 0.1) without pepsin or pH 7.4 buffer solution by dilution. UV absorbance of the standard solutions in pH 7.4 buffer and simulated gastric fluid was measured by UV spectrophotometer at 236 nm. Standard curves of observed absorbance versus diltiazem hydrochloride concentration in pH 7.4 buffer and simulated gastric fluid are seen in Figures 3.3 and 3.4, respectively.

In Vitro Dissolution Testing of Diltiazem HCl semisolid matrix capsules

Dissolution studies were performed according to the USP XXV using apparatus 2. Test products were placed first in 750 ml of simulated gastric fluid for the first 2 hours with a stir rate of 50 rpm and maintained at 37 ± 0.5^0C, then 242 ml of 0.2 M Na_3PO_4 was added and the final pH was adjusted to pH 7.4 using 6 N NaOH or concentrated hydrochloric acid. 4 ml dissolution samples were filtered through flow filters (0.70 μm), and collected via an autosampler at predetermined time intervals for 24 h dissolution studies. Filtered solutions were centrifuged at 3000 rpm for 10 minutes, supernatants from 2 h to 24 h were filtered again through 0.45 μm membrane and diluted to appropriate concentrations and measured to determine absorbance at 236 nm. Dissolution drug concentrations were determined via standard curves (Figures 3.3 and 3.4) in each medium and converted to percentage drug released.

Average drug released at various time points and their standard deviations were calculated from three replications in all dissolution experiments. Diltiazem HCl dissolution profiles are presented as percent drug release versus time curves.
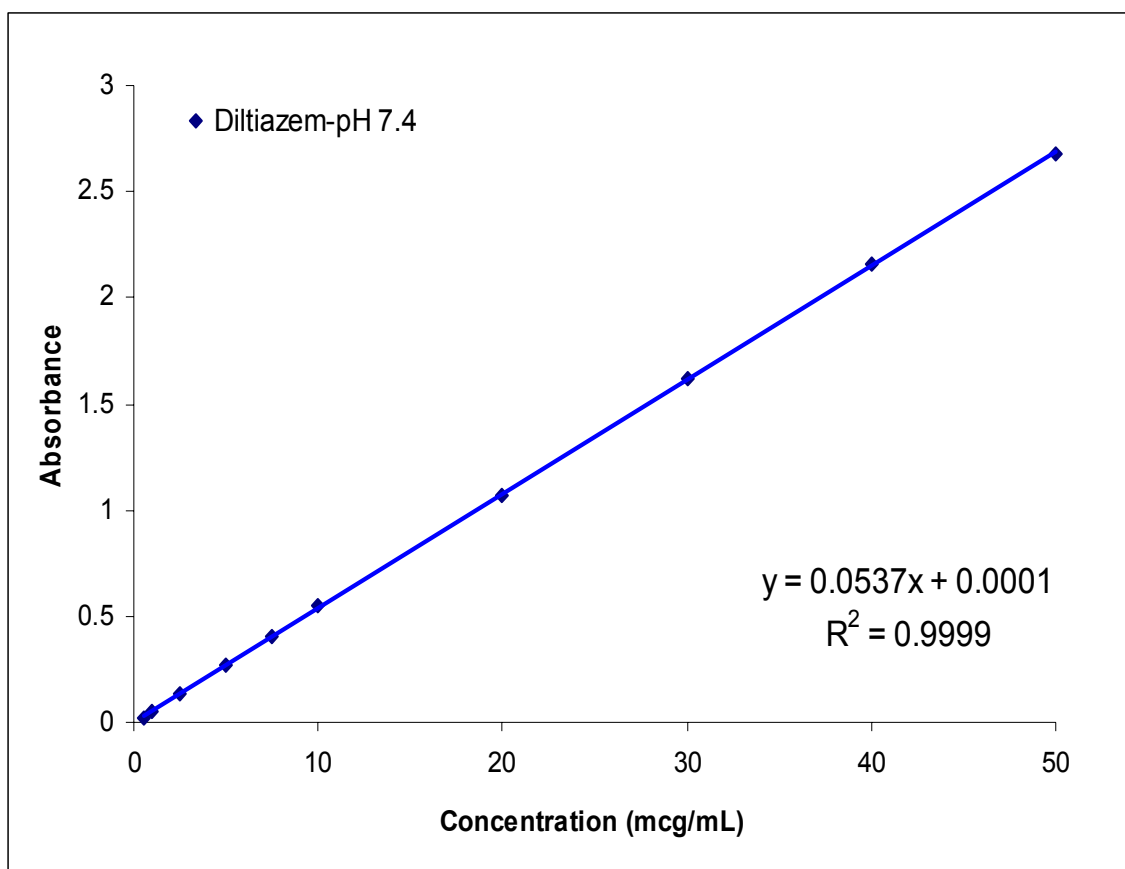
Figure 3.3: Standard curve of observed absorbance versus diltiazem hydrochloride concentration in pH 7.4 buffer (UV wavelength at 236 nm)
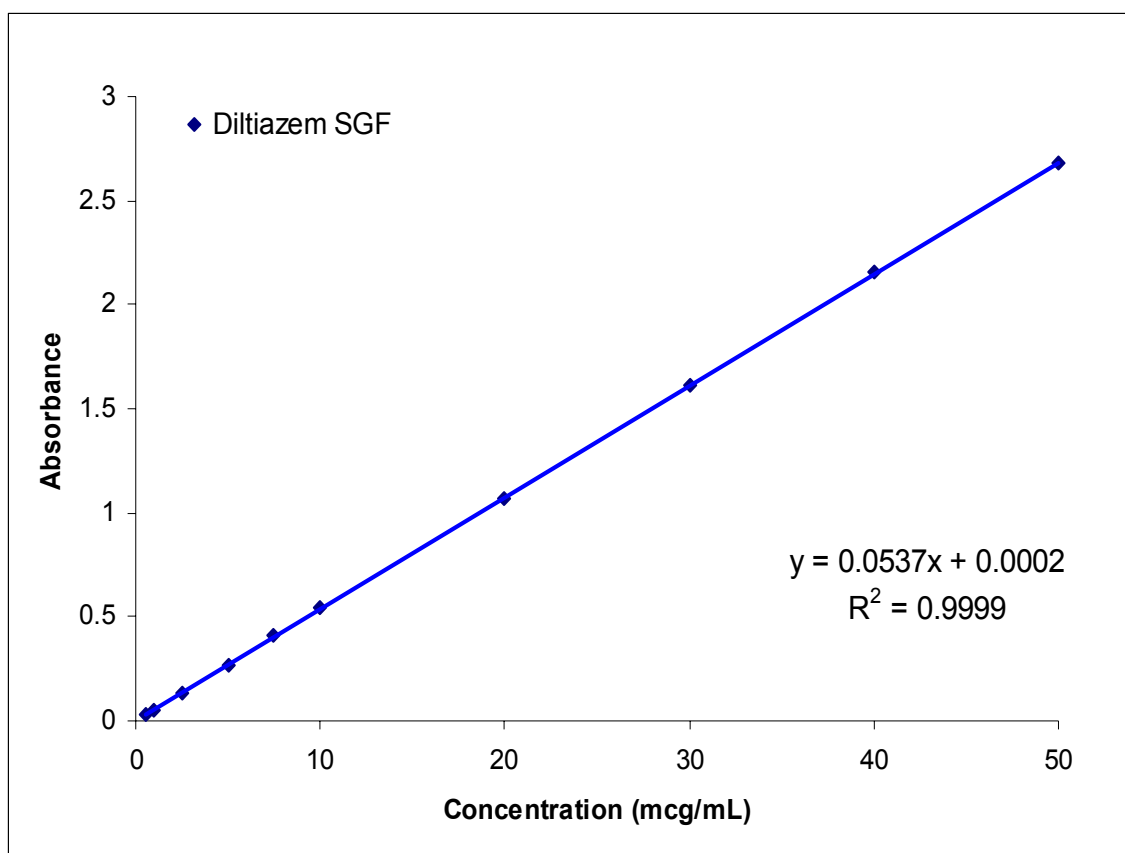
Figure 3.4: Standard curve of observed absorbance versus diltiazem hydrochloride concentration in simulated gastric fluid (UV wavelength at 236 nm*)*

Simulated gastric fluid preparation

Add 8 grams of sodium chloride and 20 ml of concentrated hydrochloric acid to 1000 ml of DI water and mix well. Add 2950 ml of DI water and mix well. Adjust to pH 1.4 ± 0.1 with concentrated hydrochloric acid. DI water was added to give a final volume of 4000 ml.

pH 7.4 buffer preparation

Add 400 ml of simulated gastric fluid pH 1.4 ± 0.1 to 100 ml of 0.2M Na_3PO_4, mix well and adjust to pH 7.4 ± 0.1 with 6 N NaOH or concentrated hydrochloric acid as needed.

RESULTS AND DISCUSSION

Verapamil HCl semisolid matrix capsules:

Figures 3.5 and 3.6 show dissolution profiles of verapamil HCl from the semisolid matrices of Gelucire 50/13 and stearic acid. Semisolid matrix capsules with Gelucire 50/13 and stearic acid floated on the medium up to about 1-2 h in the dissolution vessels. From 2 h to 5 the capsules sunk to the bottom of dissolution vessels. After 5 h, semisolid matrix capsules were turning around and hit by the paddle. Semisolid matrix capsules eroded and disintegrated completely when formulated with the combination of Gelucire 50/13 and stearic acid after 5 h. However, for Gelucire 50/13 alone formulation or stearic acid alone formulation, capsules continued to float for 8 h (some longer). These matrices showed both erosion and disintegration occurring. Addition of stearic acid reduced the viscosity of Gelucire 50/13. As seen in Figure 3.5, stearic acid greatly sustains drug release. With the ratio of stearic acid and verapamil HCl = 1:1 (formulation F4, stearic acid only), less than 20% of drug was released during the first 2 h. Then only a small amount of drug was released from 2 to 24 h. Stearic acid suppresses verapamil HCl release. On the other hand, with Gelucire 50/13 only (formulation F3), drug release is prolonged up to 24 h, but releases at a faster rate and more completely than reference capsules, Verelan capsules. The combination of 2 parts of Gelucire 50/13 with 1 part of stearic acid reduced the release rate compared with Gelucire 50/13 only, but increased the release rate compared with using stearic acid only. The dissolution profile of the formulation of Gelucire 50/13:stearic acid = 2:1, was very close to that of the reference Verelan capsules for the first 5 h, then drug release was faster after that (Figure 3.5).
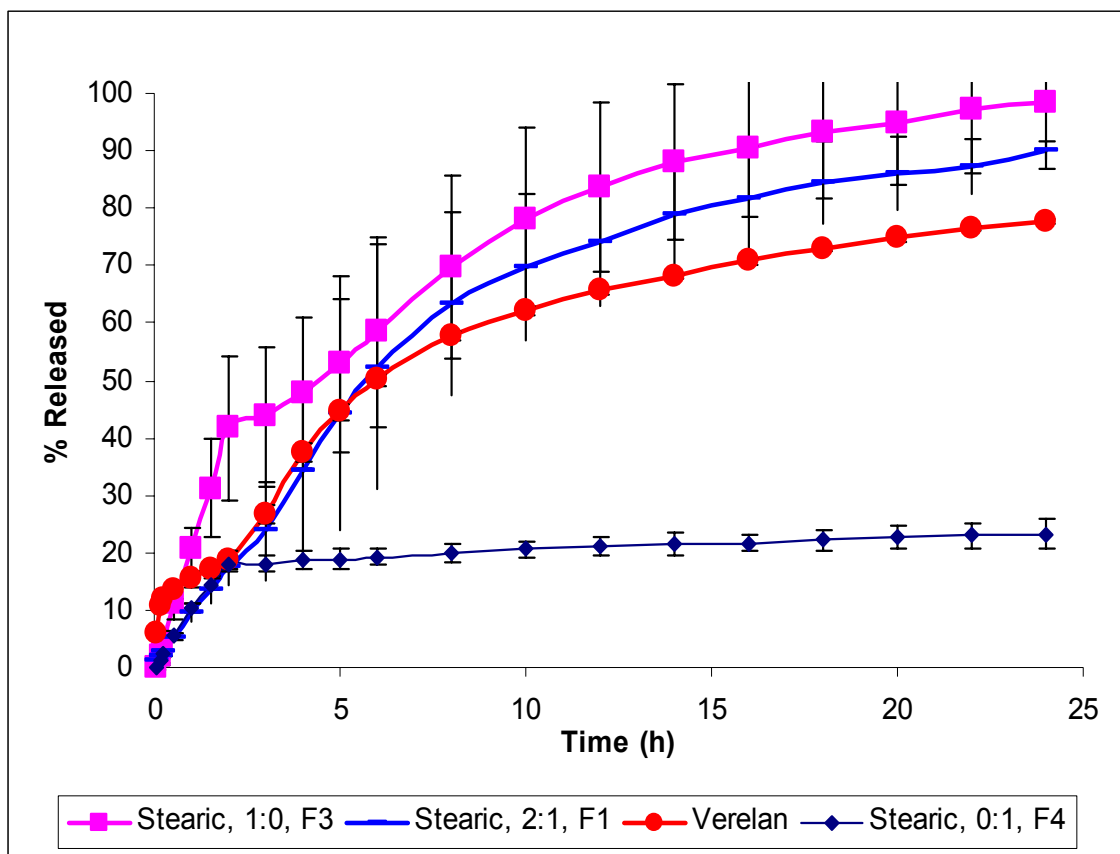
Figure 3.5: Dissolution profiles of verapamil HCl versus time: Effect of Gelucire 50/13 and stearic acid combination, 50 rpm paddle speed, 240 mg of wax

Stearic, 1:0, F3 = F3 formulation, with Gelucire 50/13:stearic acid = 1:0.

Stearic, 2:1, F1 = F1 formulation, with Gelucire 50/13:stearic acid = 2:1.

Verelan = sustained-release Verelan capsules.

Stearic, 0:1, F4 = F4 formulation, with Gelucire 50/13:stearic acid = 0:1.
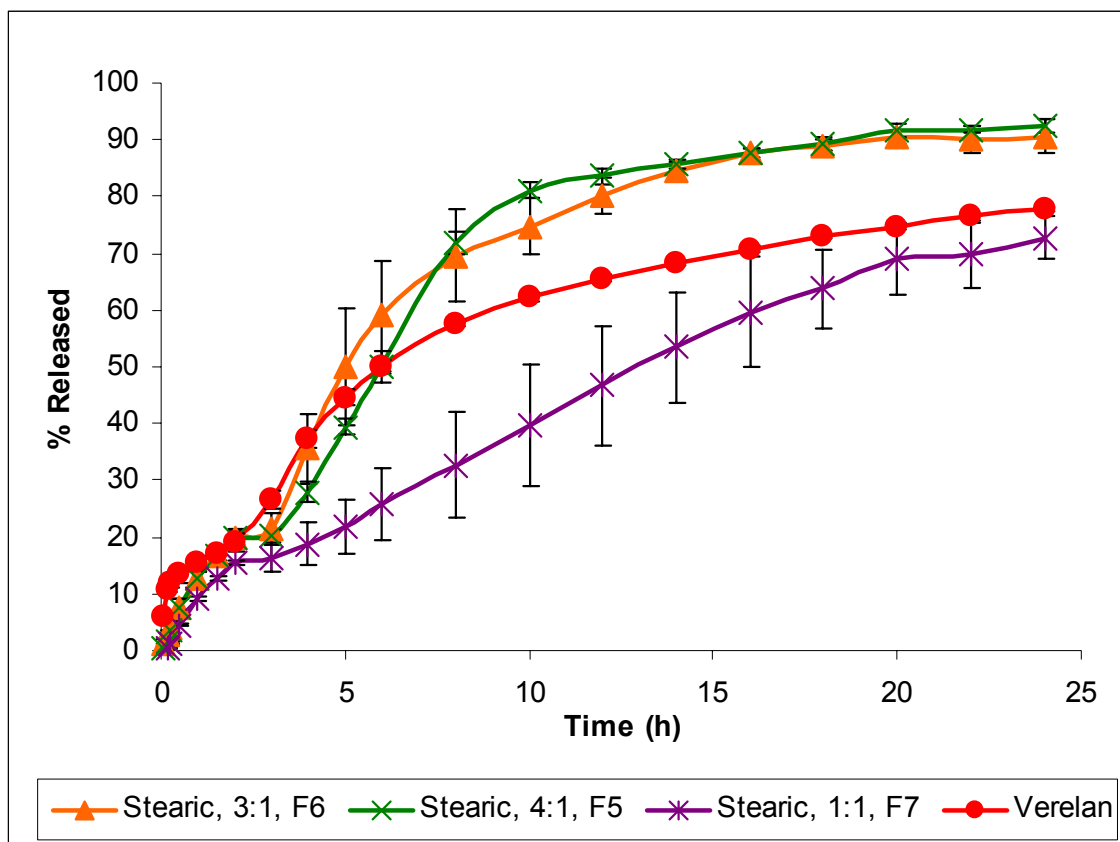
Figure 3.6: Dissolution profiles of verapamil HCl versus time: Effect of Gelucire 50/13 and stearic acid of ratio of 1:1 to 4:1, 50 rpm paddle speed, 240 mg of wax

Stearic, 3:1, F6 = F6 formulation, with Gelucire 50/13:stearic acid = 3:1.

Stearic, 4:1, F5 = F5 formulation, with Gelucire 50/13:stearic acid = 4:1.

Stearic, 1:1, F7 = F7 formulation, with Gelucire 50/13:stearic acid = 1:1.

Verelan = sustained-release Verelan capsules.

Figure 3.6 shows that there is little difference in drug release rate or percent drug release at various time points between formulations of Gelucire 50/13: stearic acid = 3:1 and 4:1, (orange and green curves, respectively) while Gelucire 50/13:stearic acid = 1:1 (red-violet curve) reduces drug release rate significantly compared with formulations of the ratios of 4:1 and 3:1.

The effects of cetyl alcohol and Gelucire 50/13 combinations are seen in Figures 3.7 and 3.8. With the same ratio and same amount of wax, Gelucire 50/13:cetyl alcohol semisolid matrix decreased drug release rate in comparison to Gelucire 50/13:stearic acid semisolid matrix. Both release rates of formulations of Gelucire 50/13:cetyl alcohol = 4:1, and 1:1 are lower than Verelan release rate (Figure 3.7). In combination with Gelucire 50/13, cetyl alcohol is more effective than stearic acid in extending verapamil HCl release from semisolid matrix capsules. It was observed that Gelucire 50/13:stearic acid semisolid matrix disintegrated faster than Gelucire 50/13:cetyl alcohol semisolid matrix. That may be why with the same ratio and same amount of wax, Gelucire 50/13:cetyl alcohol semisolid matrix decreased drug release rate in comparison to Gelucire 50/13:stearic acid semisolid matrix. To increase verapamil release rate, the amount of wax used in the matrix was decreased from 240 mg to 210 mg and ratio of Gelucire 50/13:cetyl alcohol was chosen as 4:1 or 5:1 (Figure 3.8). The less wax used produces a higher drug release rate. The higher percentage of Gelucire 50/13 in combination with cetyl alcohol increased percentage of verapamil release at different times, particularly at later times (Figures 3.7 and 3.8).
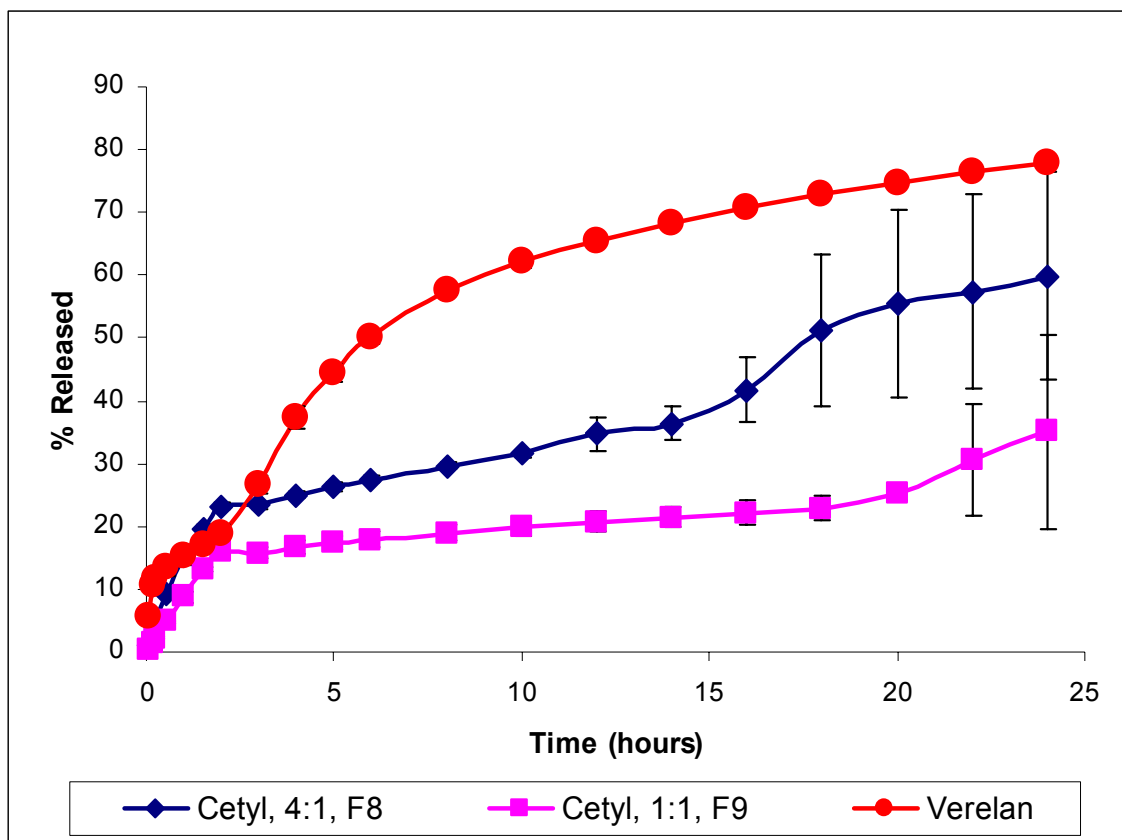
Figure 3.7: Dissolution profiles of verapamil HCl versus time: Effect of Gelucire 50/13 and cetyl alcohol, 240 mg of wax, 50 rpm paddle speed

Cetyl, 4:1, F8 = F8 formulation, with 240 mg of Gelucire 50/13:cetyl alcohol = 4:1.

Cetyl, 1:1, F9 = F9 formulation, with 240 mg Gelucire 50/13:cetyl alcohol = 1:1.

Verelan = sustained-release Verelan capsules.
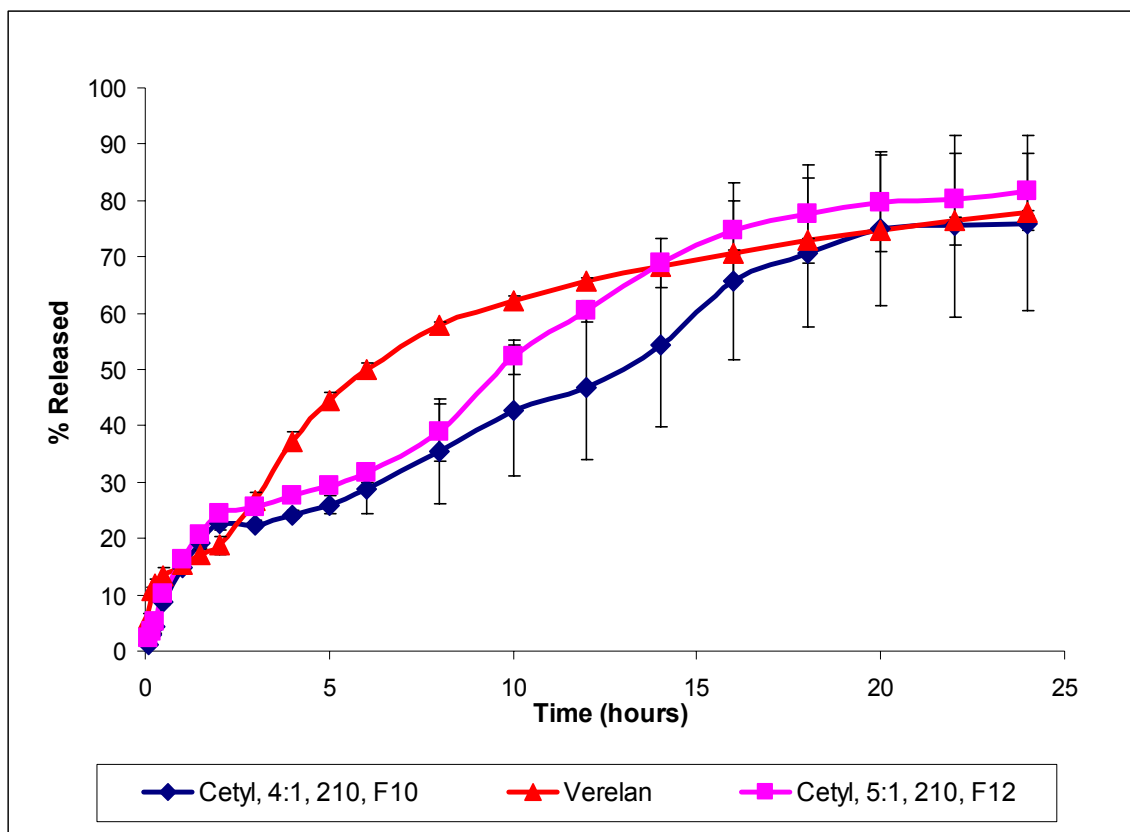
Figure 3.8: Dissolution profiles of verapamil HCl versus time: Effect of Gelucire 50/13 and cetyl alcohol combination, 210 mg of wax, 50 rpm paddle speed

Cetyl, 4:1, 210, F10 = F10 formulation, 210 mg of Gelucire 50/13:cetyl alcohol = 4:1.

Verelan = sustained-release Verelan capsules.

Cetyl, 5:1, 210, F12 = F12 formulation, 210 mg of Gelucire 50/13:cetyl alcohol = 5:1.

The effect of stearic acid is less than cetyl alcohol effect in combination with Gelucire 50/13 on verapamil release rate aforementioned. With the ratio of 4:1, and 210 mg of wax (the blue curve, F10 in Figure 3.8), verapamil release rate from Gelucire 50/13:cetyl alcohol formulation is lower than reference Verelan capsule (the red curve in Figure 3.8). With the same ratio of 4:1, and 240 mg of wax (the green curve, F5 in Figure 3.6), verapamil release rate from Gelucire 50/13:stearic acid formulation is higher than reference (the red curve in Figure 3.6). Thus, combining the two formulations of Gelucire 50/13, stearic acid and cetyl alcohol was investigated. The dissolution profiles of these two formulations are shown in Figure 3.9.

Both Gelucire 50/13:stearic acid and Gelucire 50/13:cetyl alcohol matrices produced milky appearing solutions which interfered with assay results, particularly at later times. Thus, filtered solutions were centrifuged at 3000 rpm for 10-20 minutes, then solutions after 3 h were filtered again through a 0.45 µm membrane. This approach solved the assay problems.
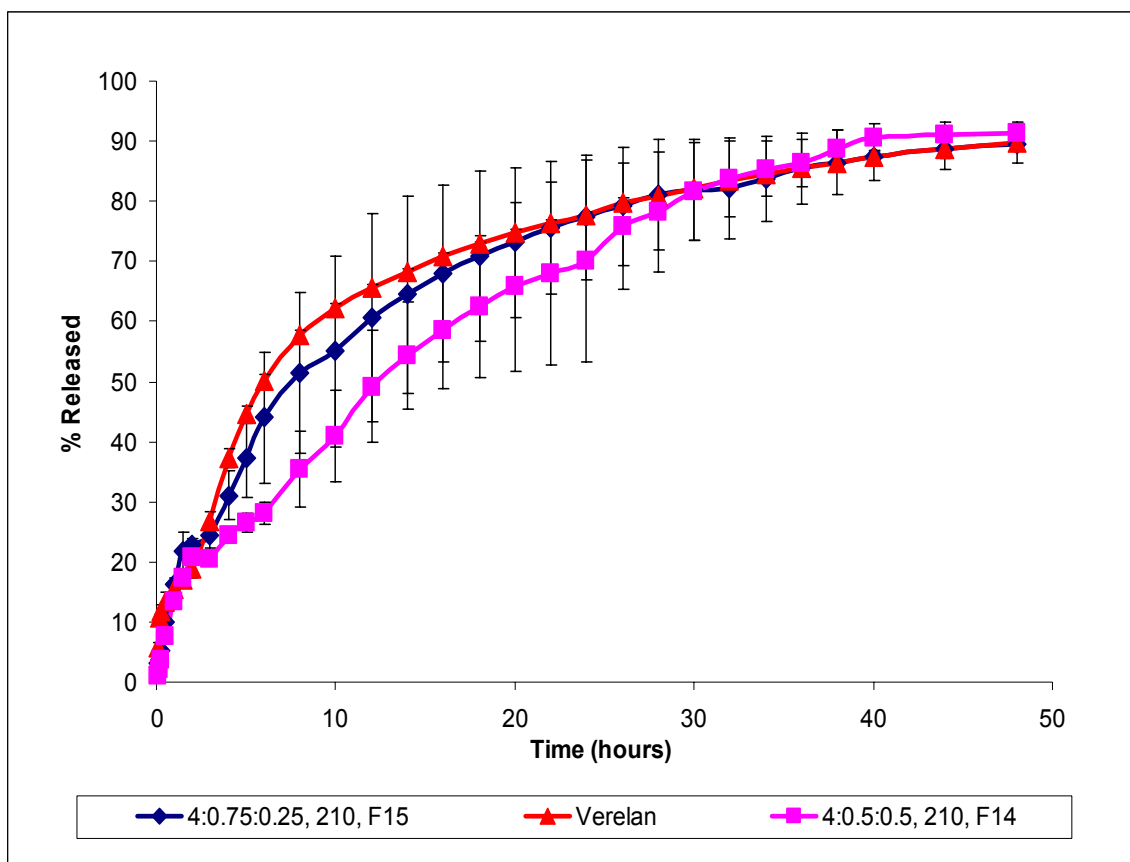
Figure 3.9: Dissolution profiles of verapamil HCl versus time: Effect of Gelucire 50/13, cetyl alcohol, and stearic acid combination, 210 mg of wax, 50 rpm paddle speed

4:0.75:0.25, 210, F15 = F15 formulation

Verelan = sustained-release Verelan capsules.

4:0.5:0.5, 210, F14 = F14 formulation.

Percent release of verapamil HCl at different time points shows little difference between F14 (Gelucire50/13:cetyl alcohol:stearic acid = 4:0.5:0.5, 210 mg of wax - the pink curve) and F15 (Gelucire 50/13:cetyl alcohol:stearic acid = 4:0.75:0.25, 210 mg of wax - the blue curve) formulations except from 4 to 10 h (Figure 3.9). In addition, the average dissolution curve of verapamil from F15 is closer to the reference product Verelan than F14. Formulation F15 was chosen to test at different paddle speeds. Figure 3.10 presents dissolution profiles at higher paddle speeds.

As seen in Figure 3.10, the higher the paddle speed the higher release rate of verapamil from F15. In contrast at high speeds, 100 and 200 rpm, Verelan capsules released verapamil at only a slightly faster rate than at 50 rpm, especially after 24 h. There was no difference in verapamil release rates from Verelan in the 100 rpm and 200 rpm paddle dissolution tests. This is expected because semisolid matrix formulations, like many other matrix formulations, are often sensitive to stirring speeds.

Diltiazem HCl semisolid matrix capsules:

Starting formulations of diltiazem HCl (called diltiazem) were mixtures of 160 mg of wax of Gelucire 50/13:cetyl alcohol with wax content ratios of 1:1, 2:1, or 4:1, and 120 mg of diltiazem HCl. The results of diltiazem HCl dissolution from these mixtures in capsules are shown in Figure 3.11.
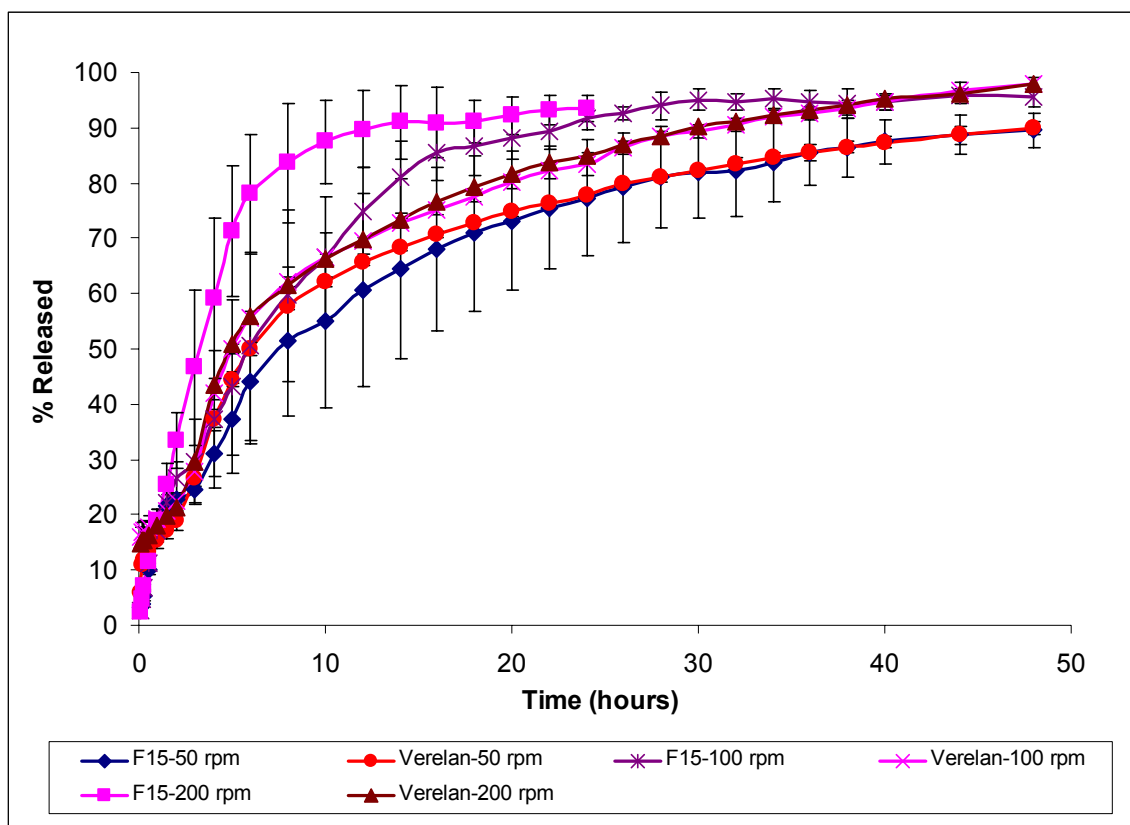
Figure 3.10: Dissolution profiles of verapamil HCl versus time: Effect of paddle speeds on formulation F15

F15-50 rpm = F15 formulation, 50 rpm.

Verelan-50 rpm = sustained-release Verelan capsules, 50 rpm.

F15-100 rpm = F15 formulation, 100 rpm.

Verelan-100 rpm = sustained-release Verelan capsules, 100 rpm.

F15-200 rpm = F15 formulation, 200 rpm.

Verelan-200 rpm = sustained-release Verelan capsules, 200 rpm.
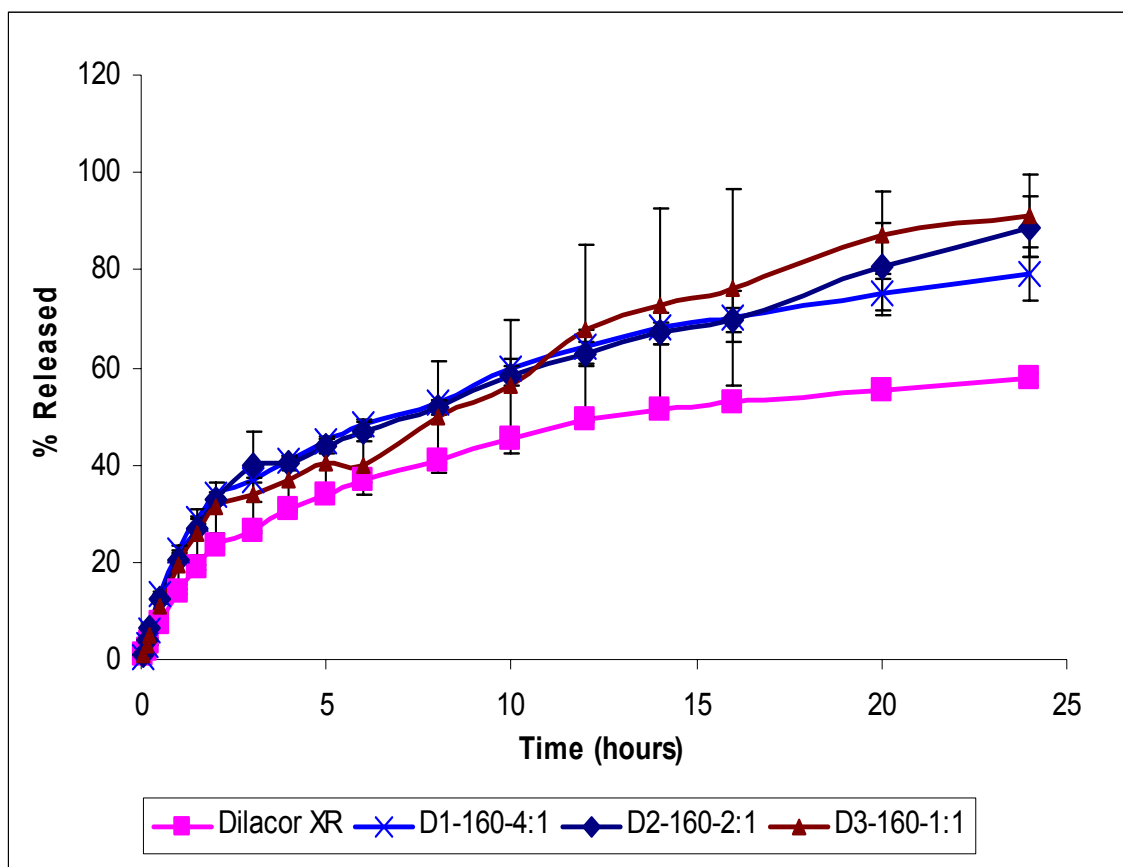
**Figure 3.11: Dissolution profiles of diltiazem HCl from semisolid matrix capsules
D1, D2, and D3 formulations, 50 rpm paddle speed**

Dilacor XR = Dilacor XR capsules.

D1-160-4:1 = D1 formulation.

D2-160-2:1 = D2 formulation.

D3-160-1:1 = D3 formulation.

Figure 3.11 shows that ratio of 1:1 to 4:1 of Gelucire 50/13:cetyl alcohol, 160 mg of wax, has little affect upon % release of diltiazem at different time points. The erosion times of the semisolid matrix capsules from these ratios were similar, which may be a reason for the similar dissolution profiles. These erosion times of the semisolid matrix capsules from these ratios were more than 20 h. All dissolution curves from these formulations are higher than Dilacor XR.

To reduce diltiazem release rate, a higher amount of wax, 240 mg, was applied with the ratio of Gelucire 50/13:cetyl alcohol of 4:1, 3:1, 2:1 and 1:1. As seen in Figure 3.12, the higher ratio of Gelucire 50/13:cetyl alcohol from 1:1 (the brown curve, D6) to 3:1 (the red curve, D7) produced a higher drug release rate. There is little difference in diltiazem release rate from wax matrices of 4:1 and 3:1 ratios of Gelucire 50/13 to cetyl alcohol. The dissolution curve of Dilacor XR is between diltiazem dissolution curves from wax matrices of Gelucires 50/13: cetyl alcohol of 1:1 and 2:1. Formulation D8 with ratio of Gelucire 50/13:cetyl alcohol of 1.5:1 was produced. The result is shown in Figure 3.13.
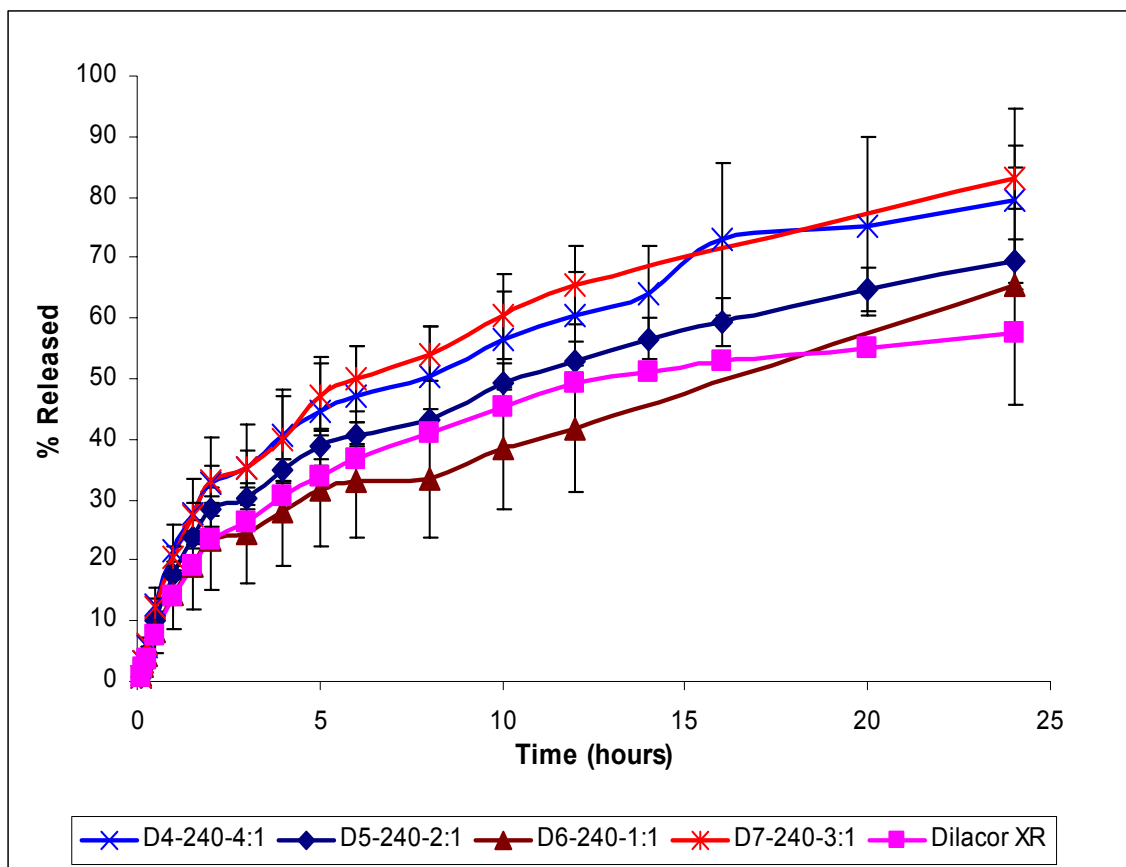
Figure 3.12: Dissolution profiles of diltiazem HCl from semisolid matrix capsules: D4-D7 formulations

D4-240-4:1 = D4 formulation.

D5-240-2:1 = D5 formulation.

D6-240-1:1 = D6 formulation.

D7-240-3:1 = D7 formulation.

Dilacor XR = Dilacor XR capsules.
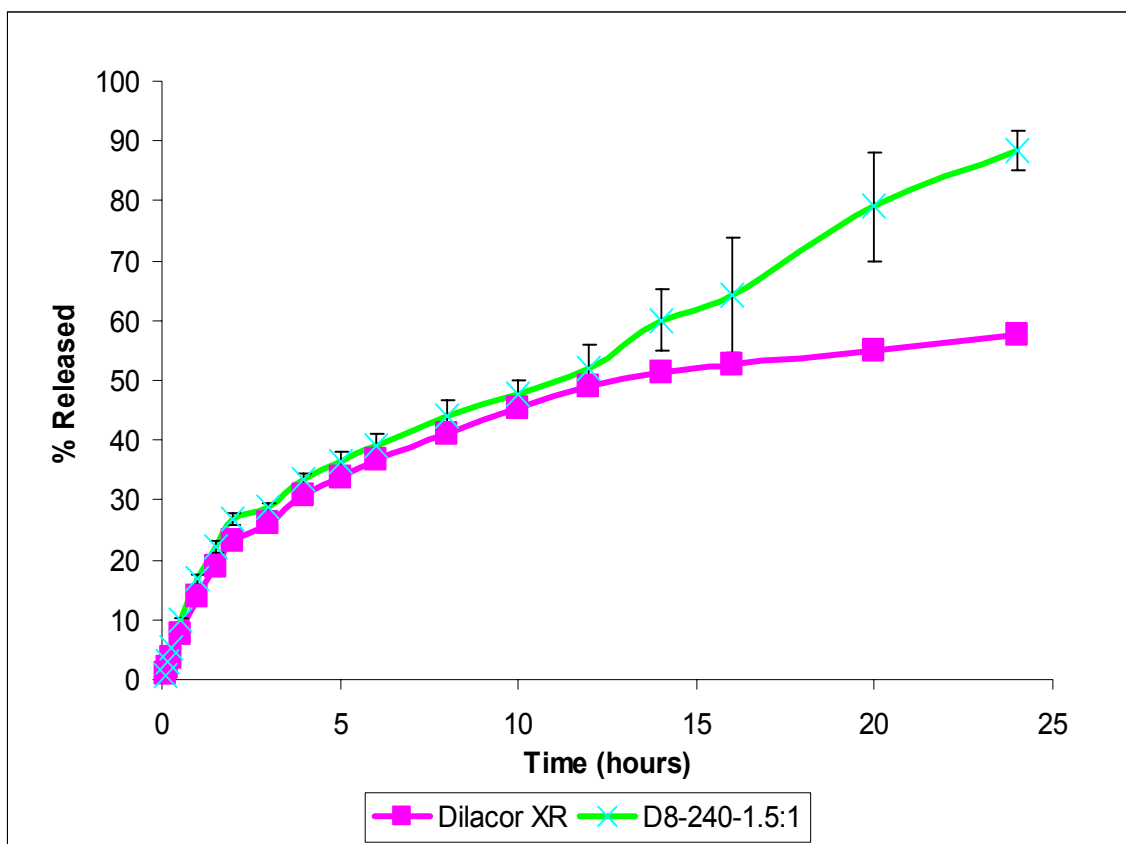
Figure 3.13: Dissolution profiles of diltiazem HCl from semisolid matrix capsule: D8 formulation, 50 rpm paddle speed

Dilacor XR = Dilacor XR capsules.

D8-240-1.5:1 = D8 formulation.

Release rate of diltiazem from formulation D8 is close to Dilacor XR for the first 12 h with differences less than 3%. After 12 h the differences increase from 8.8 to 30.6%. D8 formulation was tested at different stirring speeds of the paddle to evaluate the effect of agitation on drug release. As expected, the release rate of diltiazem from D8 formulation was sensitive to paddle stirring speeds. The higher the paddle stirring speed the higher the release rate of diltiazem from the D8 formulation (Figure 3.14). The magnitude of the sensitivity of Dilacor XR capsules to paddle speed was less.

For both verapamil HCl and diltiazem HCl semisolid matrix capsules, the matrices eroded and disintegrated after time depending on the combination of waxes used. For Gelucire 50/13 and stearic acid combinations, the semisolid matrix disintegrated faster than the semisolid matrix of the same ratio of Gelucire 50/13 and cetyl alcohol combinations. However, the semisolid matrix of only stearic acid did not erode or disintegrate completely and released around 20% of its drug content over 24h.
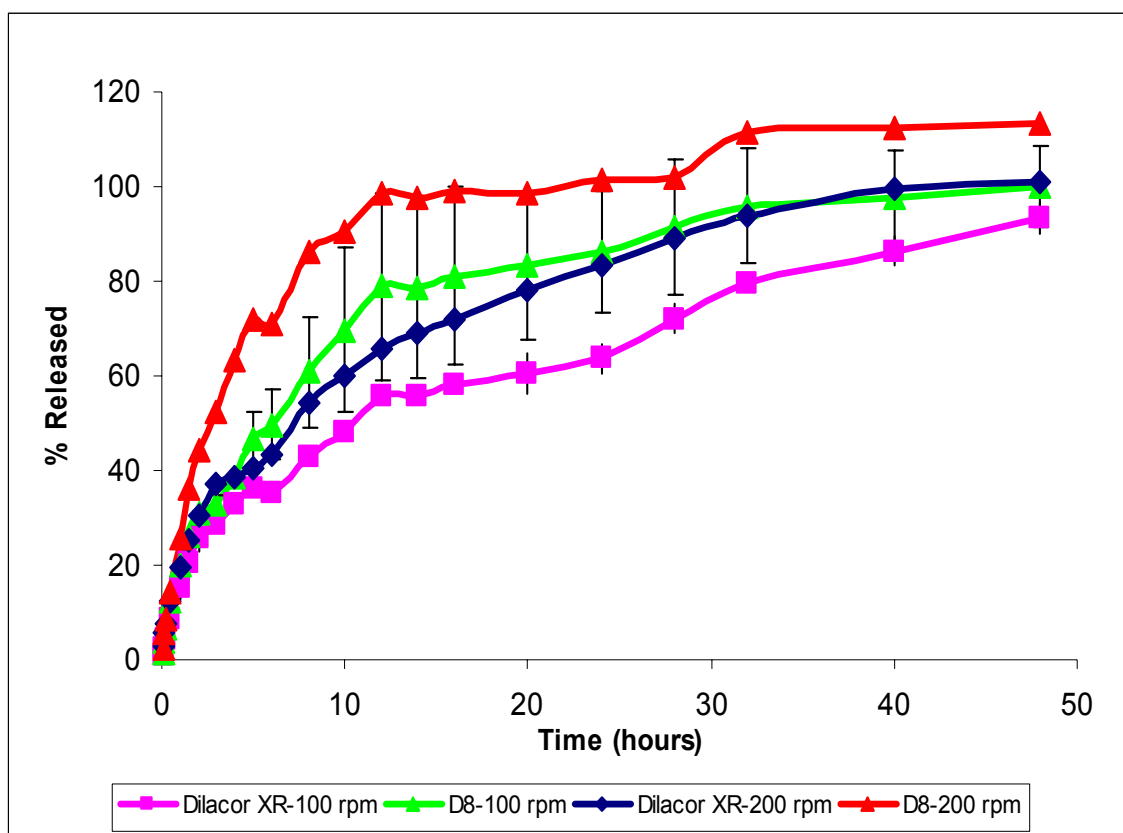
Figure 3.14: Dissolution profiles of diltiazem HCl from Dilacor XR and D8 formulation: Effect of paddle speeds

Dilacor XR-100 rpm = Dilacor XR capsules, 100 rpm paddle.

D8-100 rpm = D8 formulation, 100 rpm paddle.

Dilacor XR-200 rpm = Dilacor XR capsules, 200 rpm paddle.

D8-200 rpm = D8 formulation, 200 rpm paddle.

CONCLUSIONS

The effects of combinations of Gelucire 50/13, stearic acid and cetyl alcohol on release of verapamil HCl and diltiazem HCl from semisolid matrix capsules were investigated. Both verapamil HCl and diltiazem HCl semisolid matrix capsules erode and disintegrate over time. The semisolid matrix of Gelucire 50/13 and stearic acid combination disintegrated after 5 h and faster than the disintegration of the semisolid matrix of Gelucire 50/13 and cetyl alcohol combination. That may be a reason that drug was released from the mixture of cetyl alcohol and Gelucire 50/13 more slowly than from the mixture of stearic acid and Gelucire 50/13. The semisolid matrix of stearic acid did not erode or disintegrate completely and released only around 20% of its drug in 24h. Semisolid matrix formulations are sensitive to stirring speeds with the higher speeds of paddle producing higher release rates of drug.

Semisolid matrix capsule or hot-melt capsule filling is an especially appealing and simple way to make sustained release formulations.

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CHAPTER 4

Novel Sustained Release Tablet of Glipizide: Compression of Coated

Drug Beads,

Formulation, Dissolution, and Convolution

Chien N. Nguyen, James W. Ayres

ABSTRACT

A novel formulation of glipizide was developed comprising compression of four-layer coated beads into tablets which has advantages of providing a lag time before drug release, retaining sustained-release characteristics, and providing approximately zero-order drug release, with drug release nearly independent of paddle speeds of 50 and 100 rpm. The effect of ingredients in each coated layer (such as ratio of ethylcellulose solids content with drug [drug loading layer], amount of HPMC [bead hardening layer], amount of ethylcellulose in the controlled release layer, ratio of ethylcellulose solid content with lactose in the controlled release layer, amount of binder and disintegrant layer [outer bead layer] on drug release) was investigated. The amount of binding and disintegration ingredients can be adjusted to produce an appropriate disintegration time for tablets. With 22.22% weight gain of lactose:Explotab = 2:1 (binder:disintergrant), beads-compressed into tablets disintegrated within 3 hours, and individual coated beads controlled drug release. The inclusion of HPMC in the beads has a large effect on increasing drug release from non-compacted beads and a smaller effect on drug release from compacted beads. Both ethylcellulose layers are important for controlling drug release, with the inner ethylcellulose with drug mixture layer being most sensitive to the amount of ethylcellulose. Tablet compression pressures from 1000 to 3000 pounds have a little effect on drug release during in vitro dissolution performed at 100 rpm. At higher dissolution paddle speeds, 150 and 200 rpm, drug release from the tablets produced with higher compression pressures become more sensitive to paddle speeds. Also the rate of

release depends on the paddle speeds ($p<0.01$) for glipizide tablets made from sustained release beads compressed into tablets.

The final formulation for this report contains beads having four layers: the drug layer of 71.25 g of sugar beads coated with 2.5 g of glipizide and 3.75 g of solid Surelease; the hardening layer of 5 g of HPMC; the controlled release layer of 7.5 g of solids with a ratio content of Surelease:lactose = 100:7, and outermost layer of 20 g of lactose:Explotab = 2:1. Then four layer beads were compressed into tablets containing 11mg of glipizide with 1500 pounds of compression pressure. This formulation matched the dissolution pattern of Glucotrol-XL osmotic pump tablets when tested with USP paddle method in two pH media testing at 100 rpm. Also dissolution patterns of Glucotrol XL and a new tablet formulation (labeled CH20) were close to each other at paddle speeds of 50, 150 and 200 rpm. The rate of release and percentage of drug release at 16 hours from CH20 did not differ from that of Glucotrol XL at any of the paddle speeds ($P> 0.05$). CH20 tablet is predicted by convolution simulation to be bioequivalent to Glucotrol-XL *in-vivo*.

INTRODUCTION

There are two expansive categories of oral sustained release drug delivery systems, single unit dosage forms and mulitpariticular dosage forms. The single unit dosage forms include capsules and tablets, while the multiple unit dosage forms are comprised of granules, pellets, beads, and microparticles (Bodmeier, 1997; Vergote et al., 2002). Multiparticular dosage forms provide many benefits over the single unit dosage forms. Multi-unit dosage forms are more uniformly distributed throughout the gastrointestinal tract, which decreases the risk of high local drug concentrations and dose dumping, which can occur in defective single unit dosage forms, and thus less probability of local and systemic toxicity (Bodmeier, 1997; El-Gazayerly et al., 2004; and Vergote et al., 2002). Additionally, bioavailability could be increased and drug release can be less variable because of better distribution of multiparticulates along the gastrointestinal tract (Vergote et al., 2002). Inter- and intra-individual variations in bioavailability, caused for example by food effects, also are reduced (Bodmeier, 1997). When taken by mouth, digestible materials need to be broken down to a size of about 1mm or less before they are allowed to pass into the duodenum (Davis et al., 1984).

"Nondigestible solids larger than 7 mm are usually retained in the fed state until other materials have emptied from the stomach and are then emptied as a bolus from the stomach. Single unit dosage forms cause a higher intersubject variability in lag time as well as an average prolongation of lag time" (Krämer and Blume, 1994).

Multi-unit dosage forms, e.g. coated beads, pellets, can either be compressed into tablets or filled into gelatin capsules. Tableting the coated particles has several advantages, including a reduced risk of tampering and less difficulty in oesophageal

transport when compared with capsules (El-Gazayerly et al., 2004). Large volume tablets generally have a higher patient compliance than capsules (Bodmeier, 1997). Tablets from pellets can be prepared at lower cost when compared to pellet-filled capsules because of the higher production rate of tablet presses (Bodmeier, 1997; El-Gazayerly et al., 2004). Note that when multiparticulates are compressed into tablets, some advantages of the multiparticulate dosage form may be lost. For example, if a non-disintegrating tablet or a slowly disintegrating tablet is formed when compressing the beads into a tablet then the individual particulates, e.g. beads, cannot empty individually but are emptied as a single unit tablet from the stomach.

Compression of polymer-coated beads into tablets also raises concerns regarding the loss of integrity of the polymer coat following compression, because coat integrity on the beads is necessary to serve as a diffusion barrier to delay drug release from these compressed tablets. Polymer coats can deform, but should not rupture (Bodmeier, 1997). The pellets should not fuse into a non-disintegrating matrix during compaction.

Four different methods to protect coated pellets from damage during compression were summarized by Vergote et al (2002). There are: 1. incorporation of a plasticizer to increase the flexibility of the coat, 2. varying the amount of coating applied to the pellets, 3. mixing the pellets with a material acting as a binder/disintegrant agent, 4. incorporation of an excipient into formulation to change the deformation behavior of the pellets. Other methods to protect coated beads are to use a sealing layer (El-Gazayerly et al., 2004) and multiple layers (Altaf et al., 1998). These techniques are often very challenging, as the

efficiency of these approaches is not only highly dependent on the type of polymer film, but also on the size and properties of the pellets themselves (Vergote et al., 2002). Vergote et al. (2002) studied the effect of compression on multiparticulates coated with Eudragit NE 30D. They found that damage to diltiazem hydrochloride multiparticulates film coated with Eudragit NE 30D can be minimized during compression by incorporating soft binder/disintegrant beads based on paraffinic wax into the formulation. Theophylline granules coated with Eudragit RS 30D, 6% weight gain, were shown to be little affected by compression force when granules present in the tablet does not exceed 40% (Palmieri et al., 1996.). However, enteric coatings based on Eudragit L30D-55 were brittle and compression of the pellets resulted in film damage, and an increase in coating thickness did not avoid the film rupture (Bodmeier, 1997).

Most studies on compression of pellets coated with ethylcellulose (EC) revealed damage to the coating with a loss of sustained release properties and resulted in faster drug release because of weak mechanical properties (Bodmeier, 1997) of ethylcellulose regardless of particle size (Bechard and Leroux, 1992). At high compression pressures, 3150 pounds, the pellets were fractured and simultaneously underwent fusion forming a nondisintegrating matrix caplet (Altaf et al., 1999). Such partial loss of sustained release effect may be due to formation of cracks in the coat during compaction (El-Gazayerly et al., 2004; Altaf et al., 1999; Bechard et al., 1992; Maganti and Çelik, 1994). The amount of polymer coating, compression pressure, bead size, number of layers, and type of binder/disintegrant excipient were important factors which affected drug release characteristics (Altaf et al., 1998). Films containing ethylcellulose plasticized with 24%

dibutyl sebacate did not have the appropriate mechanical properties to withstand compaction stress without rupturing, regardless of the pellets particle size and excipients used (Bechard and Leroux, 1992). Controlled release properties of the pellets were therefore lost during compaction. To reduce damage to ethylcellulose coated pellets, one of the methods is to put compressed pellets in an oven at 70^0C for 24 h to obtain retardation in the drug release (Bodmeier, 1997).

The use of microcrystalline cellulose (MCC) as a binder/disintegrant agent in powder form, in the form of spheres, and as granules has been investigated for prevention of polymer coat fracture. The use of placebo spheres requires additional consideration of factors such as sphere density and strength (Altaf et al., 1999). However, the use of microcrystalline cellulose (MCC), or lactose as a binder/disintegrant agent is not efficient. Hand-mixed MCC granules with drug-coated beads did not protect the polymer coat from fracture (Altaf et al., 1999). Mixing α-lactose monohydrate granules (ratio 50:50, w/w with coated drug pellets) or microcrystalline cellulose pellets with the coated drug spheres did not offer sufficient protection to the film coat (Vergote et al., 2002). On the other hand, tablets containing 50% (w/w) drum-dried corn starch/Explotab/wax beads had a drug release profile similar to that of the drug pellets (Vergote et al., 2002). The soft binder/disintegrant beads sufficiency protected the film coat during compression, preferentially deforming under the pressure and embedding the drug pellets within a protective wax matrix. But drug loading in the tablet was less than 50% which is undesirable for drugs with a dose of 200 mg or more. The use of a combination of MCC and croscarmellose sodium in the production of freeze-dried binder/disintegrant beads by

extrusion-spheronization produced highly compactible beads, which upon compaction produced tablets with high tensile strengths (Habib et al., 2002) and helped protect coated drug beads.

"Upon compression, initial fragmentation into primary powder particles of the freeze-dried beads would fill the voids between the drug-loaded beads, and surround them. Further, plastic deformation of the fine particles would then enhance the excipient-excipient interaction producing stronger compacts" (Habib et al., 2002).

Inclusion of binder/disintegrant agents, such as MCC powder or beads made from glyceryl palmitostearate and MCC between brittle MCC spheres, is an effective method of formulation modification which permits compaction without fracture, and provides satisfactory tablets having the same dissolution profile characteristics as the uncompacted beads (Mount et al., 1996). However, mixing the coated drug beads with a binder/disintegrant agent, in powder form, in the form of spheres, and as granules can lead to segregation issues.

Spray-layering of binder/disintegrant excipient onto beads can provide an effective way to circumvent segregation issues associated with mixing of the polymer-coated beads, and powdered or spherical/nonspherical binder/disintegrant excipients, can provide excellent flow properties of the final formulation (Altaf et al., 1998), and also protect film coats.

Another way to protect film coats on beads is to use sealant agent.

"Sealant layer of hydrophilic gel-forming agent is beneficial to help maintain sustained release properties of compacted beads by partially blocking cracks in ruptured polymer coating. Upon contact with the dissolution medium, this gel-forming layer

hydrates and swells, offering sufficient sealing to damaged areas in the sustained release polymer coating resulting from compaction" (El-Gazayerly et al., 2004).

Coating beads with 20% of PEG 8000 as a binder/disintegrant agent provides little advantage in protection against polymer coat rupture when compacted at 300 or 3000 pounds pressure. Since PEG 8000 is soluble, it should not be a good sealant. HPMC and polyox N-80 were proven a good combination for sealant effect (El-Gazayerly et al., 2004).

For development of a new beads-compressed tablet in the current research, glipizide was chosen as model drug. Glipizide, or K 4024 (D'Onofrio et al., 1972), chemically N-{4[β-(5-methyl-pyrazine-2-carboxamido)-ethyl]-benzenesulfonyl}-N'-cyclohexylurea, is a synthesized sulfonylurea congener characterized by a strong hypoglycemic activity both in normal human subjects and in diabetic patients. The dosage of glipizide used in these patients was between 5 and 10 mg daily, as a single daily dose or two divided doses. Glipizide has a stimulating action on the insulin-secreting pancreas to result in better utilization of glucose for several hours. D'Onofrio et al. (1972) observed clinical and metabolic characteristics of glipizide in 70 diabetic patients. They found that glipizide proved effective in a relatively high percentage (80%) of cases including many patients who had failed to respond to previous therapeutic attempts with other sulfonylureas (D'Onofrio et al., 1972). During administration no major side effects, no evidence of gastrointestinal intolerance, and no changes involving the liver or renal function were observed. The drug is specifically indicated for patients

presenting maturity-onset diabetes, not insulin-dependent, and with no tendency to ketoacidosis (D'Onofrio et al., 1972).

Fuccella et al. (1973) studied metabolism and kinetics of glipizide in two healthy males. They observed that absorption of radioactive glipizide from the gastrointestinal tract was rapid and practically complete with a lag-time of 20 to 30 minutes. Peak concentrations of glipizide were reached 1 hour after administration. Glipizide is rapidly and extensively metabolized, and the more polar metabolites are quickly eliminated in the urine. Up to 12 hours after administration, the drug circulates in blood mainly as the unchanged product. Excretion through feces represented about 11 per cent of the administered dose (Fuccella et al., 1973.). No radioactivity was detectable in plasma seventy-two hours after administration. Unchanged drug accounted for about 3 per cent of the dose administered eliminated via urine up to 24 hours. The two main metabolites of glipizide, 3-cis-hydroxy-cyclohexyl-derivative and 4-trans-hydroxy-cyclohexyl-derivative, amounted respectively to 12 to 14 per cent and 59 to 65 per cent of the administered dose. N-(β-acetylaminoethyl benzene-sulphonyl)-N'-cyclohexyl-urea was present in very small amounts (1.7 and 0.72 per cent of the dose).

The disposition of glipizide after oral administration can be described by a two-compartment open model (Fuccella et al., 1973.) or one-compartment open model (Kradjan et al., 1995.) with first order absorption rate. Half life of elimination phase is 3 to 4 hours approximately, and plasma clearance is between 2.43 to 3.033 liters/hour (Fuccella et al., 1973.). The drug is extensively bound to plasma proteins, approximately

98 per cent, which results in the small apparent volume of distribution of the drug (6 to 7 liters). One of the well known dosage forms of glipizide is Glucotrol XL osmotic pump tablets with zero-order drug release.

It is well known that approximating zero-order drug release is desired for many sustained action products but such zero-order drug release is difficult to obtain. One goal of this research was to identify a novel formulation approach using FDA approved excipients and readily available processing equipment to produce "beads-compressed into tablets" that would provide nearly zero-order drug release, be relatively independent of dissolution media and stirring speeds (and G.I. agitation and transit times), and be equivalent to an established reference standard, the osmotic pump formulation Glucotrol XL. Developing a product bioequivalent to an osmotic pump formulation is very difficult because the osmotic pump drug delivery has a lag time, is independent of pH and GI transit times, nearly independent of presence or absence of food, independent of G.I. agitation, and provides zero-order release kinetics for the drug.

There are three kinds of osmotic pump systems as summarized by Wong et al. (1993). Osmotic pump tablet (Oros) is one kind of osmotic pump systems. Osmotically controlled tablets are the first example of osmotic pump systems. Oros system consists of an osmotic drug-containing core surrounded by a semipermeable membrane with orifices for drug release. Since the system core contains osmotic agents which produce high osmotic pressure inside a tablet, water is only allowed to imbibe across semipermeable membrane at a rate controlled by the composition and thickness of the membrane and

limits the passage of ions, and drug release is through orifices (Wong et al., 1993.). Thus,
drug release is not affected by outside environment, like motility, pH, or the presence of
food in gastrointestinal tract, particularly in the colon.

"Drug in solution or suspension is released through the orifices at the same rate
that water is imbibed into the system. Drug in the layers of a multicompartment osmotic
pump tablet system can be insoluble as long as soluble excipients help to form a
suspension during operation" (Wong et al., 1993.).

Another kind of osmotic pump systems is Oros Push-Pull Osmotic system. This
system uses a multicompartment core to deliver drugs of any solubility (Wong et al.,
1993.). The basic push-pull system has two layers. The drug layer contains the drug
substance, osmotically active hydrophilic polymers, and other excipients, like
electrolytes. The push layer contains a hydrophilic expansion polymer like
hydroxylpropyl methylcellulose, and other osmotically active agents and tablet
excipients. To assist in the transport of drug, the push layer expands and gently pushes
the drug suspension or solution out through the orifices (Wong et al., 1993.). The third
kind of osmotic pump system is Patterned Drug Delivery which combines the basic Oros
Elementary Osmotic Pump and push-pull designs. Patterned drug delivery allows zero-
order, pulsed, ascending, or delayed release of any drug regardless its solubility (Wong et
al., 1993.).

Figures 4.1 and 4.2 show respectively the surface of a cross section of push-pull
osmotic pump tablets, and a schematic representation of drug release from a new
(developed as described herein) beads-compressed into tablets formulation (For drug
release: see "Dissolution mechanism" in "Results and Discussion" part).

Delivery Orifice

Active Core

Semi-permeable
membrane

Push compartment
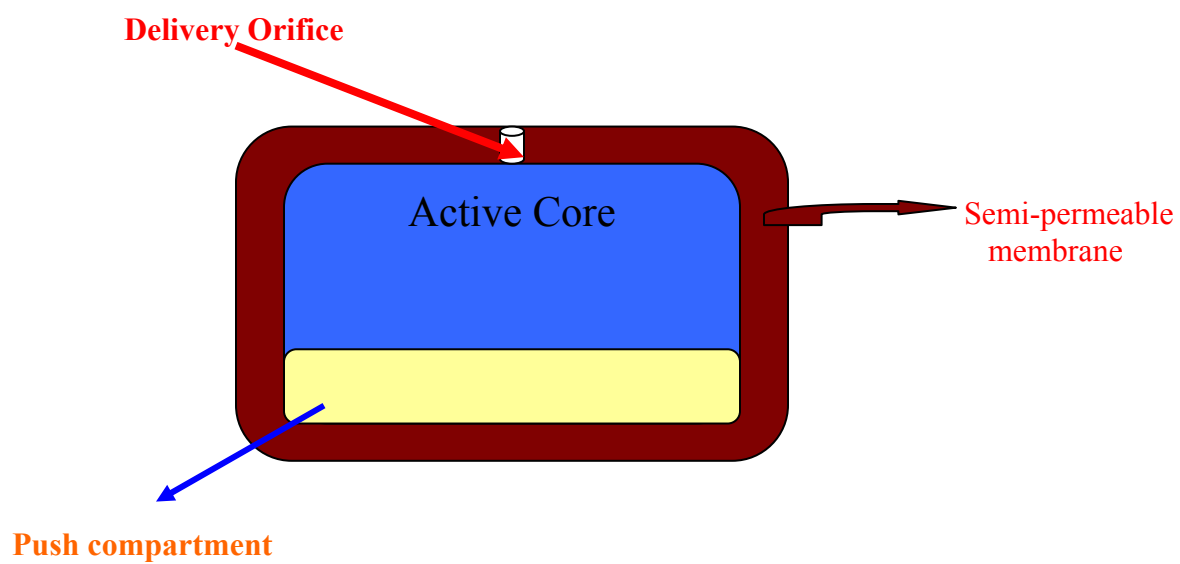
Figure 4.1: Cross surface of push-pull osmotic pump tablets.

Disintegrates into individual beads

Drug diffuses out through cracks, produced by compaction pressure from beads, and channels

Drug diffuses out through Channels created by channeling agents from beads

after a period of time
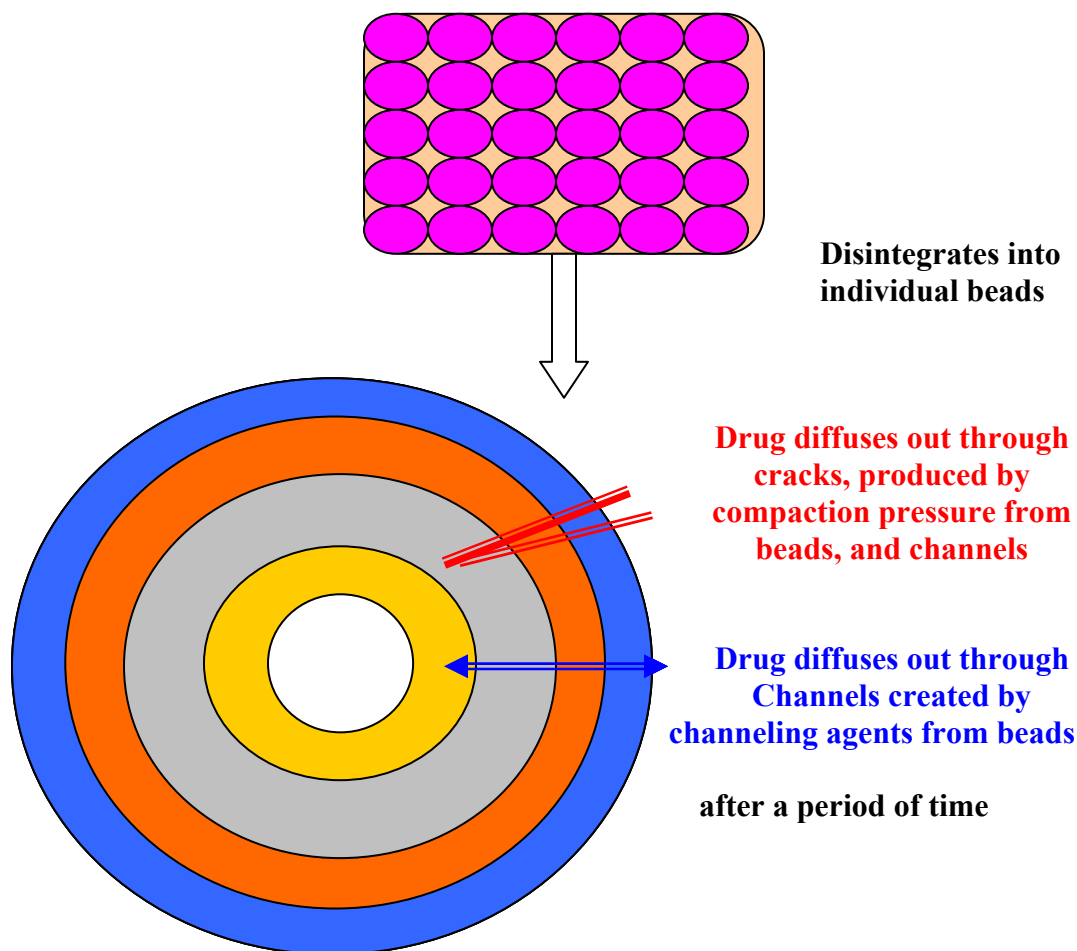
Figure 4.2: A schematic representation of drug release from a new beads-compressed into tablet formulation

The purposes of this study were: 1. to investigate the effect of ingredients in each coated layer, such as ratio Surelease solid content to drug, amount of HPMC, amount of Surelease in the controlled layer, ratio of Surelease solid content to lactose, amount of binder and disintegrate layer on drug release, 2. to evaluate the effect of compression pressures and 3. to investigate the effect of paddle speeds on glipizide release from beads-compressed into tablets.

MATERIALS AND METHODS

Chemicals

Active drug was glipizide from Teva Pharmaceuticals, USA (Sellersville, PA). Hydroxypropyl methylcellulose (HPMC) type 2910 viscosity 15 (Methocel E15 prem LV) was from Dow Chemical Company (Midland, MI), lactose monohydrate was a gift from Teva Pharmaceuticals, USA. Surelease® (Surelease or ethylcellulose), formula No.: E-7-19010 with solids content of 25.0%, and Opadry® (Opadry or hydroxypropyl methylcellulose) white 31K58901 were gifts from Colorcon (West Point, PA). Sodium starch glycolate low pH (Explotab®) was from Mendell, a Penwest company (Patterson, NY). White sugar spheres, mesh size 18-20, were a gift from Paulaur Corporation (Cranbury, NY). Glucotrol-XL is manufactured by Pfizer Corporation (New York, NY). Glucotrol-XL was purchased from the Oregon State University campus pharmacy.

Equipment:

The equipment used in this study was Laboratory Niro STREA spray coater (Figure 4.3) for bead coating and Carver tablet machine for compression (Figure 4.4).

A laboratory Niro STREA spray coater was used
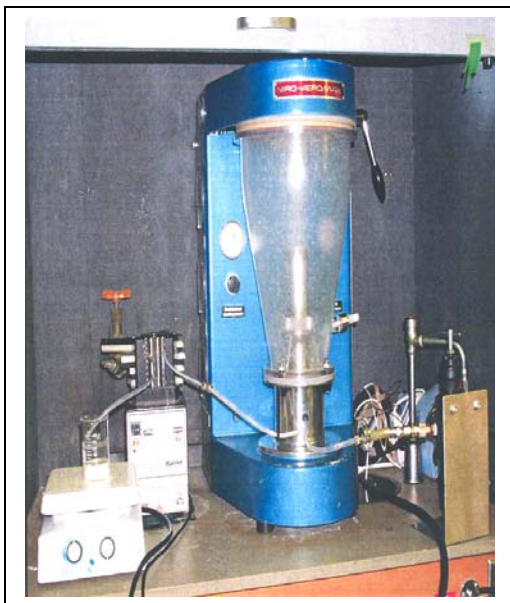
Figure 4.3: Spray coater

Figure 4.4: Tablet machine (Carver)

Method

Weight compositions of tablet formulations are shown in Table 4.1. The bead coating procedure and bead compaction procedure are discussed below.

Table 4.1: Weight compositions of different experimental tablet formulations

Formulation	Sugar beads	Drug layer			Hardening layer	Controlled release membrane layer (g)	Outside most layer
		Glipizide	Surelease solids content	HPMC	HPMC	Surelease solid content : Lactose	Lactose: Explotab = 2:1
CH-S-2	75 g	2.5 g	0	2.5 g	7.5 g	7.5 g (100:3)	15 g
CH4	60 g	2.5 g	10	0	7.5 g	8.5 g (100:3)	14 g
CH5	60 g	2.5 g	0	2.5 g	5 g	10 g (100:3)	20 g
CH6	67.5 g	2.5 g	5 g	0	7.5 g (6.82%)	7.5 g (100:5)	20 g
CH7	67.5 g	2.5 g	2.5 g	Not work out			
CH8	65 g	2.5 g	Not work out				
CH10	70 g	2.5 g	5 g	0	5 g (4.55%)	7.5 g (100:5)	20 g
CH11	70 g	2.5 g	5 g	0	5 g	7.5 g (100:7)	20 g
CH12	70.625 g	2.5 g	4.375 g	0	5 g	7.5 g (100:5)	20 g
CH14	71 g	2.5 g	5 g	0	4 g (3.64%)	7.5 g (100:5)	20 g
CH15	70 g	2.5 g	5 g	0	2.5 g (2.27%)	7.5 g (100:5)	20 g
CH16	70.625 g	2.5 g	4.375 g	0	5 g	6.0 g (100:7)	20 g
CH17	70.625 g	2.5 g	4.375 g	0	5 g	5.4 g (100:7)	20 g
CH18	70.625 g	2.5 g	4.375 g	0	5 g	5.4 g (100:10)	20 g
CH19	71.25 g	2.5 g	3.75 g	0	5 g	5.4 g (100:7)	20 g
CH20	71.25 g (64.77%)	2.5 g (2.27%)	3.75 g	0	5 g	7.5 g (100:7)	20 g
CH21	76.25 g	2.5	3.75	0	0	7.5 g (100:7)	20 g

CH7 and CH8 used Povidone as a binder to load drug on sugar beads, which did not perform well.

The numbers (e.g. 100:3) in parenthesis in the column of "Controlled release membrane layer" are the ratios of Surelease solid content : lactose in each formulation. Batch size is 110 grams of beads

Bead -Coating procedure

Loaded drug coating with Surelease: Surelease for each formulation (Table 4.1) was accurately weighed into a beaker. Then weighed amount of de-ionized (DI) water equal to the amount of Surelease was added and mixed well with Surelease dispersion. Measured concentrated ammonium hydroxide, 0.2 to 0.5 ml, to adjust pH to 10-10.4, was added to help dissolve glipizide. Accurately weighed glipizide in each formulation that would produce 2.3 to 2.5 g of glipizide in the 110 g final product (see Table 4.1) was dissolved in the above dispersion and mixed well for at least one hour. This dispersion was gently stirring while coating. The weighed amount of sugar beads in each formulation (Table 4.1), mesh size 18-20, placed into a laboratory Niro STREA spray coater, with the following parameters: Nozzle-needle 1.0 (air flow pressure valve), drying temperature: 50^0C, outlet air temperature: 41^0C, pressure: 2-5 psi, flow: 1 ml/minute.

Loading drug coating with HPMC: accurately weighed HPMC in formulation CH2-S or formulation CH5 (Table 4.1) was added to measured DI water and mixed well until HPMC dissolved producing a 5% solution. Measured concentrated ammonium hydroxide, 1.5 to 2 ml, to adjust pH to 10-10.4, was added to help dissolve glipizide. Accurately weighed glipizide in each formulation that would produce 2.3 to 2.5 g of glipizide in the 110 g final product (see formulation CH2-S and CH5 in Table 4.1) was dispersed in the above solution. This solution was gently stirring while coating. The weighed amount of sugar beads in each formulation (Table 4.1), mesh size 18-20, placed into a laboratory Niro STREA spray coater, with the spraying parameters: Nozzle-needle

1.0 (air flow pressure valve), drying temperature: 50^0C, outlet air temperature: 41^0C, pressure: 2-5 psi, flow: 1 ml/minute.

HPMC hardening coating: accurately weighed HPMC (see Table 4.1) was added to hot water (30% of total water in the formulation) at 80^0C in a beaker and stirred for 20 seconds. Then the rest of water (70% of total water in formulation) that was at room temperature was added producing a 5% solution of HPMC. This solution was stirred until HPMC was completely dissolved and the solution was gently stirring while coating. Drug loaded beads were put into the spray coater with the spraying parameters: Nozzle-needle 1.0, drying temperature: 50^0C, outlet air temperature: 41^0C, pressure: 10-12 psi, flow: 1.1 ml/minute.

Controlled release layer coating: Surelease (see Table 4.1) for each formulation was accurately weighed into a beaker. Then an equal amount to Surelease of weighed DI water was added. Accurately weighed lactose monohydrate for each formulation respectively (see Table 4.1) was dissolved in the above dispersion and mixed well for at least one hour and was gently stirring while coating. The spraying parameters were: Nozzle-needle 1.0 (air flow pressure valve), drying temperature: 50^0C, outlet air temperature: 41^0C, pressure: 10-15 psi, flow: 1.1 ml/minute.

Binder/disintegrant layer coating: accurately weighed lactose monohydrate was dissolved in water to produce a 8.2% (w/v) solution. Accurately weighed Explotab (half of the amount of lactose) was added in the above solution and mixed well for 30 minutes and was gently stirring while coating. The amount of coating weight gain for each

formulation is shown in Table 4.1. The coating parameters were: Nozzle-needle 1.0, drying temperature: 30^0C, outlet air temperature: 28^0C, pressure: 10-12 psi, flow: 0.75 ml/minute for 45 grams of beads.

Cross surface of four layer coated beads is described in Figure 4.5. From inside to outside of each bead, is the sugar bead, a drug-Surelease layer, a HPMC layer, a Surelease controlled release layer, and finally a binder and disintegrant layer.

Surelease and drug layer

Sugar bead

HPMC (hardening) layer

2nd Surelease layer: controlled release layer

Lactose:Explotab layer (binder and disintegrant layer)
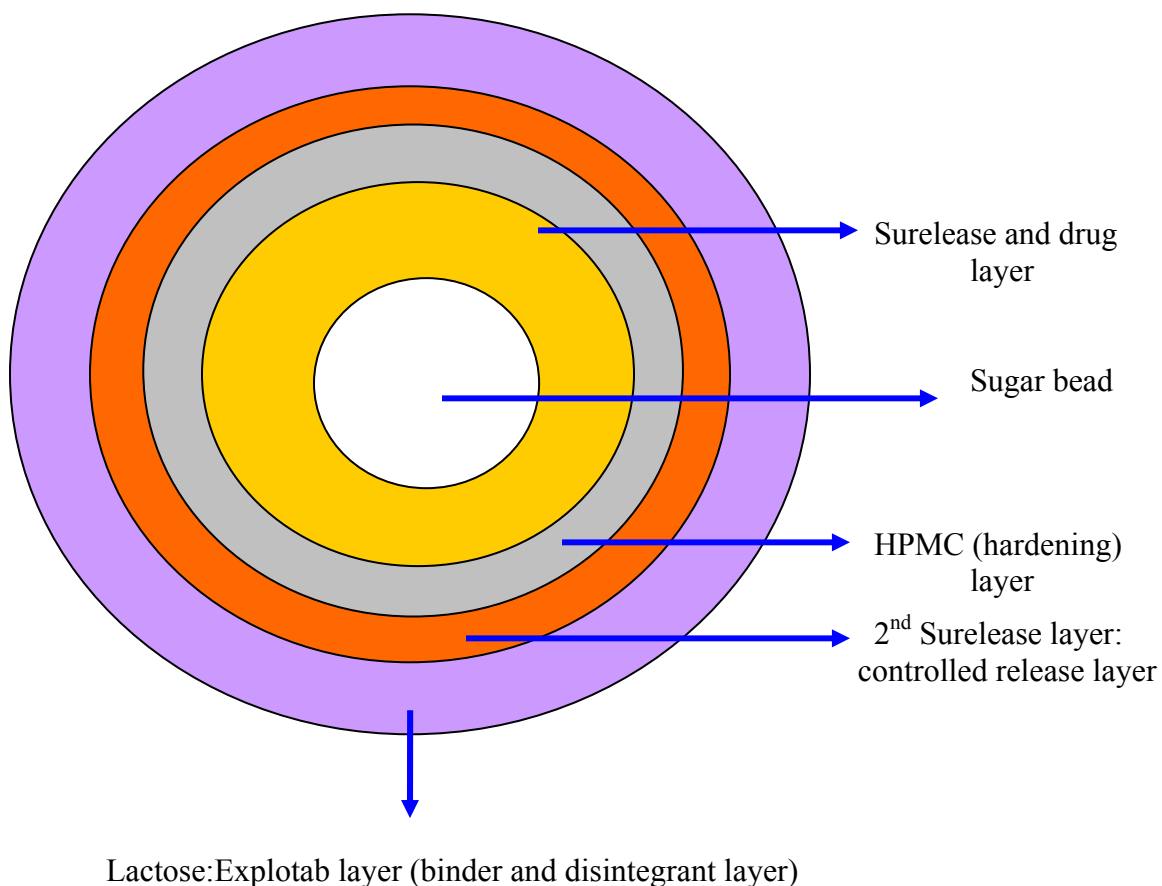
Figure 4.5: Cross surface of four layer coated beads

Bead Compaction

The beads were compressed into round tablets with diameter of 11.1 mm; thickness of 5.2 mm at the center and 3 mm at the edge using a Carver press fitted with a tablet punch and die. There were separate tablets made by applying 1000, 1500, 2000, or 3000 pounds (lbs) of pressure under a dwell time of 10 seconds after target pressures were reached. Each tablet contains 11 mg (110%) of glipizide based on drug content assay of the beads.

Glipizide Assay

<u>Standard Curves of Glipizide</u>

An exact amount (50 mg) of glipizide was weighed and dissolved in 10 ml of buffer pH 7.4 with the aid of 5 ml of 6 N sodium hydroxide in a 1000-ml volumetric flask. The sample was diluted in either simulated gastric fluid (pH 1.4 ± 0.1) without pepsin or pH 7.4 buffer medium and adjusted to final volume. A series of standard solutions with a concentration range of 0.5-10 µg/ml were prepared from the initial stock solution by dilution with simulated gastric fluid medium, and 0.5-50 µg/ml standard solutions were also prepared from the initial stock solution by dilution with pH 7.4 buffer medium. UV absorbance of standard solutions was measured by UV spectrophotometer at 275 nm in simulated gastric fluid and in pH 7.4 buffer medium. Standard curves of absorbance versus concentration of glipizide in simulated gastric fluid and pH 7.4 buffer medium are seen in Figures 4.6 and 4.7, respectively.

In Vitro Dissolution Testing of Formulations

Dissolution studies were performed according to the USP XXV apparatus 2. Test formulations were added to 700 ml of simulated gastric fluid without pepsin for the first 2 h, then 158 ml of 0.2 M Na_3PO_4 was added and the pH was adjusted to 7.4 ± 0.1 with 6N NaOH or concentrated hydrochloric acid. The dissolution media was stirred at different rpm (see results), and a constant temperature maintained at 37 ± 0.5^0C. 5-mL dissolution sample were filtered through flow filters (0.35 μm), and collected via an autosampler at predetermined time intervals for 24-h dissolution. Filtered solutions were centrifuged at 3000 rpm for 20 minutes; supernatants were measured to determine absorbance at 275 nm. Dissolution drug concentrations were determined via standard curves (Figures 4.6 and 4.7) in each medium and converted to percentage glipizide released. Three or six runs of each dissolution experiment were performed and the mean $\pm$ S.D. was calculated. Release of glipizide from tablets was compared to that obtained from Glucotrol-XL osmotic pump reference tablets.

Average drug released and their standard deviations were calculated from three or six replications in all dissolution experiments. Glipizide dissolution profiles are presented as percent drug release versus time curves.

Drug Content Assay

Drug content assay was performed in duplicate. An amount of coated beads equivalent to 11mg of glipizide was weighed and compressed into a tablet at 1500 pounds

pressure. Single tablets were transferred to 100-ml volumetric flasks. A pH 7.4 buffer solution was used to dissolve drug using a stirring bar to facilitate the dissolution for 25 hours. Then the samples were centrifuged at 3000 rpm for 10 minutes. Supernatant was then collected. Supernatant solutions were diluted 12.5 times with pH 7.4 buffer solution and filtered through a membrane of 0.45 μm diameter. The filtered solutions were measured by UV spectrophotometer at 275 nm in pH 7.4 buffer. The amount of glipizide contained in each formulation was determined using an appropriate standard curve (standard curve in Figure 4.7).

Simulated gastric fluid preparation.

Add 8 grams of sodium chloride and 20 ml of concentrated hydrochloric acid to 1000 ml of DI water and mix well. Add 2950 ml of DI water and mix well. Adjust to pH 1.4 ± 0.1 with concentrated hydrochloric acid. Add DI water up to 4000 ml.

pH 7.4 buffer preparation

Add 400 ml of simulated gastric fluid pH 1.4 ± 0.1 to 100 ml of 0.2M Na_3PO_4, mix well and adjust to pH 7.4 ± 0.1 with 6 N NaOH or concentrated hydrochloric acid as needed.
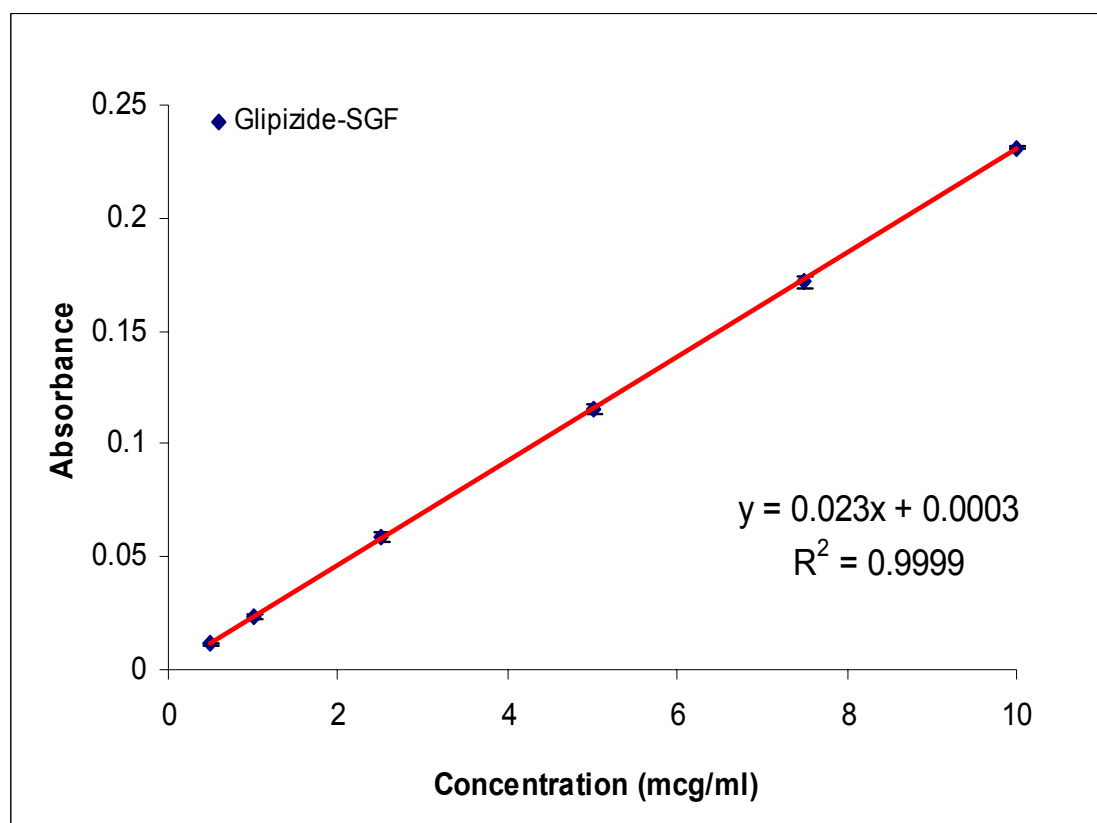
Figure 4.6: Standard curve of absorbance versus concentration of glipizide in SGF (simulated gastric fluid pH 1.4, UV wavelength at 275 nm)
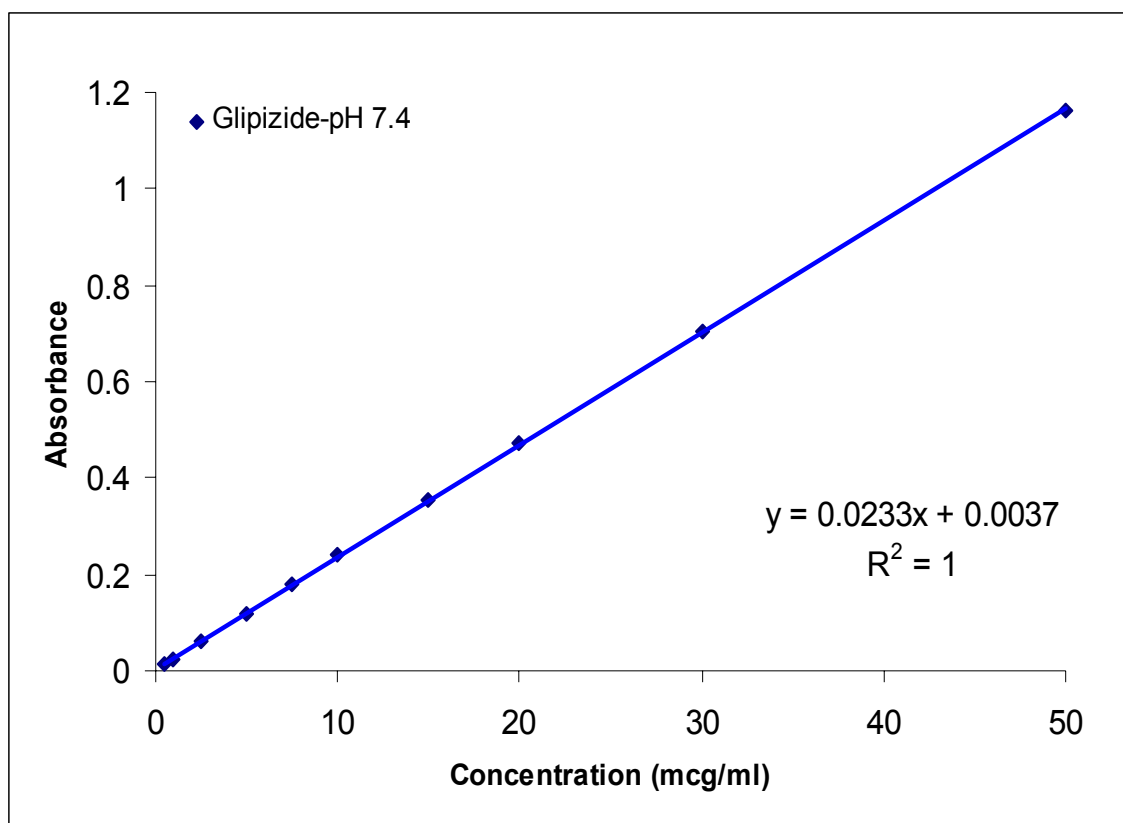
Figure 4.7: Standard curve of absorbance versus concentration of glipizide in pH 7.4 buffer medium (UV wavelength at 275 nm)

Statistical analysis

Influence of various preparation parameters on drug release from beads compressed into tablets

To investigate the influence of ingredients in each layer, the ratio of Surelease solids content to drug, amount of HPMC, varying amounts of Surelease in the controlled release membrane layer, ratio of Surelease solids content to lactose, and the amount of binder and disintegrate layer on percent drug release at 16 hours (%release 16) were considered. The release rate over time and % release at 16 hours were compared between CH20 formulation and Glucotrol XL. For zero-order release, the release rate is equal to the slope of the dissolution curve. The release rate following the lag time is calculated as follows:

$$\text{Release rate} = \text{slope of dissolution curve} = \frac{\% release16h - \% release2h}{16-2}$$

To obtain information on the most influential formulation parameters on %release 16, and release rate, these response variables were evaluated by several statistical methods using S-plus 7.0 statistical software including i) one way analysis of variance models (ANOVA), (ii) two-way ANOVA, and iii) multiple linear regression. Every experiment was performed in triplicate. The significance level was set at $\alpha = 0.05$. Residual plots were used to check the assumption of constant variance and normal quantile quantile (QQ) plots were used to check the assumption of normality.

To compare %release 16, and release rate of CH20 formulation with Glucotrol XL, these variables were evaluated by two-way ANOVA. Every experiment was performed in triplicate. The sample sizes of each model are presented in each ANOVA table as needed. The significance level was set at $\alpha = 0.05$.

Differences between groups were evaluated by multiple comparisons using 95% simultaneous confidence intervals for specified linear combinations with the Tukey method. Intervals excluding 0 flagged by '****' are considered "statistically significant differences". The Tukey assumptions are an ideal normal model with equal spreads and equal sample sizes in all groups. Since there are equal sample sizes in the treatments, the Tukey method appears appropriate.

Influence of compression pressures and paddle speeds on drug release from beads compressed into tablets

A factorial analysis was conducted by analysis of variance models (ANOVA) using S-plus 7.0 statistical software to identify the influence of paddle speeds and compression pressures on %release 16 and release rate. Table 4.2 summarizes the factors and levels studied. Every experiment was performed in triplicate. The significance level was set at $\alpha = 0.05$.

Table 4.2: Factors and levels studied for the influence of paddle speeds and compression pressures on %release 16 and release rate

Factors	Code of factors	Levels
Compression pressures	Pressures	1500, 2000 and 3000 pounds
Paddle speeds	rpm	50, 100, 150 and 200

Convolution:

Convolution was conducted to simulate plasma concentrations time curves for Glucotrol XL and CH20 tablet using spread sheets. Although simulated data are not always close to real data, convolution is still a good tool to predict the time course of drug in the body. Convolution was completed with the following assumptions. The first assumption is that the drug after being instantly absorbed, is only eliminated via first order elimination. The second assumption is that no absorption phase is considered; drug is treated like a series of intravenous (IV) bolus injections with appropriate adjustment of bioavailability. For the third assumption, absorption rate constant is greater than dissolution rate constant. Finally, glipizide follows linear pharmacokinetics.

RESULTS AND DISCUSSION

Figure 4.8 below shows preliminary investigation results. A preliminary study showed that the ratio of Surelease:drug of 4:1 in the drug layer (Surelease here is understood as the solids content of Surelease), with HPMC in the hardening layer, combined with 8.3% of Surelease:lactose = 100:3 in the controlled release membrane layer (CH4) resulted in drug release that was too slow when compared to Glucotrol XL. The CH5 formulation with HPMC as drug binder, and in the hardening layer, and 10% of Surelease:lactose = 100:3 in the controlled release membrane layer released drug much faster than the reference Glucotrol XL (the pink curve versus the red curve in Figure 4.8). In CH5, only Surelease in the controlled release membrane layer is used as a sustained release agent, thus suggesting the amount of Surelease in controlled release layer must be greater than 10% of total weight of beads to reduce drug release rate. Dissolution profile of CH-S-2 was close to that of reference Glucotrol XL at 100 rpm paddle speed, but dissolution profile of CH-S-2 was much higher than that of the reference Glucotrol XL at 200 rpm paddle speed. CH-S-2 also did not disintegrate into individual beads, probably because the coated multi-particles were fused into matrix tablets and the matrix itself controlled drug release. Drug release rate from matrix tablets is well known to be strongly affected by several factors like paddle speeds and compression pressures. Thus, CH-S-2 may not be a suitable candidate to meet current goals.
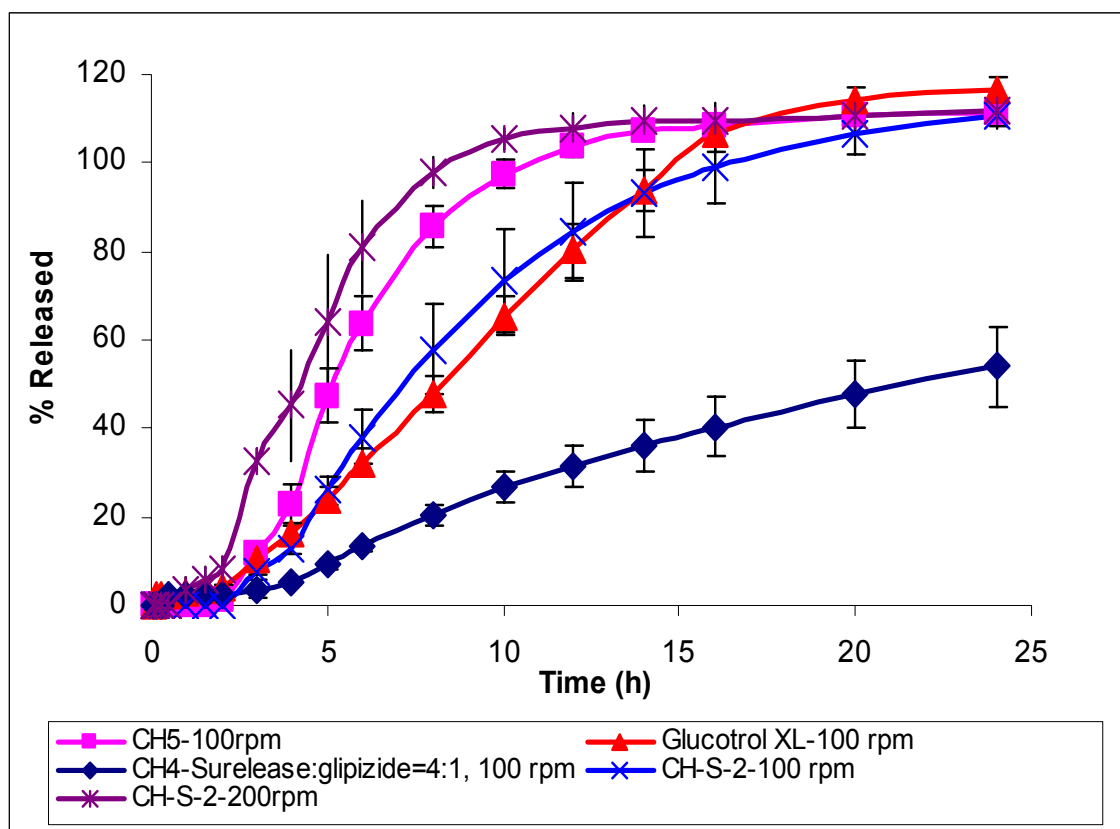
Figure 4.8: Dissolution profiles of glipizide from preliminary formulations, paddle method

CH5-100rpm = CH5 formulation, 100 rpm.

Glucotrol XL-100 rpm = Glucotrol XL push pump osmotic tablet, 100 rpm.

CH4-Surelease:glipizide = 4:1, 100 rpm = CH4 formulation, 100 rpm.

CH-S-2-100 rpm = CH-S-2 formulation at 100 rpm.

CH-S-2-200 rpm = CH-S-2 formulation at 200 rpm.

In this study, concentrated ammonium hydroxide was added into the drug loading dispersion to help dissolve glipizide and improve coating ease. The amount of ammonium hydroxide to adjust pH was critical. If pH was less than 10.0, the coating dispersion became stuck in the spray nozzle-needle. This may be due to the large size of glipizide particles. In this case a colloidal mixer may be needed to reduce glipizide particles if ammonium hydroxide is avoided. When HPMC was used as a drug binder an apparent overload of glipizide of more than 30 to 50% of expected drug loading on the beads in lab scale production occurred if based on the following assay procedure. The concentrated and centrifuged drug solutions were filtered through a membrane of 0.45 μm diameter (see Method part). Then the filtered solutions were diluted 12.5 times with pH 7.4 buffer solution and measured by UV spectrophotometer at 275 nm in pH 7.4 buffer. The amount of glipizide in each tablet was determined using the standard curve in pH 7.4 buffer (Figure 4.7). These results suggest an assay error was made. However, if the concentrated and centrifuged drug solutions were diluted first then filtered, then the percent of glipizide was close to expected drug loading. Povidone alone was not suitable as a binder for loading glipizide in terms of coating efficiency.

In an earlier study (El-Gazayerly et al., 2004) a combination of HPMC and Polyox WS N-80 was used as sealing agents for compressed beads. But, in this study the combination provided poor coating efficiency and was very difficult to control. Thus, HPMC was chosen as a single hardening agent and sealing for the new glipizide formulations.

While Surelease and HPMC are easy to coat, successful coating using lactose and Explotab dispersion in the laboratory spray coater depended on some critical factors. First, the amount of beads must be large enough, requiring 45 grams or more for lab scale. Generally, the more beads the higher coating efficiency. Second, the solids content of coating suspension should be in the range of 10-12.5%. For solids content greater than 12.5%, dispersion gets stuck in the spray nozzle-needle during coating. Solids concentration less than 10% gives low coating efficiency. Third, the drying time in spray coater after coating is critical. This time is less than 3 minutes, and then coated beads are dried in a regular oven at 50^0C for 2 hours or 37^0C for 4 hours. Finally, the drying temperature should be maintained at $30-33^0C$ to give better coating efficiency. The effect of drying temperature for 45 g of beads, flow rate of 0.75 ml/min, pressure of 10psi is shown in Table 4.3.

Table 4.3: Effect of drying temperature on approximate coating efficiency of Lactose and Explotab dispersion

Drying temperature	55^0C	45^0C	Less than 33^0C
Coating efficiency	Less than 10%	Less than 25%	Greater than 60%

As seen in Table 4.3, the high drying temperature produced low coating efficiency. The best drying temperature is $30 - 33^0C$.

Effect of binder/disintegrant layer:

Based on preliminary formulation results, CH6 started with a ratio of Surelease:glipizide of 2:1, 6.82% of HPMC in the hardening layer, and then 6.82%

(compared to total tablet weight) of Surelease to lactose = 100:5 in the controlled layer to evaluate the appropriate amount of binder/disintegrant layer. The results are shown in Table 4.4 and Figure 4.9.

Table 4.4: Effect of amount of disintegrate on disintegration time of CH6 tablets

CH6	10.00% of disintegrate (11.11% weight gain)	14.28% of disintegrate (16.67% weight gain)	18.18 % of disintegrate (22.22% weight gain)
Disintegration time	From 5h to more than 24 h, after 24h: 30% left	From 3 h, after 5h 50% left; completely before 20h.	From 2h, completely at 3 h

10.00%, 14.28% or 18.18% disintegrant layer in Table 4.4 are compared with total weight composition of each beads compressed into tablet, while 11.11%, 16.67% or 22.22% weight gains are calculated based on weight increase of disintegrant layer compared with three layer coated beads.

Table 4.4 shows that with 11.11% weight gain of binder/disintegrant layer, the beads were fused when compressed into a tablet to form a non-disintegrating matrix tablet which did not disintegrate after 24 hours. With 16.67% weight gain of binder/disintegrant layer, disintegration of tablet started at 3h and was complete before 20 h. For 22.22% weight gain of binder/disintegrant layer, tablets were disintegrated into individual beads within 3 hours and four layer coated beads then controlled drug release. Lactose in the 4th layer acts a binding agent, and sodium starch glycolate is a super disintegrant, which causes the tablet to fall apart in dissolution medium. Note that drug release depended on disintegration time (or on the amount of disintegrant layer) as seen in Figure 4.9. The more weight gain of disintegrating agents the higher %release 16, and the faster release as seen in Figure 4.9.
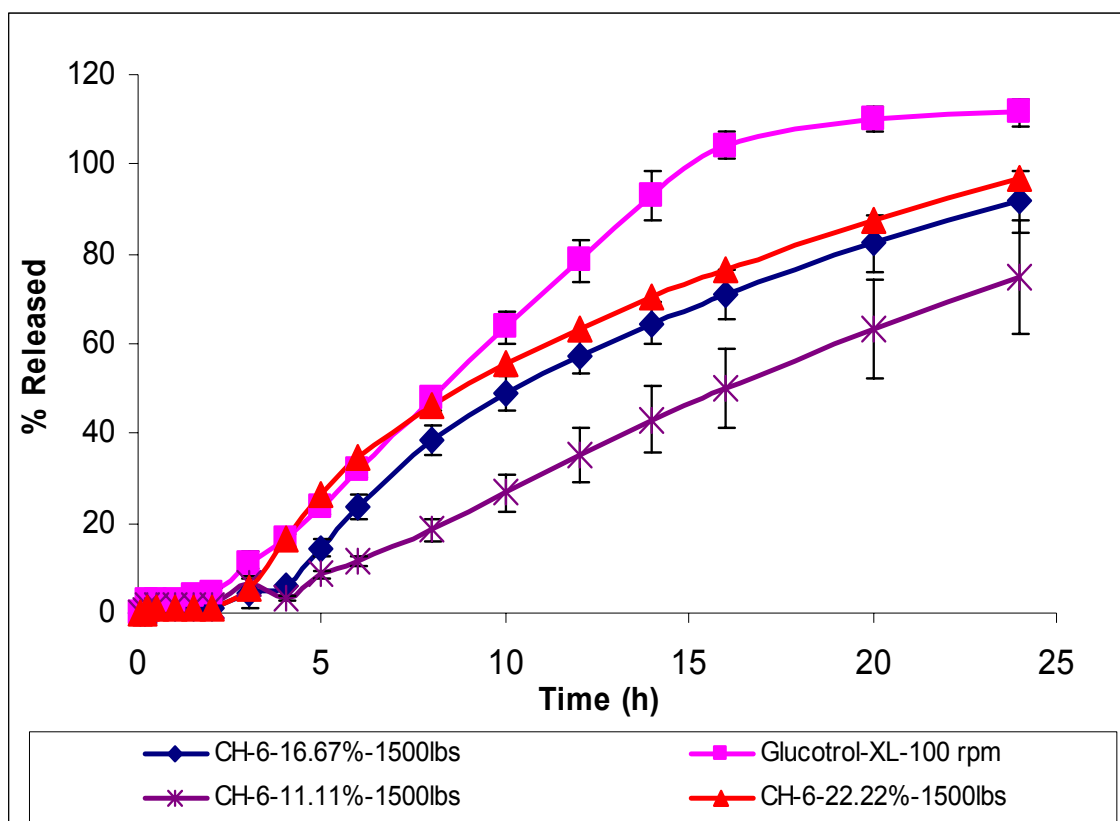
Figure 4.9: Effect of amount of binder/disintegrant layer on glipizide release from CH6

CH-6-16.67%-1500lbs = CH6, with 16.67% weight gain of binder/disintegrant layer, compressed at 1500 pounds.

Glucotrol-XL-100 rpm = Glucotrol XL push pump osmotic tablet.

CH-6-11.11%-1500lbs = CH6, with 11.11% weight gain of binder/disintegrant layer, compressed at 1500 pounds.

CH-6-22.22%-1500lbs = CH6, with 22.22% weight gain of binder/disintegrant layer, compressed at 1500 pounds.

When the multilayered beads are compressed into tablets the outermost layers (the binder/disintegrant layer, the controlled-Surelease layer, and HPMC) will absorb the pressure, which can produce some cracks in the Surelease-controlled release membrane layer. The hardening-HPMC layer protects drug from getting out of the Surelease-drug layer and provides lag time before drug is released and supports sustained drug release. Tablets compacted from these coated drug beads were more cohesive and made it easy to produce hard tablets with low compression pressures. Upon compaction, discrete beads can still be clearly distinguished on the surface of the tablet for all applied compression pressures. The 1500 lbs compaction pressure was chosen because beads compressed into tablets with this pressure passed friability testing. To evaluate the effect of amount of binder/disintegrant layer, %release 16 (percent of drug released after 16 hours of dissolution testing) was also used as a response variable versus percent coating weight gain of binder/disintegrant layer. Table 4.5 shows results of the linear regression model with percents of binder/disintegrant weight gain treated as a continuous variable, e.g. 11.11, 16.67 and 22.22 (% weight gain) when fitting models. The normal probability plot and residual plot were used to check the assumptions of normality and constant variance, respectively.

Table 4.5: ANOVA table for effect of binder/disintegrant amount on %release 16

	DF	Sum of square	Mean square	F value	Pr (F)
Model 4.1: %release16_CH6 ~ Weight gain of binder/disintegrant					
Weight gain	1	1049.286	1049.286	21.021	0.003
Residuals	7	349.411	49.916		

A linear model was first fit to these data. A lack of fit test was done to test the adequacy of the model (see Appendix 1). The result indicated that a linear model (model 4.1 in the Table 4.5) is adequate to relate %release 16 to percent weight gain of binder/disintegrant. The multiple R-squared for model 4.1 is equal to 0.75. The normal QQ plot of model of %release16_CH6 ~ Weight gain given in Figure A.1 (Appendix 1) exhibits normality. There is a strong relationship between mean %release 16 and % weight gain of binder/disintegrant (P = 0.003). The relationship between mean %release 16 discussed in model 4.1 of Table 4.5 and % weight gain of binder/disintegrant is as follows.

%Release 16_CH6 = 26.164 + 2.381* (%weight gain of binder/disintegrant) (Eq. 4.1)
(8.969) (0.519)   (The numbers in parenthesis are the standard
error for each corresponding coefficient.)

An increase of 5% weight gain of binder/disintegrant layer is associated with a 11.903% increase (95% confidence interval is 6.820-16.990%) in %release 16 as seen in equation Eq. 4.1.

With 22.22% weight gain of binder/disintegrant layer, the drug release rate was higher than that of 11.11% and 16.67% weight gain of binder/disintegrant layer and

closer to the drug release rate of reference product Glucotrol XL (see Figure 4.9). More importantly, tablets of 22.22% weight gain of binder/disintegrant ingredients disintegrated into individual beads within 3 hours. Aforementioned, individual beads are preferable to single tablet in controlling drug release. Thus, 22.22% of weight gain of binder/disintegrant ingredients was appropriate and chosen for binder/disintegrant layer.

Before further formulations were made, glipizide powder dissolution was tested to elucidate the behavior of glipizide tablets in simulated gastric and intestinal fluids. Placebo beads compressed-tablets were evaluated to eliminate the effect of ingredients and dissolution materials on drug absorbance. The results are seen in Figure 4.10.

Figures 4.10 shows the dissolution result of glipizide powder only and placebo CH6 without drug, 22.22% weight gain of binder/disintegrant layer, compressed at 1500 pounds. Glipizide, a weak acid, is poorly soluble in acidic solution. In simulated gastric fluid for the first 2 hours, only about 2.5% of powder is dissolved. It can be a confounding factor when *in vitro* dissolution using simulated gastric fluid for the first 2 hours is tested for the lag time. Since glipizide does not dissolve in an acidic medium, a formulation might be thought to have a lag time of two hours in simulated gastric fluid, but the real lag time can be smaller if the formulation was put directly into a medium with pH greater than 7. However, the *in vivo* times for 50% gastric emptying of pellets were 119 ± 15 (light breakfast) and 285 ± 45 min (heavy breakfast) (Davis et al., 1984). Therefore, it is reasonable to test beads compressed into tablets for the first two hours in simulated gastric fluid and then buffer medium pH 7.4.
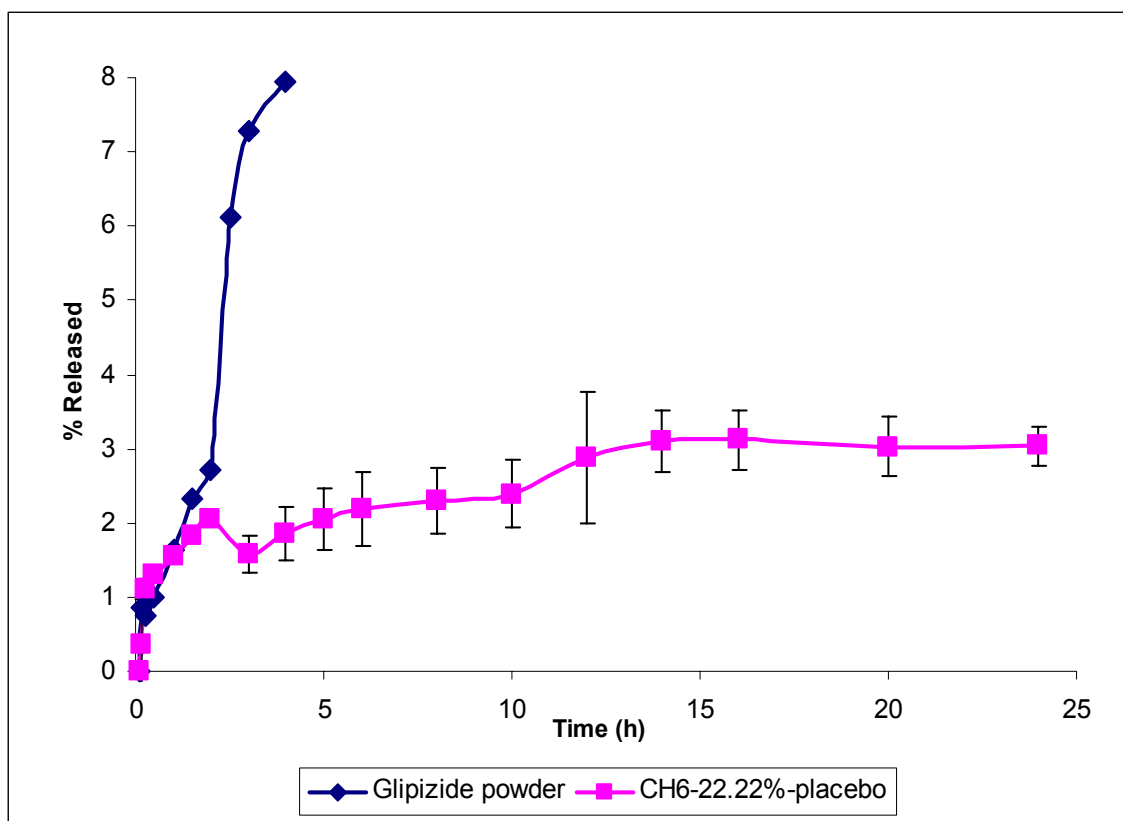
Figure 4.10: Dissolution profiles of placebo CH6 formulation and glipizide powder, 100 rpm paddle speed

Glipizide powder = 10 mg of glipizide powder only.

CH6-22.22%-placebo = placebo CH6.

Inactive ingredients and dissolution equipment have little effect on UV-VIS absorbance. The absorbance of placebo formulation was less than 3%. This may be due to some UV-absorbed particles in the tubes, cannulas, and the absorbance of inactive ingredients. Absorbance of solutions from placebo CH6 were less than 0.015, percent release of drug by UV interference was less than 3% (Figure 4.10). With an assumption of little effect from interference, when formulations were modified the adjustment of subtracting real % release to % release from placebo CH6 was performed for all formulations, except preliminary formulations to calculate the percent drug released during dissolution testing. The dissolution data presented hereafter were adjusted as stated.

Effect of hardening and sealing agent, HPMC:

HPMC is a very good bead hardening agent, both for ease of use and to create strong beads. Figure 4.11 shows the effect of the inclusion of HPMC between 2.27% and 6.82% on drug release from beads-compressed into tablets. HPMC hardened beads were preferred for physical stability during spray-coating with the sustained release membrane layer. The 6.82% in total tablet composition (CH6), 4.55% (CH10), or 3.64% (CH14) of HPMC showed little effect on glipizide release, however 2.27% of HPMC (CH15) reduced drug release to a small degree from beads-compressed into tablets compared with 6.82%, 4.55%, or 3.64% of HPMC formulations (see Figure 4.11). A one way ANOVA with % release at 16 hours as the response variable using an independent variable of percent of HPMC is summarized in Table 4.6.
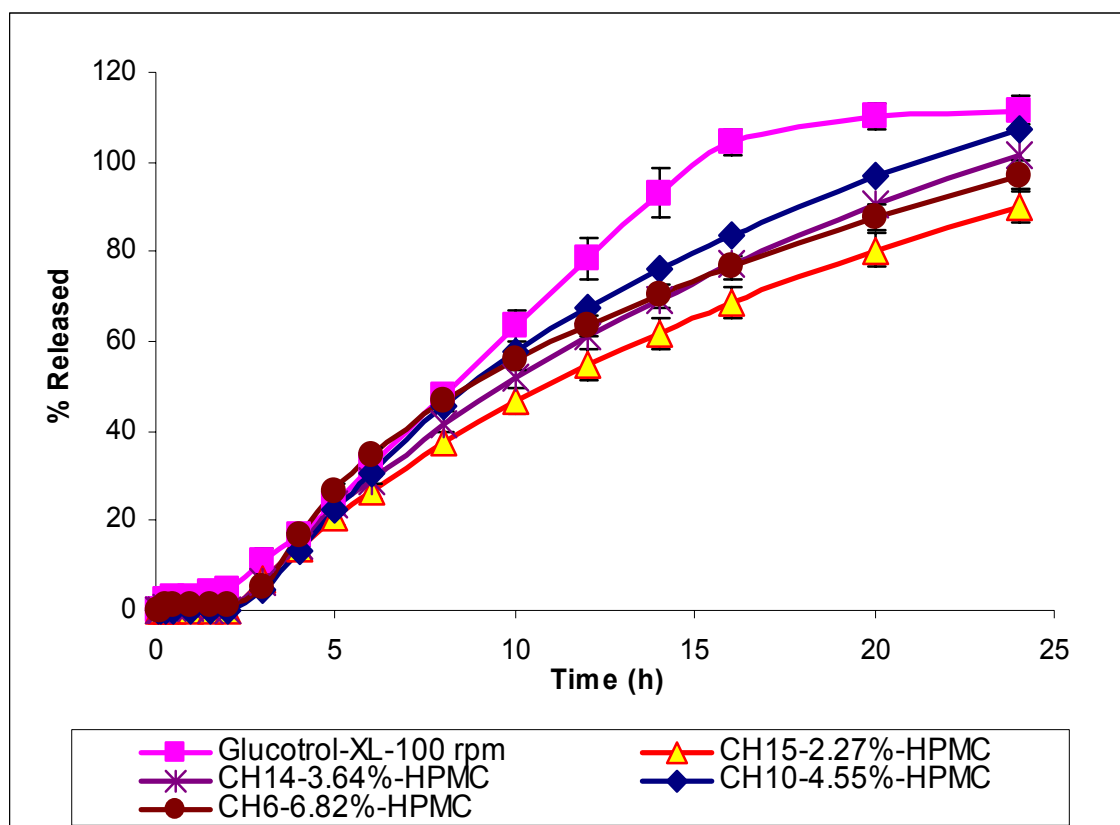
Figure 4.11: Effect of the amount of incorporated HPMC on glipizide release from beads-compressed into tablets, 100rpm paddle

Glucotrol-XL-100 rpm = Glucotrol XL push pump osmotic tablet.

CH15-2.27%-HPMC = CH15 formulation.

CH14-3.64%-HPMC = CH14 formulation.

CH10-4.55% = CH10 formulation.

CH6-6.82%-HPMC = CH6 formulation.

Table 4.6: One way ANOVA table for effect of amount of HPMC on %release 16

	DF	Sum of square	Mean square	F value	Pr (F)
HPMC group	3	416.783	138.928	6.028	0.019
Residuals	8	184.372	23.047		

Table 4.6 shows that at least one HPMC group differs from the others (P < 0.05).

The 95% simultaneous confidence intervals with a Tukey adjustment for specified linear

combinations are shown in Table 4.7.

Table 4.7: 95% simultaneous confidence intervals for specified linear combinations, by the Tukey method (intervals excluding 0 are flagged by '**')**

	Estimate	Std.Error	Lower Bound	Upper Bound
forCH6 - forCH15	2.38	3.92	-10.20	14.90
forCH6 - forCH10	-12.90	3.92	-25.40	-0.298 ****
forCH6 - forCH14	-6.00	3.92	-18.60	6.55
forCH15 - forCH10	-15.20	3.92	-27.80	-2.67 ****
forCH15 - forCH14	-8.37	3.92	-20.90	4.18
forCH10 - forCH14	6.85	3.92	-5.70	19.40

forCH6 = formulation CH6, 6.82% of HPMC
forCH10 = formulation CH10, 4.55% of HPMC, or 6.54% coating weight gain.
forCH14 = formulation CH14, 3.64% of HPMC
forCH15 = formulation CH15, 2.27% of HPMC.

There were no statistically significant differences (simultaneous confidence

interval including 0) between CH10 (4.55% of HPMC) and CH14 (3.64% of HPMC) on

% release at 16h. However, the differences between CH15 (2.27% of HPMC) to CH10

(4.55% of HPMC), and CH6 (6.82% of HPMC) to CH10 were statistically significant. The % release at 16 hours from CH10 (4.55% of HPMC) formulation was the highest and nearest to the reference standard Glucotrol XL (see Figure 4.11). In order to make strong beads that are resistant to compaction pressure, the more HPMC in the hardening layer the stronger the bead. However, increasing amount of HPMC may increase labor time of coating and decrease % release at 16 hours. The 4.55% of HPMC (or 6.45% weigh gain) of HPMC seems an appropriate compromise in terms of producing proper lag time and tensile strength of sealing and hardening layer and % release at 16 hours. Thus, 4.55% of HPMC in hardening layer was the adopted amount used for further study.

Effect of Surelease on Glipizide release:

The influence of various amounts Surelease in the Surelease-drug layer and Surelease-controlled release layer on drug release is seen Figure 4.12.
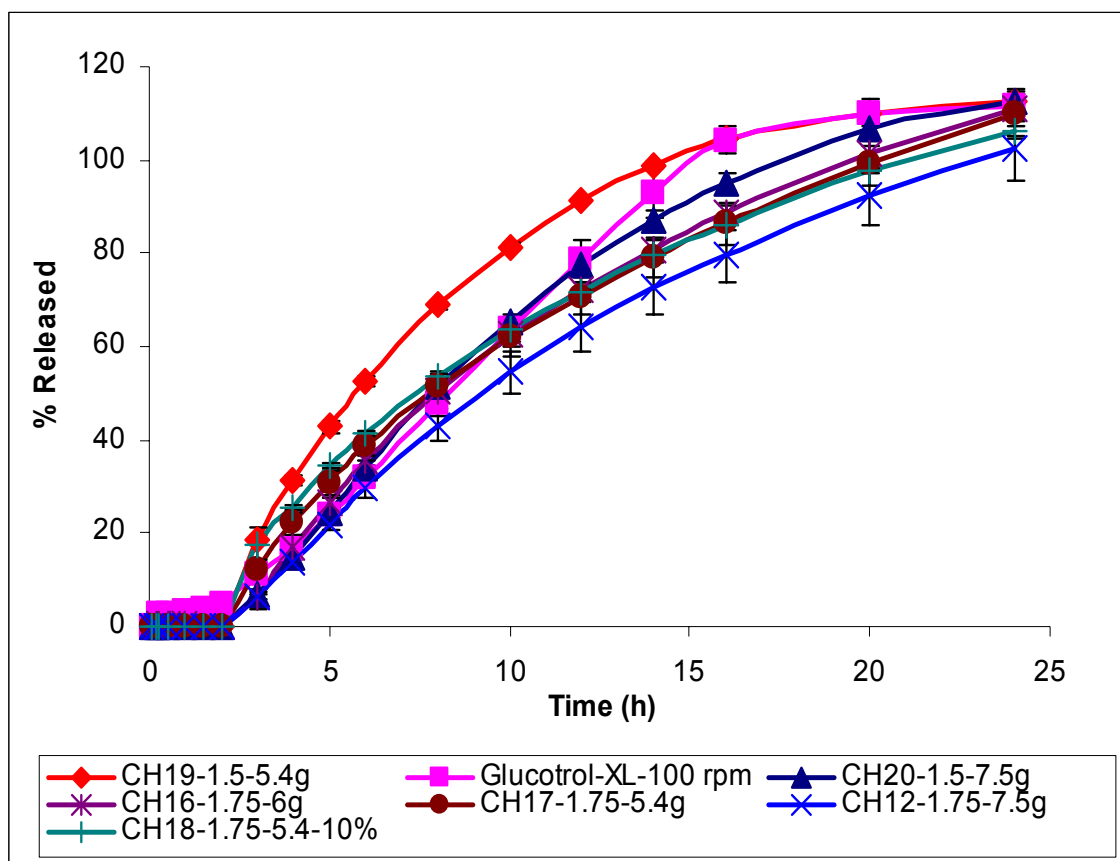
Figure 4.12: Effect of increasing amounts Surelease on glipizide release from beads-compressed into tablets

CH19-1.5-5.4g = CH19, 5.4 g of Surelease:lactose = 100:7.

Glucotrol-XL-100 rpm = Glucotrol XL push pump osmotic tablet.

CH20-1.5-7.5g = CH20, 7.5 g of Surelease:lactose = 100:7.

CH16-1.75-6g = CH16, 6 g of Surelease:lactose = 100:7.

CH17-1.75-5.4 = CH17, 5.4 g of Surelease:lactose = 100:7.

CH12-1.75-7.5 = CH12, 7.5 g of Surelease:lactose = 100:5.

CH18-1.75-5.4-10% = CH18, 5.4 g of Surelease:lactose = 100:10.

As seen in Figure 4.12, as the amount of Surelease increases in either the Surelease-drug layer or the Surelease-controlled release layer the more slowly drug is released. The inner amount of Surelease in drug layer predominates over the controlled release layer when comparing CH19 and CH17 and comparing CH16 and CH17. Formulation CH16 (the red violet curve) and formulation CH17 (the brown curve) show little differences, probably due to small differences (0.6 g or 0.55% compared with total weight) in the amount of Surelease in controlled release layer. In contrast, with a similar small difference in the amount of Surelease in the drug layer (0.62 g or 0.57% compared with weight total), CH19 (the red curve) released drug much faster than CH17 (the brown curve). When increasing 1.5 g or 1.29% of Surelease in the controlled release layer, CH12 (Surelease:lactose = 100:5, the light blue curve) released drug more slowly than CH16 (Surelease:lactose = 100:7), with the assumption that there is no effect due to % lactose in the Surelease-controlled layer. Also, when increasing the amount of Surelease in the Surelease-controlled release layer from 5.4 g in CH19 to 7.5 g in CH20 (the blue curve), CH20 released drug more slowly than CH19. Table 4.8 gives results of one way ANOVA for effect of amount of Surelease with highly significant evidence that at least one Surelease group differs from the others. The 95% simultaneous confidence intervals with Tukey adjustment for specified linear combinations are shown in Table 4.9.

Table 4.8: One way ANOVA table for effect of amount of Surelease on %release 16

	DF	Sum of square	Mean square	F value	Pr (F)
Surelease group	4	845.938	211.484	36.440	< 0.001
Residuals	10	58.037	5.804		

Table 4.9: 95% simultaneous confidence intervals for Surelease groups, by the Tukey method (intervals excluding 0 are flagged by '**')**

	Estimate	Std.Error	Lower Bound	Upper Bound
forCH16 - forCH18	-0.27	1.97	-6.75	6.20
forCH16 - forCH19	-19.20	1.97	-25.60	-12.70 ****
forCH16 - forCH20	-9.59	1.97	-16.10	-3.12 ****
forCH16 - forCH17	-0.78	1.97	-7.26	5.69
forCH18 - forCH19	-18.90	1.97	-25.40	-12.40 ****
forCH18 - forCH20	-9.32	1.97	-15.80	-2.84 ****
forCH18 - forCH17	-0.51	1.97	-6.98	5.96
forCH19 - forCH20	9.57	1.97	3.10	16.00 ****
forCH19 - forCH17	18.40	1.97	11.90	24.80 ****
forCH20 - forCH17	8.80	1.97	2.33	15.30 ****

forCH16 = CH16, Surelease:drug =1.75, and 6 g of Surelease:lactose = 100:7.

forCH17 = CH17, Surelease:drug =1.75, and 5.4 g of Surelease:lactose = 100:7.

forCH18 = CH18, Surelease:drug =1.75, and 5.4 g of Surelease:lactose = 100:10.

forCH19 = CH19, Surelease:drug =1.5, and 5.4 g of Surelease:lactose = 100:7.

forCH20 = CH20, Surelease:drug =1.5, and 7.5 g of Surelease:lactose = 100:7.

CH 12 was excluded from comparison because it has two changed factors, while the other formulations have one changed factor. The factors for CH12 include weight gain of the Surelease controlled release layer or the weight gain of Surelease drug layer

and percent of lactose, but the interest was in focusing on one changed factor each time of comparison. CH20 was used in the "Friability test" to choose an appropriate compression pressure (see Table 4.10). CH20 was also used to quickly check both effects of amount of Surelease and percent lactose in controlled release membrane on drug release (see Figure 4.12). Table 4.9 shows that there were no statistically significant differences (simultaneous confidence interval including 0) between CH17 (Surelease:lactose = 100:7) and CH18 (Surelease:lactose = 100:10) on % release at 16 hours. It means that when changing the ratio of Surelease:lactose = 100:7 to 100:10 in the controlled release layer did not affect % release at 16 hours. There were also no statistically significant differences between CH17 (5.4 g of Surelease:lactose = 100:7) and CH16 (6 g of Surelease:lactose = 100:7) on % release at 16hours. In other words, percent release at 16 hours did not differ when decreasing by the amount of 0.55% of Surelease:lactose = 100:7 in the controlled release layer from CH16 to CH17. By decreasing the amount of Surelease:lactose (0.62g of Surelease:lactose = 100:7) in the Surelease-drug layer from CH17 to CH19, % release at 16 hours increased significantly. Formulation CH19 released drug more rapidly than the reference Glucotrol XL. To reduce the drug release rate from CH19, 2.1 g (or 1.9%) of Surelease:lactose = 100:7 was added to the controlled release layer (CH20). The difference between CH19 and CH20 was significant. The dissolution profile of CH20 matched Glucotrol XL tablet up to 14 h. Thus, CH 20 was selected for further study.

Effect of compaction pressure:

Requirement for the friability test in the USPXXV is less than 1% of weight loss of tested tablets compared with the weight of the tested tablets. Tablets produced with compression pressures from 1500 lbs to 3000 lbs passed this friability testing requirement as seen in Table 4.10. Compression pressure of over 3000 lbs may be applied, but it is not suggested because it may affect punch life-span and punches can be fractured. Figures 4.13 and 4.14 show the effects of compaction pressures on glipizide release.

Table 4.10: Effects of compression pressures on friability and hardness tests of CH12 (Requirement for friability test is less than 1%)

	Compression pressure (n = 10)			
	1000 lbs	1500 lbs	2000 lbs	3000 lbs
Friability test (% lost)	1.22%	0.72%	0.36%	0.29%
Hardness test (kg)	4.17 ± 0.28	5.43 ± 0.57	6.0 ± 0.54	7.77 ± 0.27

All tablets produced with compression pressures from 1000 to 3000 pounds had "tablet breaking forces" higher than 4 kg. This means that all tablets should be strong enough to resist chipping and breaking during coating and shipping process.
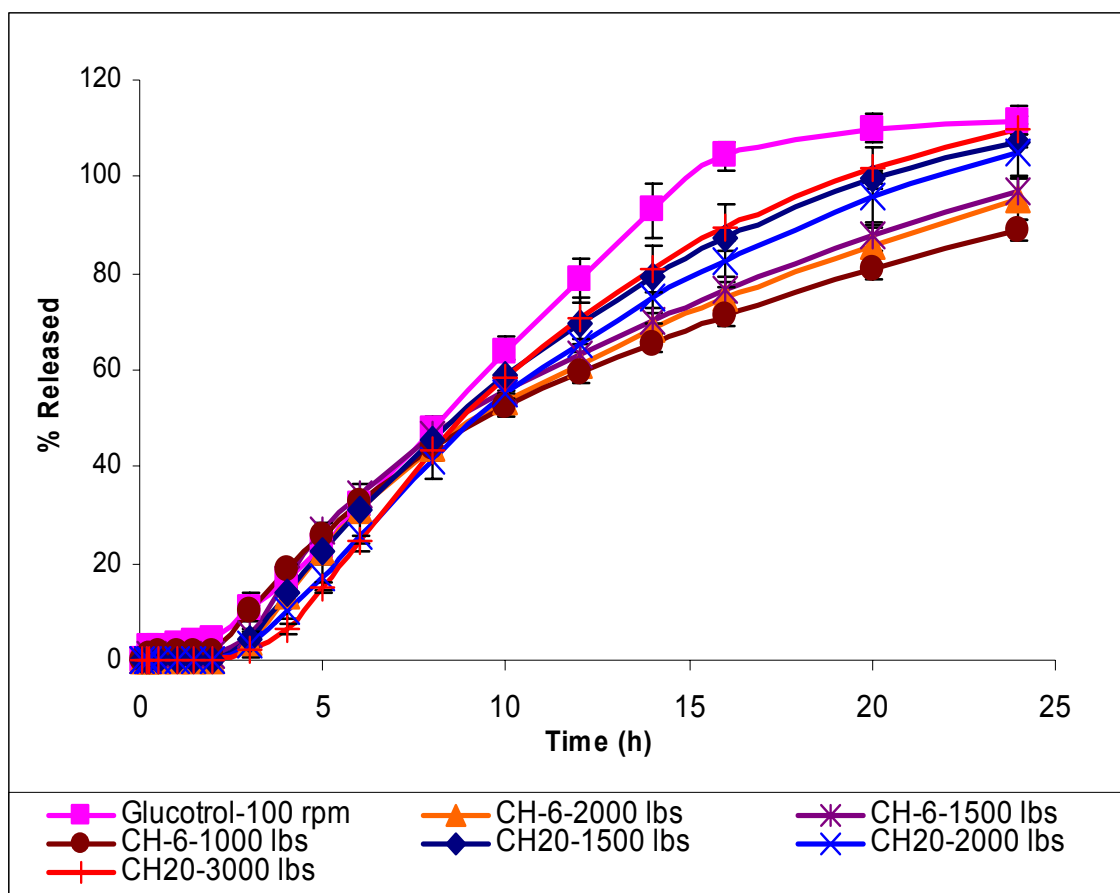
Figure 4.13: Effect of compression pressures on glipizide release from beads-compressed into tablets, 100 rpm paddle speed

Glucotrol-XL-100 rpm = Glucotrol XL push pump osmotic tablet.

CH-6-2000 lbs = CH6, 2000 pounds compaction pressure.

CH-6-1500 lbs = CH6, 1500 pounds compaction pressure.

CH-6-1000 lbs = CH6, 1000 pounds compaction pressure.

CH20-1500 lbs = CH20, 1500 pounds compaction pressure, 104% glipizide.

CH20-2000 lbs = CH20, 2000 pounds compaction pressure, 104% glipizide.

CH20-3000 lbs = CH20, 3000 pounds compaction pressure, 104% glipizide.
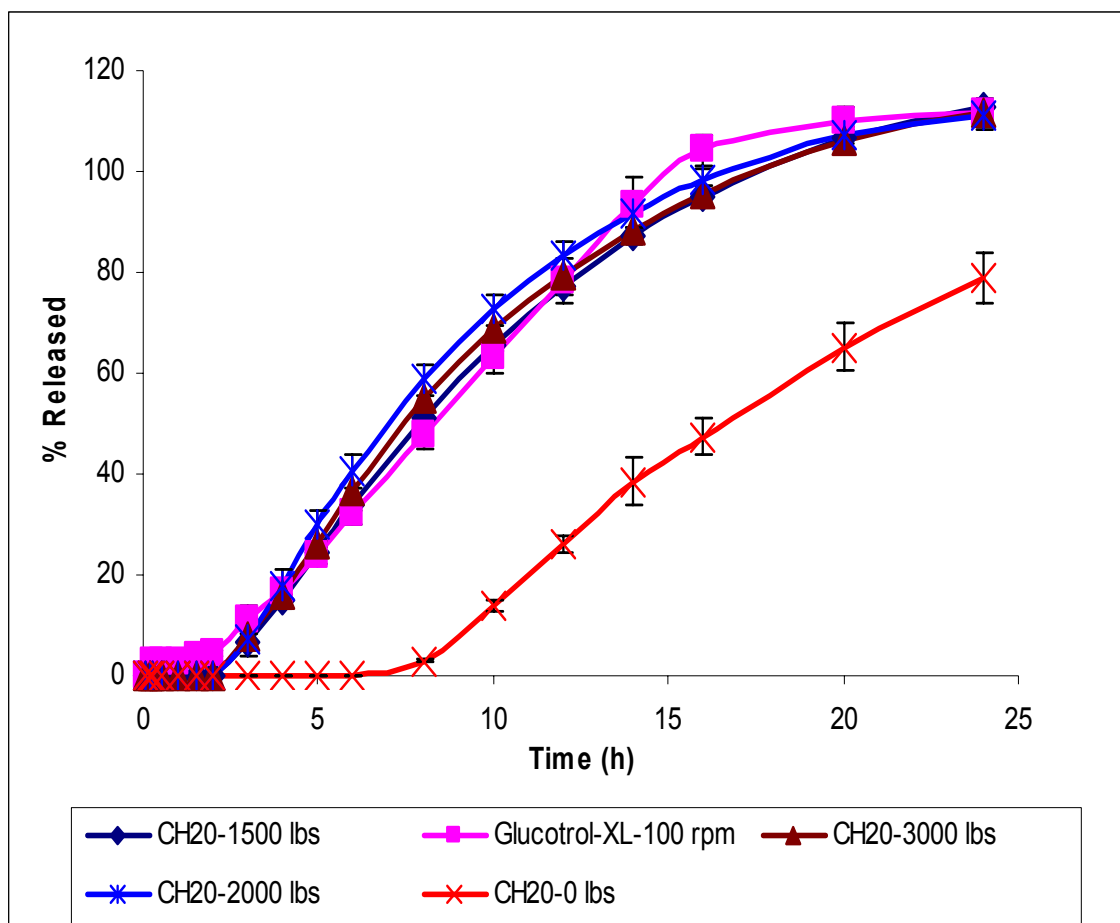
Figure 4.14: Effect of compression pressures on glipizide release from beads-compressed into tablets, CH20, 110% glipizide, 100 rpm paddle speed

CH20-1500 lbs = CH20, 1500 pounds compaction pressure.

Glucotrol-XL-100 rpm = Glucotrol XL push pump osmotic tablet.

CH20-3000 lbs = CH20, 3000 pounds compaction pressure.

CH20-2000 lbs = CH20, 2000 pounds compaction pressure.

CH20-0 lbs = CH20, 0 pounds compaction pressure.

As shown in Figure 4.13, compression pressure from 1000 lbs to 3000 lbs has little effect on drug release from CH6 at 100 rpm, paddle method. Compression pressure from 1500 lbs to 3000 lbs has also little effect on drug release from CH20 at 100 rpm paddle speed (Figures 4.13 and 4.14). As known, reported effect of compaction pressure on drug release from coated beads can be conflicting. Compaction pressure affected drug release from tablets compressed from EC coated beads (Maganti and Celik, 1994; and Altaf et al., 1999). But, compression force is not a critical parameter in influencing drug release rate from Eudragit RS 30D coated granules formulated into tablets. There are no significant differences between the dissolution profiles of the tablets compressed from Eudragit RS 30D coated beads with hardnesses 4, 8 or 12 kg/cm^2 (Palmieri et al., 1996). Figure 4.14 shows the lag time of 8 hours from tablets made with zero compaction pressure (CH20 beads), but tablets made using compaction pressures of 1000-3000 lbs pressure give a lag time of 2 hours before drug release. Dissolution curve of CH20-beads is nearly parallel in slope to beads-compaction tablets, only lag times are different.

Figure 4.15 shows the effect of both paddle speeds and compression pressures and on beads compressed into tablets.
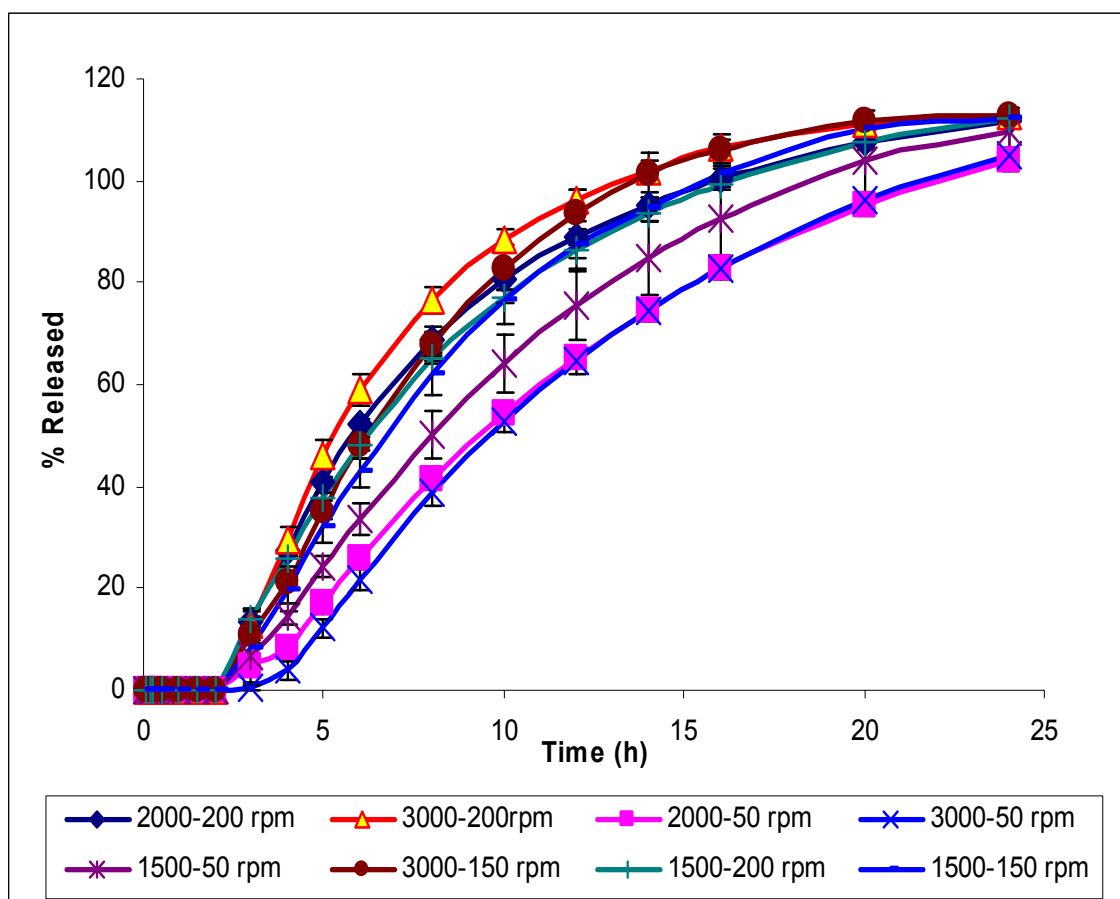
Figure 4.15: Effect of compression pressures on glipizide release from beads-compressed into tablets, CH20, 110% glipizide, 50- 200 rpm paddle

2000-200 rpm = CH20, 2000 pounds compaction pressure, 200 rpm.

3000-200 rpm = CH20, 3000 pounds compaction pressure, 200 rpm.

2000-50 rpm = CH20, 2000 pounds compaction pressure, 50 rpm.

3000-50 rpm = CH20, 3000 pounds compaction pressure, 50 rpm.

1500-50 rpm = CH20, 1500 pounds compaction pressure, 50 rpm.

3000-150 rpm = CH20, 3000 pounds compaction pressure, 150 rpm.

1500-200 rpm = CH20, 1500 pounds compaction pressure, 200 rpm.

1500-150 rpm = CH20, 1500 pounds compaction pressure, 150 rpm.

Although compression pressures from 1500 lbs to 3000 lbs have little effect on drug release from CH20 at 100 rpm paddle (Figure 4.14), these compression pressures have more effect at paddle speeds of 50, 150, and 200 rpm (Figure 4.15). At 50 rpm paddle speed, CH20 with 2000 and 3000 lbs compression pressures had similar drug release that was a little lower than CH20 compressed at 1500 lbs. At 150 rpm paddle speed, there was a little difference in drug release from CH20 at 1500 and 3000 lbs compaction pressure. At 200 rpm paddle speed, CH20 tablets compacted at 1500 and 2000 lbs gave similar dissolution profiles, but lower than 3000 lbs (Figure 4.15).

Dissimilarity with time-controlled explosion systems

Beads-compressed into tablet are different from reported time-controlled explosion systems (European patent, application number: 86109733.5). Beads of time-controlled explosion systems (TCES) include layers (1): is a seed of sucrose (core); (2) is a drug, either a core comprising drug or a mixture comprising drug and swelling agent; (3) is a swelling agent, and (4) is a controlled release membrane, like ethylcellulose membrane. In these systems, gastrointestinal fluid penetrates through the controlled release membrane into the TCES and swells the swelling agent incorporated into the TCES resulting in the explosion of the controlled release membrane. Because of the time variance of the explosion of the controlled release membrane in each bead or granule, drug is released with a zero order pattern after a definite lag time from mixtures of different batches of TCES beads or granules. The lag times can be controlled by the sort or amount of the swelling agent and controlled membrane, and the size of TCES. TCES

beads are not for compression into tablets and the reference (European patent, application number: 86109733.5) teaches that TCES tablets are quick release tablets following a lag time. In the new beads-compressed into tablet reported herein, the outside most layer of the beads is a binder/disintegrant layer and the hardening agent does not explode the beads. In addition, the multiple layer-coated beads were compacted into tablets. The TCES beads use either low substituted hydroxypropyl cellulose, carboxymethylcellulose calcium, Explotab, synthesized polymer, inorganic salt, organic salt, or sugar as a swelling agent, but in beads-compressed into tablet, HPMC is used as a hardening agent. The tablet in TCES is very different. TCES containing a quick dissolving mixture of drug, swelling agent, diluents, and lubricants are compressed into tablets and then the tablets are coated with water-insoluble material with additives.

Effect of exclusion of HPMC:

It seems that HPMC has little effect on drug release, or decreases %release 16 h if amount of HPMC deviates from 4.55%. Another formulation, CH21, was produced without HPMC, with other ingredients being the same as CH20. Figure 4.16 shows the effect of exclusion of HPMC on drug release from beads only and beads-compressed into tablets. For beads only, exclusion of HPMC convincingly reduced extent and rate of drug release significantly from 2 to 24 hours. After 24 h, less than 5% of drug was released from CH21-beads (without HPMC), compared with more than 78% from CH20-beads (with HPMC). When CH21 beads were compacted into tablets, the drug release was much faster than CH21 beads, and closer to the dissolution profile of Glucotrol-XL, but

still not as close as desired. Formulation CH20, and CH21 have the same % and % weight gain of Surelease in the Surelease-drug layer and controlled release layer, and lactose:Explotab = 2:1 in the disintegrant layer. Exclusion of HPMC increases the percent of sugar beads used and reduces surface area of beads slightly. Consequently, the thickness of coating layers, Surelease and disintegrant, were a little thinner. If only these factors were changed, drug would have been expected to be released faster. However, drug release was reduced due to the absence of HPMC in the formulation. Convolution for CH21 tablets showed simulated Cmax was greater by an 18% difference when compared with simulated Cmax of Glucotrol XL. It was also noted that compressed CH21 tablets began disintegrating after 2 hours but was not complete until 5 hours, but for CH20, tablets disintegrated within 3 hours. It was concluded that the HPMC layer helps achieve the desired glipizide release profile. The data suggest sustained release membrane of beads was damaged significantly when coated CH21 beads were compressed into tablets, which agrees with the summary of Bodmeier (1997), and finding of Altaf et al. (1999). HPMC layer protects two Surelease layers, Surelease in drug-Surelease layer and Surelease in controlled release layer, from being fused into a matrix which can slow disintegration time and reduce drug release rate and extent. In addition, when water penetrates into HPMC, the HPMC hydrates and may widen the gap between the two Surelease layers, and hydration of HPMC may also widen cracks and lactose channels to diffuse drug out without exploding or rupturing the membrane.
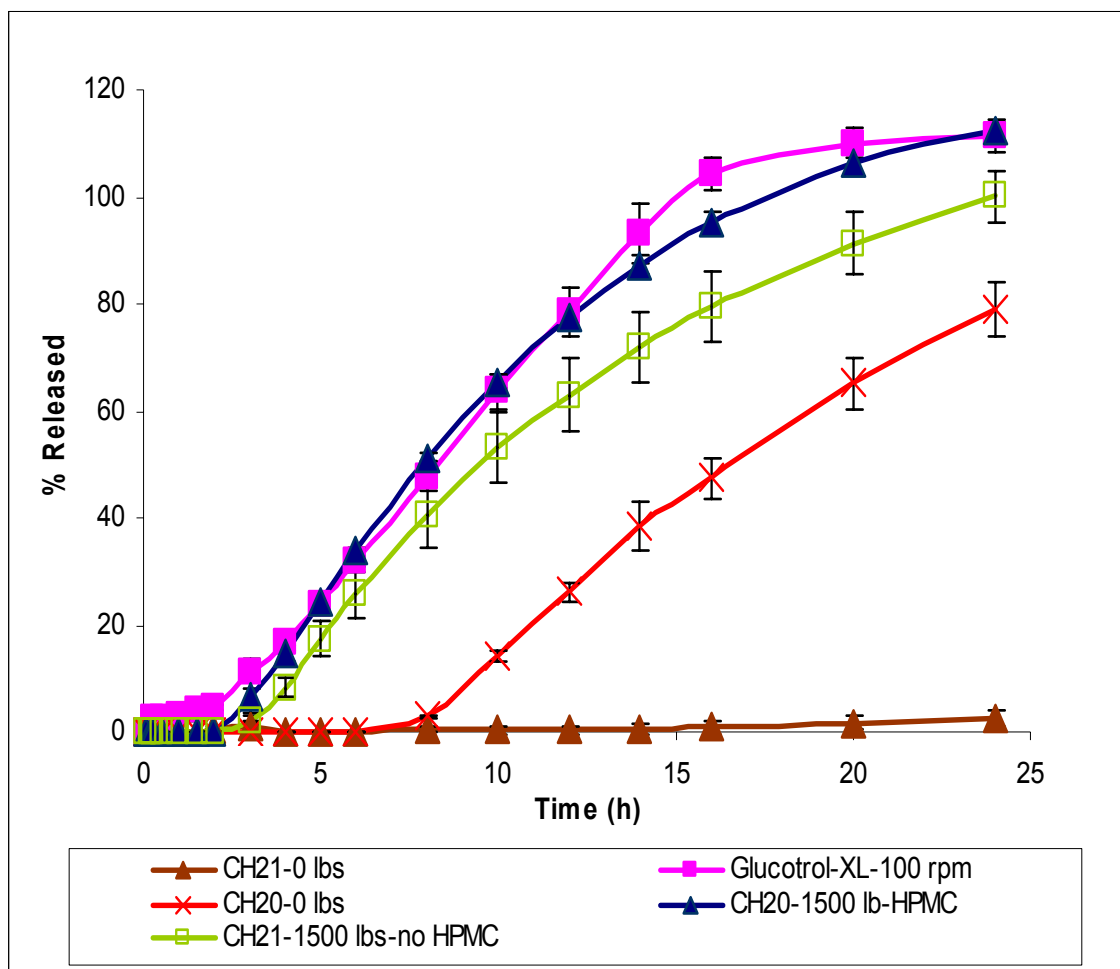
Figure 4.16: Effect of exclusion of HPMC on glipizide release from CH20, 1500 pounds, 110% glipizide, 100 rpm paddle speed

CH21-0 lbs = CH21, beads only.

Glucotrol-XL-100 rpm = Glucotrol XL push pump osmotic tablet.

CH20-0 lbs = CH20, beads only.

CH20-1500 lb-HPMC = CH20, 1500 pounds compaction pressure.

CH21-1500 lbs- no HPMC = CH21, 1500 pounds compaction pressure.

Dissolution mechanism:

The lag time is created in part by the EC (ethylcellulose)/lactose -controlled release layer. With beads only, dissolution medium dissolves lactose and penetrates through lactose channels, reaching HPMC which hydrates and dissolves and may swell slightly to widen channels. When aqueous medium contacts drug in Surelease-drug layer, drug dissolves and comes out through created channels. The time it takes from when a formulation is placed into a dissolution medium until drug release begins is "lag time".

With beads-compressed into tablets, all layers are deformed, sustained release layer is at least partially damaged, and lag time is reduced. When tablets are put into a dissolution medium, the aqueous medium penetrates into binder/disintegrant layer between beads of tablet and then disintegrates tablet into individual beads. At the same time, the aqueous medium reaches into inner layers through lactose channels and cracks created by compaction pressure. Dissolution medium still needs to hydrate and dissolve HPMC, then dissolve drug and carry drug out through channels. Cracks created by compaction pressure shorten lag times. The Surelease-drug layer plays a role in controlling drug release. It can control the rate of drug release from the core even when the Surelease/lactose-controlled-layer is deformed seriously. HPMC is not only a hardening agent but also helps protect two Surelease layers from being fused into each other under the compression pressures. Surelease- controlled release layer is "strong" and hydrating HPMC does not swell sufficiently to explode the Surelease-controlled release layer. Control of drug release is through cracks and channels. This release mechanism

differs from time-controlled explosion systems. The new formulation system reported herein is a novel way to produce sustained-release tablets from coated-pellets. Ethylcellulose is incorporated with drug to form a matrix drug release layer. Then this matrix is protected by HPMC-hardening layer, and overcoated by EC controlled release layer. Three coated layer pellets were then over coated with binder/disintegrant layer, which with HPMC and EC controlled release layers, reduced the effects of compression pressure. The particular structure of this formulation gives advantages of providing lag time, and approximately zero-order release that is nearly independent of paddle speeds at 50 and 100 rpm. No other "beads in a tablet" have been reported with these characteristics.

Effect of paddle speeds on Glipizide release from tablets

The effect of stirring speeds on glipizide release from tablets is seen in Figures 4.17, 4.18 and 4.19.

As shown in Figure 4.17, paddle speeds at 100, 150 and 200 rpm did not affect drug release from Glucotrol XL, but surprisingly paddle speed of 50 rpm slowed drug release from Glucotrol XL significantly.
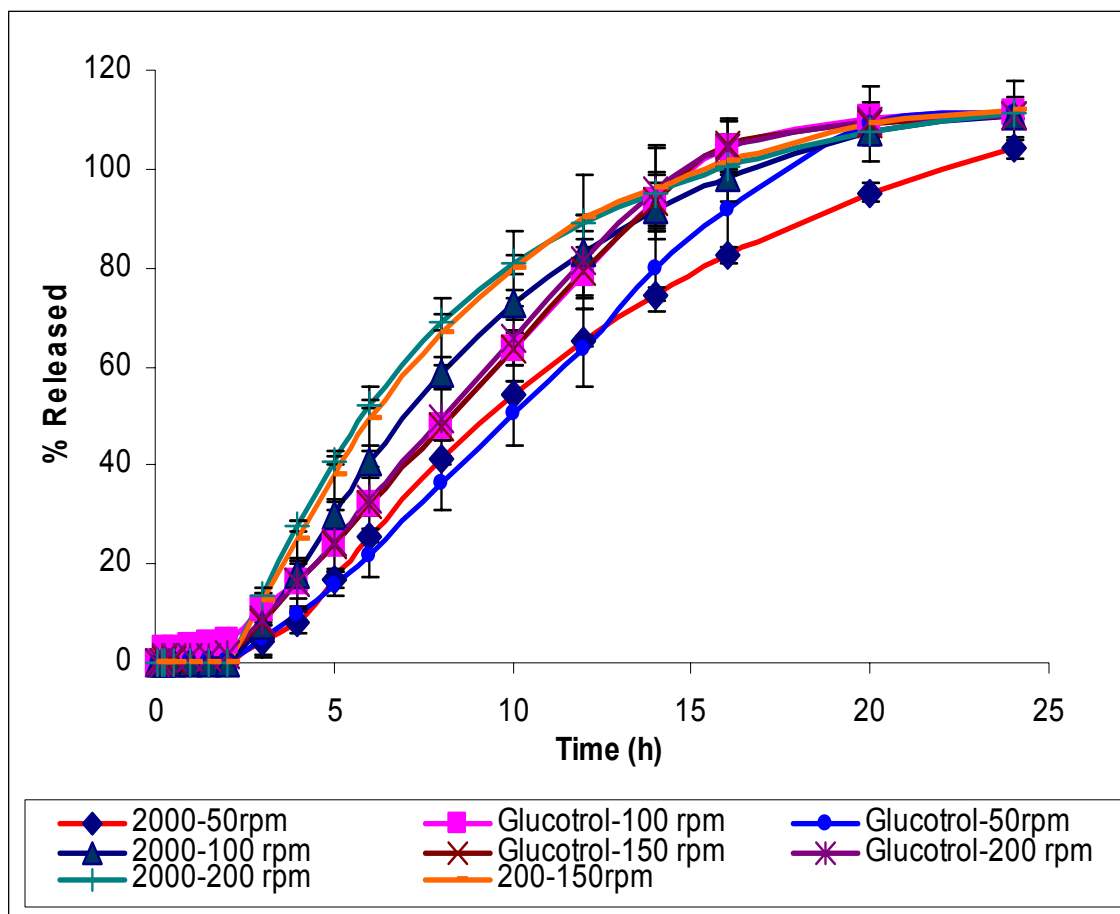
Figure 4.17: Effect of paddle speeds on glipizide release from CH20, 2000 pounds, 110% glipizide

2000-50 rpm = CH20, 2000 pounds compaction pressure, 50 rpm.

Glucotrol-100 rpm = Glucotrol XL push pump osmotic tablet, 100 rpm.

Glucotrol-50 rpm = Glucotrol XL push pump osmotic tablet, 50 rpm.

2000-100 rpm = CH20, 2000 pounds compaction pressure, 100 rpm.

Glucotrol-150 rpm = Glucotrol XL push pump osmotic tablet, 150 rpm.

Glucotrol-200 rpm = Glucotrol XL push pump osmotic tablet, 200 rpm.

2000-200 rpm = CH20, 2000 pounds compaction pressure, 200 rpm.

2000-150 rpm = CH20, 2000 pounds compaction pressure, 150 rpm.
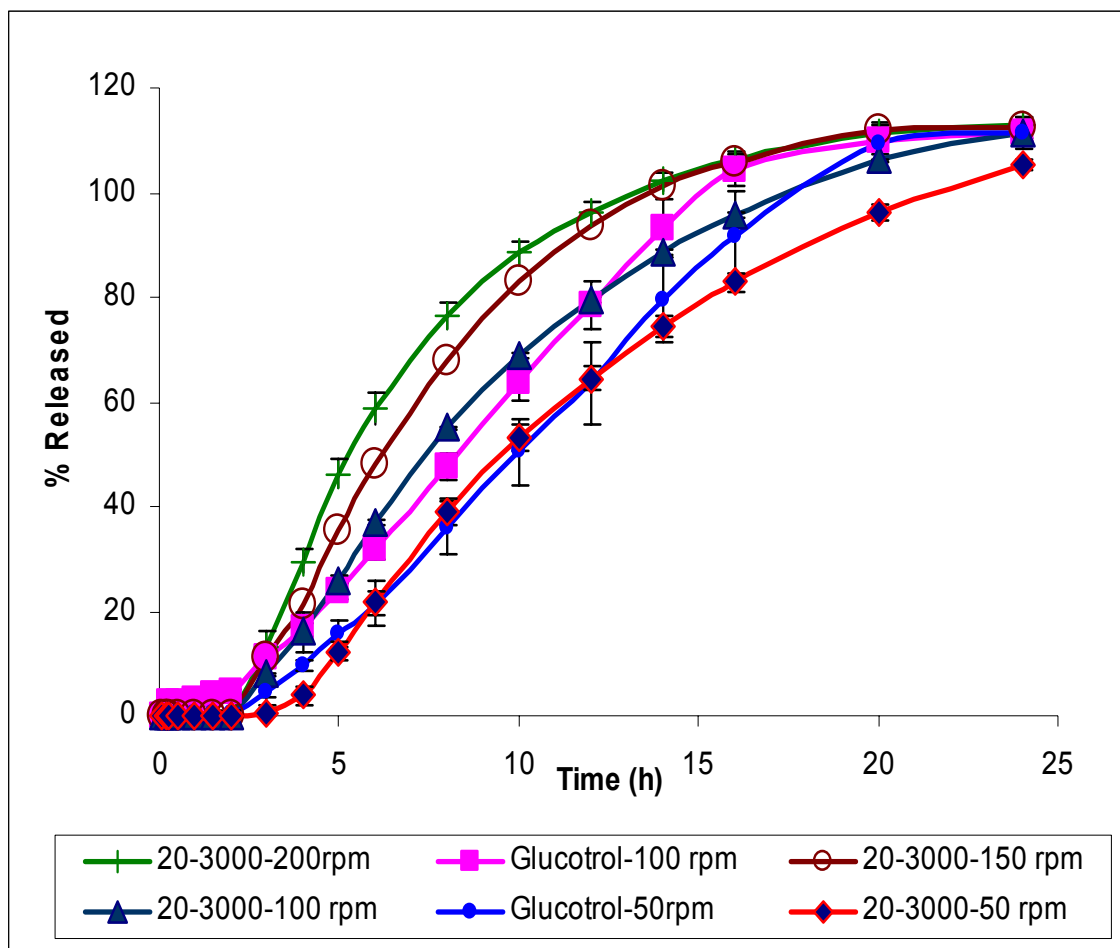
Figure 4.18: Effect of paddle speeds on glipizide release from CH20, 3000 pounds, 110% glipizide

20-3000-200 rpm = CH20, 3000 pounds compaction pressure, 200 rpm.

Glucotrol-100 rpm = Glucotrol XL push pump osmotic tablet, 100 rpm.

20-3000-150 rpm = CH20, 3000 pounds compaction pressure, 150 rpm.

20-3000-100 rpm = CH20, 3000 pounds compaction pressure, 100 rpm.

Glucotrol-50rpm = Glucotrol XL push pump osmotic tablet, 50 rpm.

20-3000-50 rpm = CH20, 3000 pounds compaction pressure, 50 rpm.
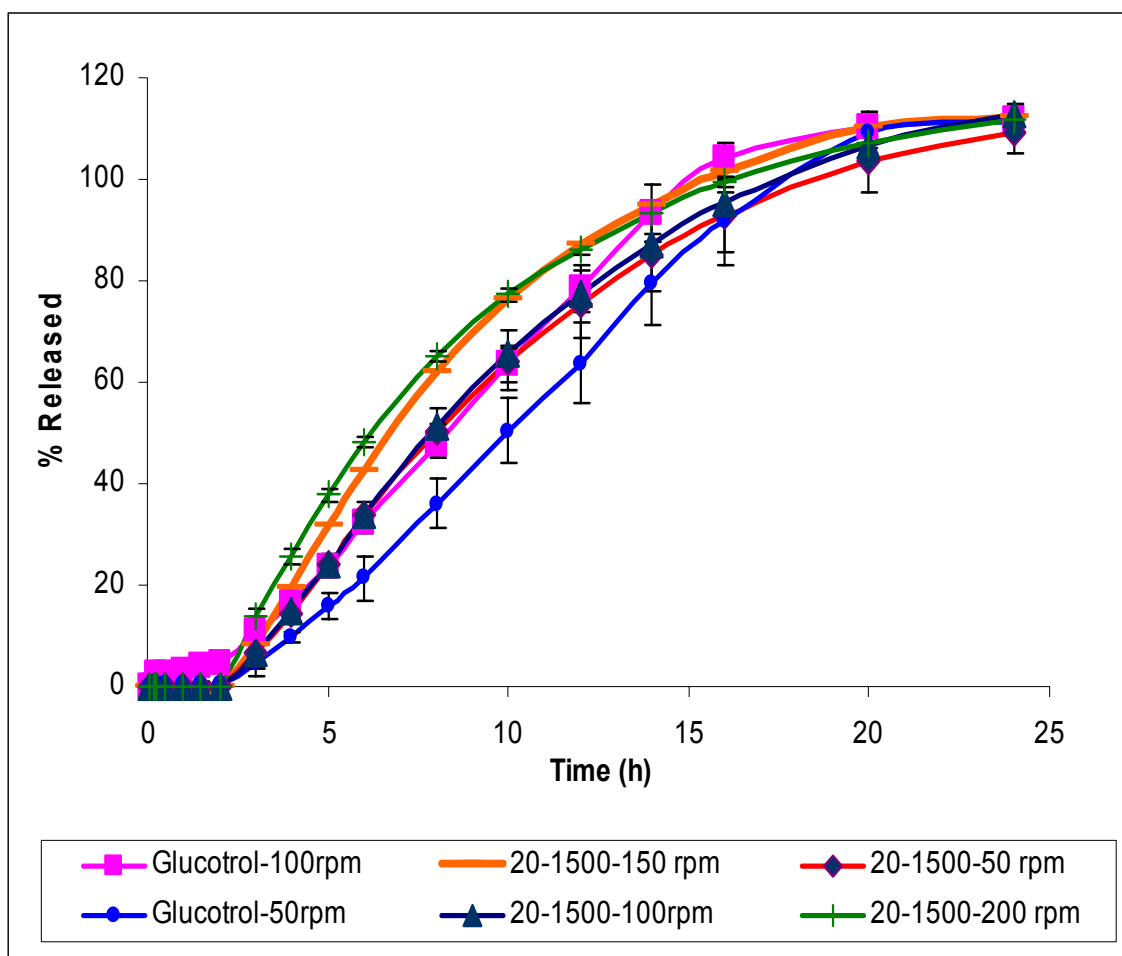
Figure 4.19: Effect of paddle speeds on glipizide release from CH20, 1500 pounds, 110% glipizide

Glucotrol-100 rpm = Glucotrol XL push pump osmotic tablet, 100 rpm.

20-1500-150 rpm = CH20, 1500 pounds compaction pressure, 150 rpm.

20-1500-50 rpm = CH20, 1500 pounds compaction pressure, 50 rpm.

Glucotrol-50rpm = Glucotrol XL push pump osmotic tablet, 50 rpm.

20-1500-100rpm = CH20, 1500 pounds compaction pressure, 100 rpm.

20-1500-200 rpm = CH20, 1500 pounds compaction pressure, 200 rpm.

Formulation CH20 at 2000 pounds compression pressure with 150 and 200 rpm paddle speeds gave the same drug release but higher than paddle speeds at 100 rpm and 50 rpm (Figure 4.17). For CH20, 3000 lbs compaction pressure, the higher the paddle speed the faster the drug release (Figure 4.18). Interestingly, the dissolution patterns of CH20 tablets made under 2000 lbs and 3000 lbs compaction pressure are close to those of Glucotrol XL at 50 and 100 rpm paddle speeds respectively. Dissolution curves of CH20 tablets made under 1500 lbs compaction pressure were not different at 50 and 100 rpm paddle speeds and matched the reference Glucotrol XL at 100 rpm and were close to the reference at 50 rpm paddle speed (Figure 4.19). At 150 and 200 rpm paddle speeds, the dissolution patterns of CH20 tablets made under 1500 lbs were similar and significantly higher than that at 50 and 100 rpm paddle speeds but still close to reference Glucotrol XL (Figure 4.19). For 150 and 200 rpm paddle speeds all tablets produced under all compression pressures, the variation from the reference Glucotrol XL is higher in the central part of the dissolution curves. This is due to an increased drug release at the beginning of the dissolution process, followed by a gradual slow decrease in the dissolution rate. While there is concave curvature for the CH20 dissolution curves shown in Figure 4.19, it should be noted that the amount of such curvature is far less than is typical for ethylcellulose coated drug beads and the slope is nearly linear in the 3 hour to 16 hour section for some curves (50 and 100 rpm), i.e., essentially zero-order drug release. Even though glipizide was released faster from CH20 tablets compacted at 1500 and 3000 lbs pressures at 150, and 200 rpm paddle speeds than that of reference Glucotrol XL, the drug release in each interval from 3h to 16 h is close to release of

reference Glucotrol XL and this portion of the drug dissolution curve is most influential on Cmax.

Effect of compression pressures and paddle speeds on drug release

Two-way ANOVA results of the influence of compression pressures and paddle speeds on %release16 and release rate are summarized in Tables 4.11 and 4.12.

Table 4.11: ANOVA table for effect of compression pressures and paddle speeds on %release 16 from CH20

	DF	Sum of square	Mean square	F value	Pr (F)
Model 4.2: %release16 versus pressure and paddle speed					
Pressure	2	57.166	28.583	1.156	0.328
Speeds	3	1794.513	598.171	24.193	< 0.001
Residual	30	741.763	24.725		
Model 4.3: %release16 versus interaction between pressure and paddle speed					
Pressure	2	57.166	28.583	2.174	0.136
Speeds	3	1794.513	598.171	45.488	< 0.001
Pressure*Speeds	6	426.163	71.027	5.401	0.001
Residuals	24	315.600	13.150		

As seen in Table 4.11, model 4.3 is more appropriate to represent %release 16 data when comparing model 4.2 and 4.3. The interaction term is significant and should be kept in the model. There is convincing evidence that the effect of compression-pressure on %release16 depends on paddle speeds (P-value < 0.01). At higher compression

pressure, the paddle speeds have more impact on %release16 than at a low compression

pressure (Figures 4.17, 4.18 and 4.19).

Table 4.12: ANOVA table for effect of compression pressures and paddle speeds on release rate from CH20

	DF	Sum of square	Mean square	F value	Pr (F)
Model 4.4: release rate versus pressure and paddle speed					
Speeds	3	8.395	2.798	26.376	< 0.001
Pressure	2	0.135	0.068	0.637	0.536
Residual	30	3.183	0.106		
Model 4.5: release rate versus interaction between pressure and paddle speed					
Pressure	2	0.135	0.068	1.026	0.374
Speeds	3	8.395	2.798	42.448	< 0.001
Pressure*Speeds	6	1.601	0.267	4.047	0.006
Residuals	24	1.582	0.066		

Results in Table 4.12 are consistent with results of Table 4.11 and also indicate

that the effect of compression pressures on release rate strongly depends on the paddle

speeds (P value = 0.006, model 4.5 in Table 4.12). At higher compression pressure the

paddle speeds have more impact on release rate than at a low compression pressure

(Figures 4.17, 4.18 and 4.19). Since both models 4.3 and 4.5 developed for %release16

and release rate included an interaction term, no general conclusion can be drawn across

all pressures since the effect of compression pressures on release rate depends on speed.

Residual plots of models 4.3 and 4.5 are seen in Appendices 2 (Figure A.2) and 3 (Figure A.3), respectively.

Effect of coating on tablets

To produce more elegant tablets and mask their appearance, a coating agent (Opadry® White) was used to coat these tablets. The effect of this coat on CH20-tablets was evaluated and is shown in Figures 4.20 and 4.21.

At 4% weight gain, for tablets produced by a compaction force of 1500 pounds, dissolution curves were the same at 100 rpm and 150 rpm paddle speeds but they are a little lower than the dissolution curve of uncoated tablets at the same paddle speeds, respectively (Figure 4.20). At 200 rpm paddle speed, drug release was the same as uncoated tablets, but drug release was higher than at 100 and 150 rpm paddle speeds for the same coated tablets.

Beads compressed into tablets, 3000 pound compression pressure, were coated with Opadry® of 2.5% weight gain. Dissolution curves of these tablets were close to dissolution curves of uncoated tablets at all paddle speeds, 100, 150 and 200 rpm paddle speeds respectively as shown in Figure 4.21. The 4% weight gain of Opadry® stabilized dissolution curves at 100 and 150 rpm paddle speeds but reduced drug release a little, maybe due to reduction of disintegration time of tablets. The 2.5% weight gain of Opadry® (Opadry) did not affect the drug release.
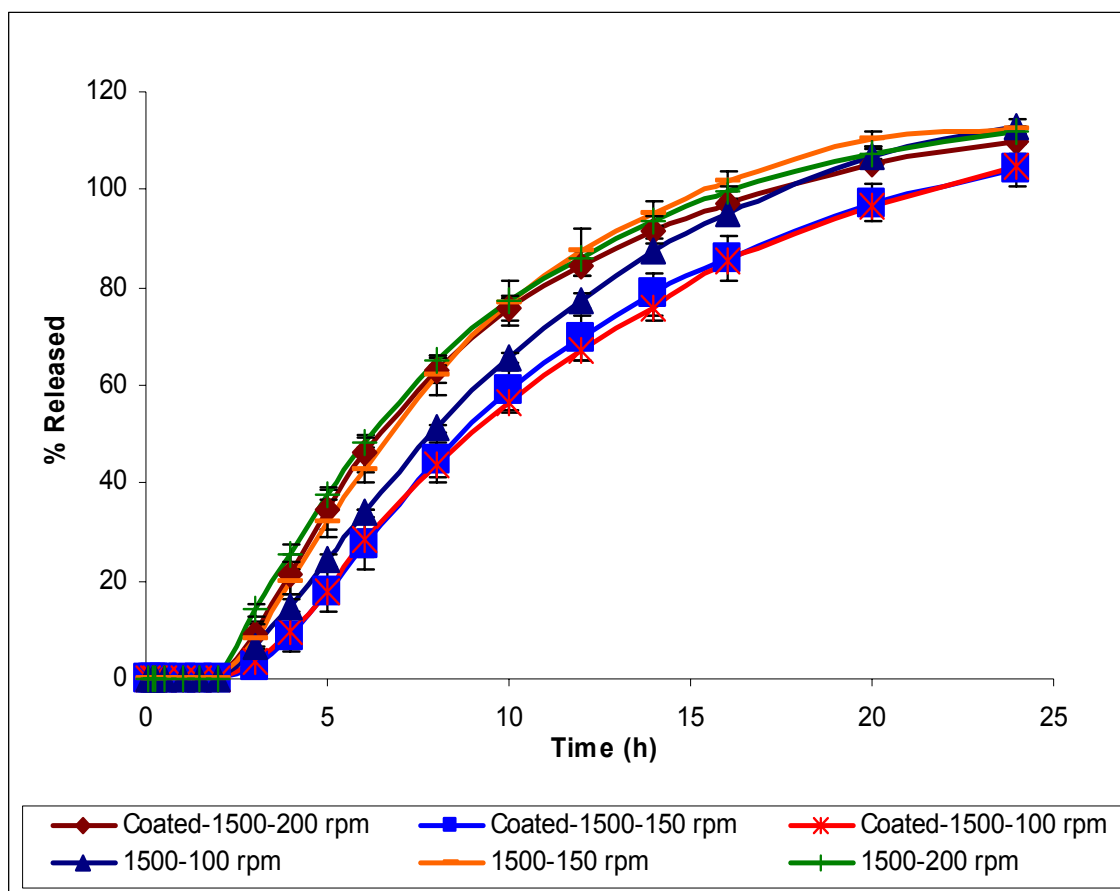
Figure 4.20: Effect of 4% Opadry coat on glipizide release from coated CH20 tablets, 1500 lbs

Coated-1500-200 rpm = CH20, coated with Opadry White - 4% weight gain, 200 rpm.

Coated-1500-150 rpm = CH20, coated with Opadry White - 4% weight gain, 150 rpm.

Coated-1500-100 rpm = CH20, coated with Opadry White-4% weight gain, 100 rpm.

1500-100 rpm = CH20, uncoated, 100 rpm.

1500-150 rpm = CH20, uncoated, 150 rpm.

1500-200 rpm = CH20, uncoated, 200 rpm.
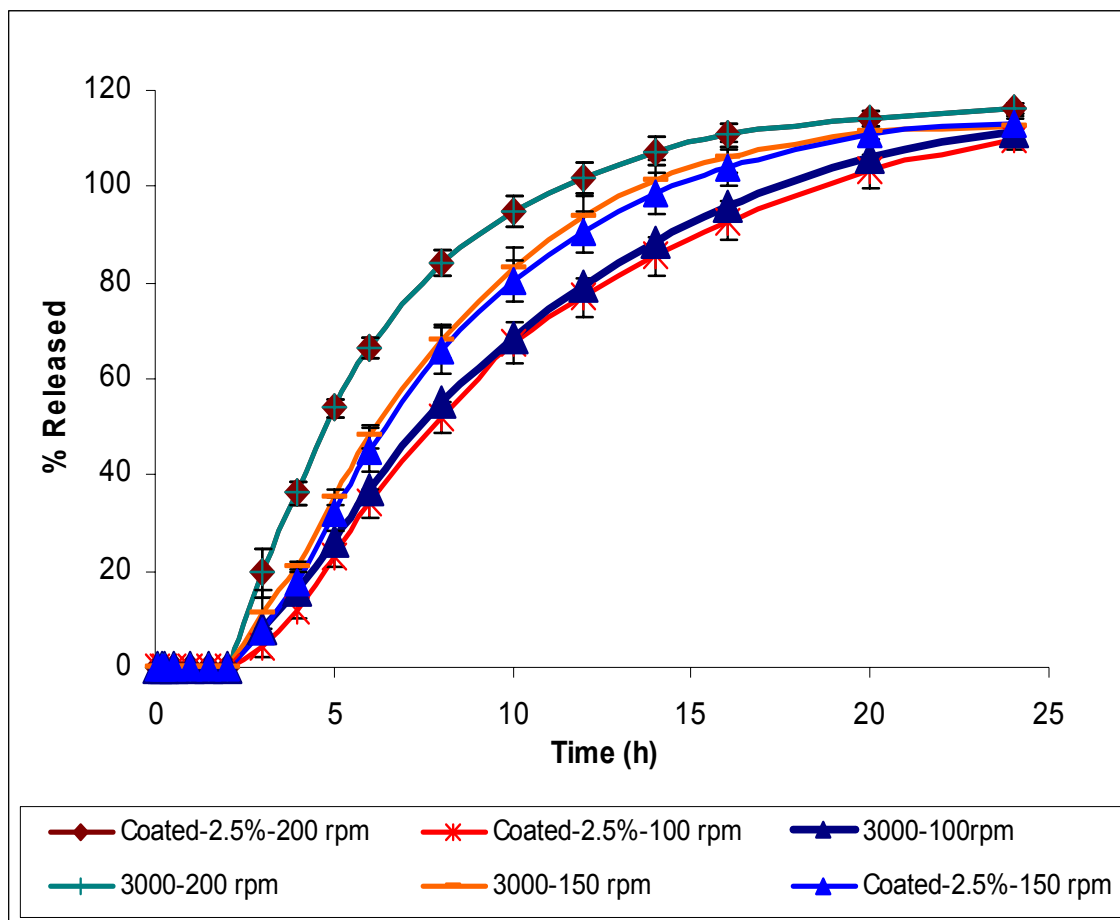
Figure 4.21: Effect of Opadry coat, 2.5% weight gain on glipizide release from coated CH20 tablets, 3000lbs

Coated-2.5%-200 rpm = CH20, 3000 pounds compaction pressure, coated with Opadry White – 2.5% weight gain, 200 rpm.

Coated-2.5%-100 rpm = CH20, 3000 pounds compaction pressure, coated with Opadry White - 2.5% weight gain, 100 rpm.

3000-100 rpm = CH20, 3000 pounds compaction pressure, uncoated, 100 rpm.

3000-200 rpm = CH20, 3000 pounds compaction pressure, uncoated, 200 rpm.

3000-150 rpm = CH20, 3000 pounds compaction pressure, uncoated, 150 rpm.

Coated-2.5%-150 rpm = CH20, 3000 pounds compaction pressure, coated with Opadry White - 2.5% weight gain, 150 rpm.

Tablet coating with Opadry® with weight gain from 2.5-4% weight gain to mask the appearance should stabilize drug release from CH20-1500 lbs because it makes tablets stronger and covers compaction cracks of beads on the surfaces of tablets.

Comparison %release 16 and release rate between CH20, 1500 pounds pressure and Glucotrol XL at different paddle speeds

Two way ANOVA results for the comparisons of release rate and %release 16 between tablets (CH20, 1500 pounds and Glucotrol XL) at different paddle speeds are summarized in Tables 4.13 and 4.14, respectively.

Table 4.13: Two way ANOVA table for comparison of release rate between CH20, 1500 pounds and Glucotrol XL at different paddle speeds

	DF	Sum of square	Mean square	F value	Pr (F)
Model 4.6: Release rate ~ Gluco-CH20 + Speed + Gluco-CH20*Speed					
Gluco-CH20	1	0.122	0.122	0.951	0.344
Speed	3	2.041	0.680	5.303	0.010
Gluco-CH20*Speed	3	0.173	0.058	0.449	0.722
Residuals	16	2.052	0.128		
Model 4.7: Release rate ~ Gluco-CH20 + Speed					
Gluco-CH20	1	0.122	0.122	1.042	0.320
Speed	3	2.041	0.680	5.808	0.005
Residuals	19	2.225	0.117		

Gluco-CH20 = Tablets have two levels (Glucotrol XL versus CH20, 1500 lbs).

Table 4.13 shows there is little evidence that the effect of paddle speeds on release rate depends on tablets, Glucotrol XL or CH 20 compacted with a force of 1500 pounds (P-value = 0.722, model 4.6). Since the interaction term is not significant, this term was dropped and model 4.7 was fit. The effect of dissolution paddle speeds on drug release rate is highly significant (P-value = 0.005, model 4.7). The drug release rate from CH20 compacted with a force of 1500 pounds pressure does not significantly differ from that of Glucotrol XL (P-value = 0.320, model 4.7).

Table 4.14: Two way ANOVA table for comparison of % release 16 between CH20, 1500 pounds and Glucotrol XL at different paddle speeds

	DF	Sum of square	Mean square	F value	Pr (F)
Model 4.8: %Release 16 ~ Gluco-CH20 + Speed + Gluco-CH20 *Speed					
Speed	3	445.406	148.469	5.910	0.007
Gluco-CH20	1	98.734	98.734	3.930	0.065
Gluco-CH20*Speed	3	79.756	26.585	1.058	0.394
Residuals	16	401.964	25.123		
Model 4.9: %Release 16 ~ Gluco-CH20 + Speed					
Speed	3	445.406	148.469	5.856	0.005
Gluco-CH20	1	98.734	98.734	3.894	0.063
Residuals	19	481.720	25.354		

Gluco-CH20 = Tablets have two levels (Glucotrol XL versus CH20, 1500 lbs).

Table 4.14 shows there is little evidence that the effect of paddle speeds on %release 16 depends on tablets, Glucotrol XL or CH 20 compacted with a force of 1500

pounds (P-value = 0.394, model 4.8). The interaction term was dropped and only main effects were kept in the model. Dissolution paddle speeds strongly affect mean %release 16 of drug (P-value = 0.005, model 4.9). There is suggestive evidence that there is a difference of mean %release 16 of drug between CH20, tablets compacted with a force of 1500 pounds, and Glucotrol XL (P-value = 0.063, model 4.9). Note that convolution results (shown later) indicate that the suggestion of statistical difference of mean %release 16 of drug between CH20 tablets compacted with a force of 1500 pounds and Glucotrol XL is not a matter of clinical importance, which is often the case in formulation. The main value of knowing the presence or absence of statistically significant formulation effects on drug dissolution is to guide the formulator in optimizing a robust formulation.

Convolution results:

Using convolution calculations and assuming a linear relationship between dissolution and absorption for both Glucotrol-XL and CH20, tablets compacted with a force of 1500 lbs, a simulation was used to predict the drug concentrations versus time curves for these two products in a bioavailability study. Results are presented in Table 4.15 and Figure 4.22.

Tablet 4.15: Simulated Tmax, Cmax, and AUC_{0-24h} of Glucotrol-XL and CH20 at 1500 lbs

Speed of paddle	Tmax (h)		Cmax (mcg/l)		AUC_{0-24h} (mcg.h/l)	
	Glucotrol-XL	CH20	Glucotrol-XL	CH20	Glucotrol-XL	CH20
50 rpm	14	10	197.49	193.98	3002.95	2978.01
100 rpm	14	10	208.34	198.24	3033.20	3060.53
150 rpm	12	10	210.17	222.91	3112.15	3172.78
200 rpm	14	8	213.79	220.39	3121.10	3125.88

Convolution was conducted for the USP paddle method at various dissolution paddle speeds after adjustment of bioavailability. Bioavailability of immediate release tablets in healthy people is 0.806 (Pentikainen et al., 1983) and relative bioavailability of Glucotrol XL to immediate release tablet is 0.81 (Chung et al., 2002). Bioavailability of Glucotrol XL for convolution was therefore calculated to be 0.65. As seen in Table 4.15 simulated Cmax and AUC_{0-24h} of CH20 tablets compacted with a force of 1500 pounds differ less than 10% of simulated Cmax and AUC_{0-24h} of Glucotrol XL respectively at all paddle speeds. In all cases, using predicted Cmax and AUC_{0-24h}, bioequivalence is predicted for all the dissolution patterns of CH20 even when dissolution patterns were far from that of Glucotrol XL at 50, 150 an 200 rpm paddle speeds.
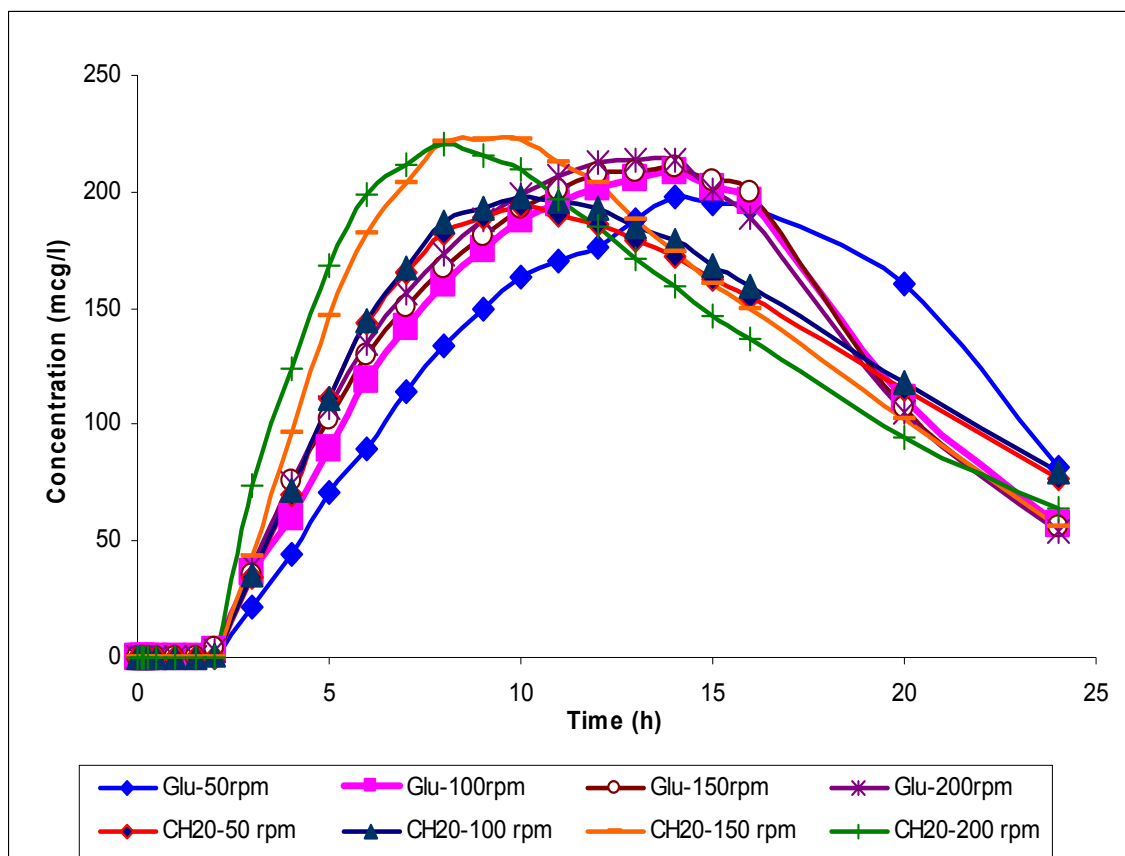
Figure 4.22: Simulated plasma concentrations versus time curves of Glucotrol XL tablets and CH20 tablets produced with 1500 pound-pressure

Glu-50rpm = Glucotrol XL push pump osmotic tablet, 50 rpm.

Glu-100rpm = Glucotrol XL push pump osmotic tablet, 100 rpm.

Glu-150rpm = Glucotrol XL push pump osmotic tablet, 150 rpm.

Glu-200 rpm = Glucotrol XL push pump osmotic tablet, 200 rpm.

CH20-50 rpm = CH20, 1500 pounds compaction pressure, 50 rpm.

CH20-100 rpm = CH20, 1500 pounds compaction pressure, 100 rpm.

CH20-150 rpm = CH20, 1500 pounds compaction pressure, 150 rpm.

CH20-200 rpm = CH20, 1500 pounds compaction pressure, 200 rpm.

CONCLUSIONS

A novel formulation of glipizide was developed comprising compression of four-layer coated beads into tablets that has advantages of keeping sustained-release characteristics and proper lag time, and providing approximately zero-order drug release, and drug release that is nearly independent of paddle speeds 50 and 100 rpm. The amount of binding and disintegrate ingredients can be adjusted to produce appropriate disintegration time for tablets. With 22.22% weight gain of binder:disintegrant (lactose:Explotab) = 2:1, beads-compressed into tablets disintegrated within 3 hours, and individual coated particulates controlled drug release. The inclusion of HPMC in the formulation as a bead hardening agent plays a role in manufacturing as well as keeping and facilitating desirable drug release with appropriate weight gain of 6.54%. There are two Surelease layers and both are important for controlling release, with the predominate sensitivity being in a Surelease-drug layer. Tablet compression pressures between 1000 and 3000 pounds have a little effect on drug release at the dissolution paddle speed of 100 rpm. At other paddle speeds of 50, 150, and 200 rpm, the greater the tablet compression pressures between 1500 and 3000 pounds the more sensitive drug release was to paddle speeds. At 150 and 200 rpm paddle speeds significantly increased drug release rate occurred from CH20 tablets compacted at 1500 pounds pressure compared with 50 and 100 rpm. There is convincing statistical evidence that the interaction between tablet compression pressure and paddle speed was associated with %release 16 and drug release rate (P-values < 0.01).

CH20 is a novel formulation of glipizide developed comprising compression of four-layer coated beads into tablets. It is possible to obtain essentially nearly zero-order drug release in two pH media at stirring speeds of either 50 or 100 rpm with the USP paddle stirring method.

The final formulation in this study contains four layer beads: the drug layer of 71.25 g of sugar beads overcoated with 2.5 g of glipizide and 3.75 g of solid Surelease; the hardening layer of 5 g of HPMC; the controlled release layer of 7.5 g of ratio solid content of Surelease:lactose = 100:7; and outmost layer of 20 g of lactose:Explotab = 2:1 Then beads were compressed into tablets containing 11mg of glipizide with 1500 pounds of compression pressure. This formulation matched the dissolution pattern of Glucotrol-XL osmotic pump tablets with paddle method in two pH medium method at 100 rpm, and dissolution patterns of Glucotrol XL and CH20 tablet were close to each other at 50, 150 and 200 rpm paddle speeds. The release rate and %release at 16 hours of CH20 did not differ from that of Glucotrol XL at all paddle speeds (P-values > 0.05). CH20 tablet is predicted by convolution simulation to be bioequivalent to Glucotrol-XL *in vivo*.

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CHAPTER 5

Verapamil Sustained Release: New Formulation and Convolution

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ABSTRACT

A novel bead formulation of verapamil hydrochloride was developed comprising a combination of extrusion and spheronization to produce a relatively high drug load, followed by coating of the bead with an insoluble polymer (ethylcellulose) that contains a water soluble channeling agent (lactose), thus allowing the application of a sufficiently thick outer coating that is uniform and robust without "shutting down" release of the relatively insoluble drug.

The effects of surfactant (Tween® 80), disintegrant (Explotab®), channeling agent, (lactose), and weight gain were investigated. Tween® 80 influenced release rate$_{14}$ (the drug release rate calculated up to 14h) significantly (P < 0.001), with the more Tween® 80 included the higher the release rate$_{14}$. Also, the greater the coating weight gain the lower the release rate$_{14}$. Presence of Explotab® is strongly associated with release rate$_{14}$ (P<0.001). The effect of lactose on release rate$_{14}$ convincingly depends on the weight gain of coating applied (P<0.001).

Release mechanism and model for dissolution rate constant were investigated. Dissolution rate constants were fit using three models, first order, square root order, and zero order models. For the customary entire dissolution curve, from time zero to 24 h, a first order release model is the best to represent dissolution data of the new verapamil HCl coated beads. However, from time zero to 14 h, zero order release model is closer to real data than other models for both Verelan PM capsules and new verapamil HCl formulated beads. The release mechanism not only is controlled by diffusion through the

barrier film itself, as well as lactose channels, but also depends on bead size. Osmotic effects are also possible influences on the mechanism of release from verapamil HCl beads coated with ethylcellulose.

New formulation OSU2 provided the unexpected benefit that by adjusting both coating thickness and ethylcellulose/lactose ratio, it is possible to obtain essentially non-agitation sensitive and zero-order drug release up to 14 hours in either KCl or two pH media, at stirring speeds of either 75 or 200 rpm with either the USP basket or USP paddle stirring method. No references have been found of any other drug bead formulations possessing this unique set of characteristics.

OSU2, the preferred formulation for this study, contains 200 mg of verapamil HCl, 85 mg of Avicel® pH 101, 15 mg of Polyethylene oxide W.M. 100000, bead mesh size 12-18, extruded and spheronized to make beads, then coated with 6.5% weight gain with ratio of solids contents in Surelease®:lactose = 100:5. This formulation matched the dissolution pattern of Verelan-PM capsules in both the basket method and paddle method in KCl medium, and two-pH medium method at different speeds. OSU2 is predicted by convolution simulation to be bioequivalent to Verelan-PM *in vivo*.

INTRODUCTION

It is well known that sustained release dosage forms have many advantages over immediate release dosage forms such as maintaining nearly constant concentrations in plasma for a longer time, reducing side effects of drug, reducing frequency of drug administration, and having a higher patient compliance. Sustained-release dosage forms can be formulated into single unit dosage forms like tablets or capsules, or multiparticulate dosage forms like pellets or beads. Multiparticulate dosage forms are becoming an increasingly popular method for providing controlled release of drugs in the gastrointestinal tract (GI), partly because they have relatively reproducible upper GI transit profiles and partly because they minimize the risk of dose dumping (Ozturk et al., 1990), and thus less probability of toxicity (Bodmeier, 1997; El-Gazayerly et al., 2004; and Vergote et al., 2002). Additionally, drug bioavailability of multiparticulate dosage forms can be increased when compared with single unit dosage forms and drug release can be less variable because of better distribution of multiparticulates along the gastrointestinal tract (Vergote et al., 2002). Inter- and intra-individual variations in bioavailability, caused for example by food effects, also are reduced (Bodmeier, 1997). Further more, pellets or beads can be programmed to release drug with desired profiles, such as proper lag time drug release profiles or pulse drug release profiles.

Multi unit dosage forms can be pellets or beads coated with insoluble polymers such as methylcellulose, ethylcellulose, propylcellulose or shellac for controlled release. Among these polymers, ethylcellulose is the most widely used water-insoluble polymer

in film coating and controlled-release membranes. The application of water-based dispersion of ethylcellulose is commonplace in pharmaceutical industry and is the method of choice for film coating (Sadeghi et al., 2003). Aqueous latex dispersions of ethylcellulose, like Aquacoat® (Aquacoat) or Surelease® (Surelease), are preferred to form controlled release coatings on pharmaceutical dosage forms. In the aqueous dispersion, the film-forming polymer latex consists of a colloidal dispersion of discrete polymer. To form a continuous film, the aqueous phase is evaporated resulting in coalescence of the colloidal polymer spheres (Ozturk et al., 1990). An ethylcellulose membrane can be formed by the deposition of a commercially available latex onto pellets to form a porous and non-discriminating membrane (Nesbitt et al., 1994).

Although differences exist in the manufacturing processes of Surelease and Aquacoat, the major difference between Surelease and Aquacoat is the plasticizer present in Surelease and the need to add a plasticizer to Aquacoat (Shah et al., 1994).

"The properties of Aquacoat ECD-30 films also are mainly determined during the heat treatment, after the coating process, whereas the coalescence and film formation of Surelease occurs to a certain extent during the coating process" (Arwidsson et al., 1991).

The necessity of curing after aqueous latex dispersion coating is still disputed among research articles. Most authors agree curing is needed after Aquacoat coating to reach constant profiles of dissolution. Shah et al. (1994), in a study of factors affecting the kinetics of cilazapril from beadlets coated with aqueous and nonaqueous ethylcellulose-based coating, indicated the curing time of Aquacoat-based colloidal beadlets exhibited a significant influence on release rates. The release rate of cilazapril

from beadlets coated with Aquacoat was significantly reduced after 12 h curing at 45^0C, and stabilized after 24 h curing at 45^0C. In comparison, after coating with Surelease the release rate before curing was the same as after 72 h curing at 45^0C. These results occur because coalescence of latex particles from Aquacoat (ethylcellulose pseudolatexes) is often incomplete after initial application of the coating, and a curing step at an elevated temperature is recommended with Aquacoat to accelerate further and complete coalescence, and form a homogenous film (Arwidsson et al., 1991). Unplasticized ethylcellulose has a Tg (glass transition temperature) of 125-130°C. At 24% dibutylsebacate, the Tg is reduced to about 44°C and with 24% triethylcitrate the Tg is about 35.5°C (Dressman et al., 1995). Thus, addition of plasticizing agents reduces curing temperature. Heating the film to above its glass transition temperature facilitates polymer movement and relaxation. Observed storage dependent release profiles might be a result of improper or inadequate processing conditions leading to lack of completeness of the coalescence process. Curing often leads to consistent release profiles under all conditions of storage even though curing may increase or decrease drug release rate. Dressman et al. (1995) found an appropriate curing (60^0C for 2 h) of phenylpropanolamine hydrochloride pellets overcoated with Aquacoat results in a faster drug release, and the release profile was not affected by usual time/temperature storage conditions or by the pH of the release medium. Sadeghi et al. (2003) showed while metoclopramide hydrochloride pellets coated with 12% Surelease E-7-7050 over a seal-coat of 2% hydroxypropyl methylcellulose exhibited a marked increase in release rate after curing at 60^0C for 24 h, diclofenac sodium pellets coated with the same polymers

and same amounts of polymers exhibited a much more stable release rate after curing at 60^0C for 24 h.

The reason curing may increase drug release rate is not obvious. Sadeghi et al. (2003) concluded that release behavior of metoclopramide HCl was probably due to an interaction between the cationic metoclopramide and the anionic ammonium oleate in Surelease. In contrast, curing of coated pellets in an oven can cause a decrease of drug release rates to an endpoint. In this case, the interdiffusion of the (pseudo-) latex particles is not completed without the curing process. Frohoff-Hulsmann et al. (1999, part 1) found the curing temperature, which is necessary to reach a constant and slow release rate of theophylline from Aquacoat coated pellets, decreases with increasing amount of plasticizer.

On the other hand, when Surelease films were allowed to coalesce at 70^0C the original amount of plasticizer in Surelease was sufficient for complete coalescence under the conditions studied (Arwidsson et al., 1991). As mentioned before, Shah et al. (1994) concluded that Aquacoat-coated pellets needed to be cured for 24 h for uniform release but pellets coated with Surelease do not need curing.

Release mechanism from ethylcellulose coated beads includes diffusion across the membrane and osmotically driven release, as summarized by many articles. In detail, drug release was affected by the nature of the plasticizers used (Kannikoski et al., 1984; Frohoff-Hulsmann et al., 1999-part 1; Opota et al., 1999), coating thickness, and viscosity grade of the ethylcellulose (Kannikoski et al., 1984), liquid inflow (Nesbitt et al., 1994;

Frenning et al., 2003), liquid efflux (Frenning et al., 2003), the ionic strength of the release medium (Frohoff-Hulsmann et al., 1999, part 1), drug load (Pinto et al., 1997; Opota et al., 1999), the porosity of the coating film (Narisawa et al., 1994; Ragnarsson et al., 1992), the drug solubility (Frenning et al., 2003; Nesbitt et al., 1994; Shah et al., 1994; Ragnarsson et al., 1992), the polymer/dissolution medium partition coefficient (Shah et al., 1994), the difference of osmotic pressure of the external dissolution medium and osmotic pressure generated inside the bead (Nesbitt et al., 1994; Ozturk et al., 1990; Narisawa et al., 1994; Dressman et al., 1995), the particle size (Ragnarsson et al., 1992; Nesbitt et al., 1994), interaction between the cationic drug and the anionic ammonium oleate (Sadeghi et al., 2003), and by an expansion of the film during drug release (Ragnarsson et al., 1992).

There are overwhelming numbers and complex discussions regarding diffusion mechanisms of drug release through insoluble polymer membranes. The mechanism of drug release from pellets coated with Surelease and Aquacoat was different at different coating amounts. At lower coating amounts, imperfections exist in the film and release of drug appears to occur through water-filled pores. Even when coating amount is high, but the coating is not homogeneous and continuous but is punctuated with pores (Ozturk et al., 1990), then release via water-filled pores still happens. Pores, and even cracks, can occur as a result of processing conditions under which coalescence of the pseudolatex particles is incomplete, or defects are produced (Ozturk et al., 1990). Transport of drug would then occur primarily through cracks or pores in the coating whenever pores remain high. Therefore, drug release rates are often dependent on solubility of drug at lower

ethylcellulose coating amounts (Shah et al., 1994). Zhang et al. (1991) studied change in release kinetics due to coating amounts at low amounts of 2-10% and high amounts of 12-20% Aquacoat for 16/18-mesh beads. They concluded at low coating amounts the drug release rate is constant based on the square root relationship of drug release versus square root of time and seems to be linear with coating amount. In the case of higher coating amounts, when the number of pores remained low or blocked, diffusion through the membrane is predominant (Shah et al., 1994; Kannikoski et al., 1984), and ionization and solubility of drug are both influential at higher coating amounts (Shah et al., 1994). Zhang et al. (1991) also indicated drug release from spheres with high amounts of coating should exhibit a zero order drug release, which appears to be proportional to the reciprocal of the coating thickness. Since all pores are blocked in high coating amounts, a film barrier predominately governs drug release. The drug must diffuse through the barrier, which can be related to drug permeability in the coating and the coating thickness. Pinto et al. (1997) using statistical moment analysis to elucidate drug release from ethylcellulose coated pellets found different stages of drug release. They concluded that at the beginning the release of drug is dependent on the drug itself. In an intermediate phase drug release mechanism and rate depends on the system, and finally when the matrix was partially depleted of the drug a first order mechanism was observed. Drug release profiles may also exhibit two phases. During a constant release phase, the release rate follows zero-order kinetics as long as the drug solution inside the membrane remains saturated and the membrane permeability for water and the drug salt remains unchanged (Ragnarsson et al., 1992; Nesbitt et al., 1994). When no more solid drug remains in the

pellet, the drug solution will gradually become diluted and the release rate will decrease. Ragnarsson et al. (1992) also noted that the percentage of total drug release during a declining phase was highly dependent on the solubility of the drug substance and the particle size was of no importance. With the same viewpoint, Pinto et al. (1997) pointed out several mechanisms are competing at the same time or sequentially in release of indomethacin from pellets coated with ethylcellulose. At the beginning, a diffusion process seems to occur for lower drug loads, whereas for the highest drug load a cube root mechanism predominated. At later stages, the release becomes dependent on the amount of drug remaining in the matrix, as suggested by the first order mechanism.

The presence of plasticizer plays a role in releasing drug. Two mechanisms of drug release were summarized by Ozturk et al. (1990). The first mechanism is solution/diffusion through a continuous plasticized polymer phase, when the plasticizer content is low and the film is complete. This mechanism assumes the polymer to be a continuous phase in which the plasticizer and other additives are dispersed uniformly. Most likely, the drug molecules diffuse through the molecular sized openings between the cross-linked polymer chains "in a process known as hindered molecular diffusion" (Ozturk et al., 1990). The second mechanism is solution/diffusion through plasticized channels. When the plasticizer is not homogeneously distributed in the film, and when the plasticizer content is high, the plasticizer may form a continuous phase in the form of patched channels. If the solubility of the drug in the plasticizer is higher than that in water, it is possible that the drug would be preferentially transported through such plasticizer channels (Ozturk et al., 1990).

In addition to diffusion mechanisms, osmotically driven release were proposed by many authors like Ozturk et al. (1990), Narisawa et al. (1994), Dressman et al. (1995), and Nesbitt et al. (1994) This is a well known process for porous membranes, when there is sufficient osmotic pressure generated by the core material (Ozturk et al., 1990). Nesbitt et al. (1994) showed each Aquacoat coated pellet works like a mini osmotic pump with many orifices (orifices are pores with diameters of smaller than 1 μm for sugar beads loaded with FD &C red dye #40 overcoated with Aquacoat or 5-10 μm for sugar beads loaded with diphenhydramine HCl, pseudoephedrine HCl and FD &C red dye #40 overcoated with Aquacoat) and releases the substrates through water-filled channels. The energy to drive the system was supplied by osmotic pressure differences generated between internal medium in the coated pellets and external dissolution medium. Ragnarsson et al. (1988) studied the effect of a membrane of ethylcellulose and hydroxypropylmethylcellulose (proportion 3:1) on drug release from three size fractions of small spherical pellets. They found that although release rate was shown to be markedly affected by osmotic pressure, evaluation of release kinetics did not reveal osmotic pumping to be the major mechanism for the release. Rather, diffusion appears to be most important for drug release from the investigated formulations. Lippold et al. (1999) investigated the release of the hydrophilic etofylline and the lipophilic propyphenazone from pellets coated with Aquacoat® ECD-30 and 20% dibutyl sebacate as plasticizer. They indicated drug release from coated pellets is a function of pH. In acidic media with pH <6, drug release from these coated pellets proceeds by a partition mechanism, and the partition mechanism is not influenced by the osmotic pressure

difference between the release medium and the saturated solution within the diffusion pellets. However, Narisawa et al. (1994) showed the driving force for drug release from porous ethylcellulose film-coated beads was mainly an osmotic pumping mechanism, irrespectively of film porosity. Ozturk et al. (1990) tested the hypothesis that release occurs via an osmotically driven mechanism. They performed dissolution experiments in urea solutions with different osmolarities and concluded that increasing the osmotic pressure in the dissolution medium caused a decrease in the rate of release by about a factor of 2.5 at each coating amount for phenylpropanolamine HCl pellets.

Drug release from ethylcellulose coated beads can also be a function of pH even for drugs that do not ionize. Lippold et al. (1999) studied release of the hydrophilic etofylline and the lipophilic propyphenazone from pellets coated with Aquacoat® ECD-30 and 20% dibutyl sebacate as a function of pH. They concluded during contact with an acidic solution, ethylcellulose chains of adjacent pseudolatex particles are able to interdiffuse further, with water acting as an additional plasticizer.

"Consequently, adjacent polymer particles are anchored to each other so strongly that the dissociation of the acidic groups of the ethylcellulose which occurs when the pH increases (pK_a=6.2), will no longer cause the opening of the hydrophilic pathway by the formation of pores and cracks" (Lippold et al., 1999).

At pH > 6 an additional hydrophilic pathway exists, with rather high drug release rates and increased permeability for hydrophilic compounds and higher water uptake of the coating (Lippold et al., 1999) as a result of dissociating carboxyl groups in the ethylcellulose. This information suggests that dissolution studies should involve at least

two-pH medium systems with treatment in gastric fluid followed by intestinal fluid to mimic physiological conditions.

To produce multiple particulate dosage units, three methods are commonly used. The first method involves granules from well-known wet and dry granulation methods. Wet-granulation granules have irregular shape (Kannikoski et al., 1984), thus surface area of these granules is quite different from spheronized pellets. Consequently it may be difficult to control thickness and uniformity of coating layer for batches if coating is based on weight gain. The second method is to load drug on nonpareil sugar beads using spraying coater or coating pan, which can be used to apply low dose drugs. Formulation of beads in a capsule for low dose drugs can often involve applying a mixture of drug and a binder in a continuous process of spraying the mixture onto nonpareil sugar beads in a spray coater. In this process the drug and binder mixture dries on the surface of the beads and forms a homogenous mixture on the outside of the sugar beads. In the process the core beads increase in size as the drug and binder are applied. For a relatively large dose of drug, such as 200 mg or more, this process may result in beads that are too large to easily fit into a capsule that is convenient to swallow. The third method, and an alternative method for bead formulation, which was chosen for this research, is to produce beads by extrusion and spheronization. In this case a homogeneous mixture of drug and binder is kneaded together with water and then extruded to produce short rods which are spun in a spheronizer yielding a mixture of smooth rods and spheres. Depending on the conditions, the product may be mostly rods or mostly spheres. An advantage of this method is that very little filler may be required, and thus relatively large

drug loads can be prepared in a relatively small number of beads. Larger amounts of drug loading can then fit into smaller capsules which are more convenient to swallow.

For development of a new beads filled into capsule, verapamil was chosen as a model drug. Verapamil [2,8-bis (3,4-dimethoxyphenyl)-6-methyl-2-isopropyl-6-azaoctanitrile] (Eichelbaum et al., 1979), a calcium-channel antagonist, was introduced for treatment of angina in the early 1960's. Verapamil acts basically through specific inhibition of the slow calcium–mediated inward current in excitable tissue. Verapamil is especially useful in supraventricular, tachyarrhythmias. It has also been used to treat angina pectoris and hypertension. Verapamil is administered as a racemic mixture of the R and S enantiomers. In the market, immediate release dosage forms usually contain 40 mg or 80 mg of verapamil, and sustained-release (SR) dosage forms contain 120, 240, or 360 mg of verapamil in tablet or capsule forms. Usual dosage of verapamil is 240-480 mg daily given in 3 or 4 divided doses.

In the United States, verapamil is approved for treatment of angina at rest and effort-associated angina. Popular sustained release verapamil products in the US market include Covera-HS tablets and Verelan PM capsules. In Europe verapamil has been used extensively for antianginal and antiarrhymic purposes. A slow-release preparation available in Europe (Isoptin Retard-Knoll AG) has been given twice a day to achieve effectiveness (Dunn et al., 1985).

In normal subjects plasma protein binding of verapamil was about 89.6% and was concentration independent over a range of 35 to 1,557 ng/ml (Keefe et al., 1981) and

binding was not affected by addition of verapamil's major metabolite, norverapamil, in ratios of 1.2 to 26.3. Plasma protein binding of verapamil was not altered in the post-surgical state or in dialysis patients. However, there was a small increase in protein binding of verapamil in renal insufficient patients ($p<0.05$), which increased an average of 17% in the free drug concentration but was probably not clinically significant (Keefe et al., 1981). Verapamil is bound to α_1-acid glycoprotein (AAG) as well as albumin. On average verapamil is bound some 86% to plasma constituents other than AAG. Protein binding of verapamil was also not affected by end-stage renal failure, or the postoperative state in coronary bypass graft patients (Keefe et al., 1981).

Verapamil undergoes hepatic metabolism before renal excretion. Only a small amount (3 to 4%) of an oral dose is excreted as unmetabolized drug. Eichelbaum et al. (1979), studied metabolism of DL-[^{14}C] verapamil in man. They concluded that the N-dealkylation of tertiary amine proceeds at a much higher rate than the N-dealkylation of the secondary amine metabolites to primary amine metabolites. Approximately 10 times more of the metabolites formed from the tertiary amine verapamil are secondary amines than are primary amines (Eichelbaum et al., 1979). The major metabolite step involves N-dealkylation with further metabolism by O-demethylation and subsequent conjugation. One of the metabolites is norverapamil, the only metabolite with pharmacological activity with 10 to 20% of the potency of verapamil as a vasodilator in the animal model. Between 67 and 71% of ^{14}C administered in verapamil was excreted in the urine within 5 days following oral administration of an aqueous solution of DL-[^{14}C] verapamil (Eichelbaum et al., 1979).

Speders et al. (1989) studied the efficacy and safety of verapamil slow release 240 mg (Isoptin RR) in 4247 patients with mild, moderate, or severe hypertension. They found adverse effects were reported by 480 of 4247 patients (11.3%). Treatment was discontinued in 5.1% (in 3.27% due to side effects). Among side effects reported, constipation was the predominant adverse reaction, whereas ankle edema-known as a rather frequent side effects of other calcium antagonists was rare. Bradycardia occurred in only 0.31%; none of the patients developed second- or third-degree atrioventricular block.

Reiter et al. (1982) investigated sustained intravenous verapamil infusion in nine patients. They found no significant side effects such as clinically significant hypotension, bradycardia, or arrhythmia during sustained infusion of verapamil. Only one patient developed a mild headache 3 hours after the start of the infusion of verapamil (Reiter et al., 1982).

Following intravenous administration verapamil exhibits two compartment open model pharmacokinetics (Mooy et al., 1985; McAllister et al., 1982; Reiter et al., 1982; Woodcock et al., 1981) or 3 compartmental pharmacokinetic characteristics (Freedman et al., 1981), with elimination only from the central compartment. For oral administration, the most appropriate model for an immediate release dosage form was a two-compartment model with first order input (Ahmed et al., 1991; Meredith et al., 1985).

Administration of 10 mg of verapamil as a single intravenous dose over 2 minutes in a study by Reiter et al. (1982) resulted in peak plasma verapamil concentrations that occurred within 3 minutes after the start of drug administration that varied widely (range

116 to 752 ng/ml; mean 426). The volume of distribution (central compartment) was equal to 10.8 liters and clearance was equal to 47.6 liters/h.

Most pharmacokinetic parameters for verapamil in normal subjects are the same after single intravenous and oral doses. Verapamil clearance (Cl) was lower after intravenous than after oral drug (p<0.05), although the difference was small (meanCl$_{oral}$-meanCl$_{intravenous}$ = 0.127 l/h/kg) (McAllister et al., 1982). After oral verapamil there was a dose-dependent increase in the peak drug plasma concentrations, with the C$_{max}$ after 120-mg oral dose approximately equivalent to that after 10-mg IV dose. Tmax did not differ substantially among the oral-tablet doses, averaging 2.2 hours. Bioavailability of verapamil after administration of tablets was of the same order of magnitude for different doses, ranging from 18.0 to 20.4% (McAllister et al., 1982). Absorption of verapamil from oral aqueous solutions and tablets has been shown to be 92% when measured in the portal vein. Thus, low F is likely due to extensive first-pass metabolism. In patients with liver disease, F is raised to 38% and is increased further to 82% after mesocaval shunting (Freedman et al., 1981). Intersubject variation after an intravenous dose was 14%, compared to 36% after a single oral dose in the same subjects (Freedman et al., 1981).

Mean apparent elimination t$_{1/2}$ after oral doses was 5.7 hr and did not significantly differ from the value obtained after intravenous doses (t$_{1/2}$ 5.0 hr, McAllister et al., 1982). Ratios of peak to trough verapamil concentrations (C$_{max}$/C$_{min}$) were 2.4 compared to 1.3 for norverapamil. Pharmacokinetic parameters such as AUC, Cmax, Tmax and half-life of verapamil and norverapamil were different for verapamil 250 mg constant-release tablet compared to an equivalent, but divided, dose of verapamil solution (Dunn et al.,

1985). AUC of verapamil was greater for verapamil 250 mg constant-release tablet than for an equivalent dose of verapamil solution. The half-life of verapamil was also longer for verapamil 250 mg constant-release tablet than for verapamil solution. The reason for differences is that tablet is a sustained-release dosage form, while verapamil solution is an immediate-release dosage form.

Mean concentration in cerebrospinal fluid observed for verapamil was 9.2 ($\pm$ 3.3 ng/ml) and for norverapamil 8.7 ($\pm$ 2.4 ng/ml), with respective mean cerebrospinal fluid/plasma ratios of 0.06 and 0.04 after dose of 120 mg every 4 hours (Doran et al., 1985).

Verapamil concentration in mother's breast milk also varied. Inoue et al. (1984), showed in their study of concentration of verapamil in human milk that verapamil concentration rose as high as 300 ng/ml. The serum verapamil in the child was 2.1 ng/ml when the verapamil concentration in the mother's milk was about 30ng/ml (Inoue et al., 1984). Thus, this serum verapamil in the baby would have been as high as 20ng/ml, if the infant had received the breast milk. Therefore, nursing women receiving verapamil should not breast-feed their babies, until it has been proved that this amount of verapamil is safe for infants (Inoue et al., 1984).

Verapamil accumulates in the body during regular dosing. In an investigation of the cause of accumulation of verapamil during regular dosing in 9 patients, Schiwartz et al. (1985) indicated that the mean $AUC_{0-\infty}$ for the first verapamil dose was 417 $\pm$ 277 ng.h/ml and the AUC for one dosing interval during regular dosing (80 mg every 6 h) was 787 $\pm$ 511 ng.h/ml yielding an accumulation ratio of 1.88. Verapamil has a high

hepatic extraction ratio and some or all factors involved in the extent of hepatic first pass extraction including hepatic blood flow, efficiency of hepatic drug extraction, and hepatic oxidative drug metabolizing capacity may therefore be altered during chronic oral administration. The AUC for verapamil during regular dosing was significantly increased when compared to that seen after the first dose and thus apparent oral clearance was decreased. The $t_{1/2}$ for verapamil increased from 8.4 ± 4.2 to 12.1 ± 3.6 h (p<0.01) (Schiwartz et al., 1985).

Steady state was reached by the seventh dose and AUC_{ss} (1999 $\pm$ 435[SD] ng.h/ml) was greater than that after the first dose (788 $\pm$ 244, P< 0.0001, Shand et al., 1981). Verapamil cumulates to a greater extent than predicted from its $t_{1/2}$, due to reduction in hepatic clearance. The verapamil $t_{1/2}$ was prolonged at steady state from 2.75 $\pm$ 1.14 to 4.52 ± 1.1 hr (p < 0.001) (Shand et al., 1981). Verapamil cumulates some 2.5-fold during the attainment of steady state after oral dosing. Apparent oral clearance decreased from 2.54 to 1 l/min. This would be expected to prolong drug $t_{1/2}$ by 64 % provided that volume of distribution remained constant (Shand et al., 1981). Oral continued administration (160 mg/day x 3 days) resulted in a significant decrease in verapamil clearance, compared to that following acute dosing (160 mg) (assessed by increases in both terminal elimination half-life, and AUC; p<0.001, Meredith et al., 1985). However, absorption rate constant (ka) and T_{max} were not significantly changed by continued oral drug administration. Decreased elimination of verapamil was observed in 12 hypertensive patients receiving oral dosage 240, 360, or 480-mg daily either BID or TID compared with the single-dose situation 80 mg or 120 mg (Anderson et al., 1987).

This decrease in plasma clearance during steady-state conditions may explain why verapamil given BID has the same antihypertensive effect as when it is given TID. These findings suggest that the disposition of the drug following continued oral administration exhibits non-linear Michaelis-Menten kinetics associated with saturation of the first pass metabolic processes (Meredith et al., 1985).

The mean elimination $t_{\frac{1}{2}}$ of 9.17 hr in children was longer than the mean $t_{\frac{1}{2}}$ of 6.40 hr reported for adults. The mean clearance of 0.500 l/min in the seven children is also lower than the mean clearances in the range 0.576 to 1.57 l/min reported for adults (Wagner et al., 1982). Thus, it appears that both the clearance and elimination rate constant of verapamil may be smaller in children than in adults

Pharmacokinetic parameters of verapamil in the elderly were investigated. The time-concentration curve for conventional verapamil formulation and SR verapamil formulation was similar in a group younger than 65 years (mean 58, range 50-64), and another group older than 65 years (mean 72, range 66-77) (Hosie et al., 1989). However, total verapamil clearance was decreased significantly in elderly (61 to 74 years of age, 10.5 ± 3.5 ml/min.kg, $P < 0.05$) and very elderly (75 to 102 years of age, 8.0 ± 4.1 ml/min.kg) when compared with that in young patients (23 to 36 years of age, 15.5 ± 4.5 ml/min.kg) (Abernethy et al., 1986). Abernethy et al. (1986) also showed volume of distribution was no different among elderly and young groups. After oral doses, bioavailability and peak drug concentration were similar among age groups. However, time to peak concentration was longer in the very elderly. This finding suggests that for verapamil, the pattern of impaired drug clearance and the pharmacodynamic effects seen

continues to increase with advancing age into the eighth and ninth decades of life (Abernethy et al., 1986).

After I.V. injection of 3mg, the terminal phase half-life and total plasma clearance of verapamil in patients with end-stage chronic renal failure and in normal subjects were similar (Mooy et al., 1985). The bioavailability (F), as determined from the AUC_{0-8}, was 11 ± 2 % in the normal controls and 16 ± 6% in the patients with renal insufficiency after receiving both intravenous dose of 3 mg and oral dose of 80 mg (Mooy et al., 1985). The lack of influence of renal function on the disposition of verapamil in man is probably because only a small percentage of the drug is eliminated unchanged via the kidneys (less then 5% of the given doses, Mooy et al., 1985). Therefore, there is no need to adjust the dose of verapamil according to the degree of renal impairment.

Woodcock et al. (1981) determined verapamil kinetics in liver disease, and intensive-care patients. After intravenous 5 mg dose, verapamil clearance was reduced in all patients with liver disease (Mean =-66%). There was considerable variation in liver disease subjects, in whom verapamil bioavailability ranged from 3.8% to 64%. Woodcock et al. (1981) also concluded that during the distribution or α-phase, which extended over a period of approximately 1 hr, there were no significant differences between the patients with liver disease and the control subjects and the increase in $t_{1/2\ \beta}$ in some liver disease patients was associated with increased distribution volume. In liver disease patients, verapamil clearance was reduced, while it was increased in most intensive-care patients. The reasons for these changes are probably due to decrease in metabolism of verapamil, and as a result drug stays in liver disease patients longer.

The drug preparation used clinically is a racemic mixture of equal amounts of the optical isomers dextro- and levo-verapamil. Verapamil exhibits stereoselective first-pass metabolism during which the more potent l-isomer is preferentially eliminated. Based on the EC_{50}, drug concentration producing 50% effect, l-verapamil is 3.3 times more potent than racemic verapamil and 11 times more potent than d-verapamil. After intravenous dosing the d- to l-verapamil plasma concentration ratio was 1.8, whereas after oral dosing this ratio averaged 6.5. The bioavailability of l-verapamil is only 20% compared with 50% for d-verapamil (Echizen et al., 1985). Thus, the more potent l-isomer was preferentially metabolized after oral racemic verapamil. L-verapamil is less extensively bound to plasma proteins than D-verapamil. The differential first-pass clearance has been invoked as the explanation for increased drug potency after intravenous as compared to oral administration.

To evaluate the progress of this research, Verelan-PM was chosen as a reference product because Verelan-PM is a "beads-in-a-capsule" formulation that releases drug in approximately zero-order fashion independently of G.I. agitation. Verelan PM capsules, a controlled absorption verapamil HCl containing pellet formulation for oral administration comprises a sugar core coated with a powder mixture of verapamil HCl and an organic acid selected from the group consisting of adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid and tartaric acid. A binder for this drug-core layer contains a major proportion of a pharamaceutically acceptable water soluble polymer freely permeable to verapamil and water and a minor proportion of a pharamaceutically acceptable water insoluble polymer slightly permeable to verapamil and water. The ratio

of verapamil HCl and organic acid is from 1:1 to 10:1 (Panoz et al., 1989). The drug core, which comprises multiple layers of the powder mixture of drug and other ingredients and the polymeric material superimposed one upon the other, has between 20 and 120 layers of the core-forming materials and is formed in a conventional coating pan. The drug core is overcoated with a multi-layer controlled membrane containing a major proportion of a film-forming, water-insoluble, non-porous polymer and a minor proportion of a film-forming, water-soluble, porous polymer. The water soluble polymer is selected from the group consisting of hydroxypropyl methylcellulose and polyvinylpyrrolidone. The water insoluble polymer is selected from the group consisting of methylcellulose, ethylcellulose, propylcellulose and shellac. The polymer which is freely permeable or slightly permeable to verapamil and water comprises a copolymer of acrylic and methacrylic acid esters (Panoz et al., 1989).

The ratio of water soluble/freely permeable to water insoluble/slightly permeable polymer is determined by the particular combination of polymers selected in the membrane being effective to permit appropriate release of verapamil from the pellet at a rate over a 24 hour period (Panoz et al., 1989). A suitable polymer which is freely permeable to verapamil and water is EUDRAGIT RL and a slightly permeable polymer to verapamil and water is EUDRAGIT RS. Porous polymers include polyvinylpyrrolidone, Eudragit RL, polyvinylalcohol and hydroxypropylmethylcellulose and non-porous polymers include Eudragit RS, methylcellulose, ethylcellulose, propylcellulose, and shellac.

A central inert core suitably consisting of a non-pareil seed of sugar or starch has an average diameter in the range of 0.3-0.7 mm, especially 0.4-0.5 mm. The core may also include other components such as a lubricant, like talc, stearic acid, a dispersing agent or a surfactant, like sodium lauryl sulphate. Preferably, the number of coats of membrane solution or suspension applied is between 8 and 30 layers (Figure 5.1). Then, coated pellets are filled into hard gelatine capsules (Panoz et al., 1989).

The following figure (Figure 5.1) is cross sections of the Verelan PM bead and the new bead formulation.

Figure 5.1a shows the cross surface of three layer coated of the Verelan PM bead. From inside to outside of each bead is the sugar bead, a drug:organic acid layer, and finally a controlled release layer. The cross surface of the new bead formulation is presented in Figure 5.1b. From inside to outside of each bead is a drug core, and then a controlled release layer.

(Verapamil HCl + organic acid), binder: major portion of soluble polymer and minor portion of insoluble polymers; 20-120 layers + lubricant and surfactant

Membrane: major portion of insoluble polymer and minor portion of soluble polymers; + lubricant and plasticizer, 8%-30% layers.
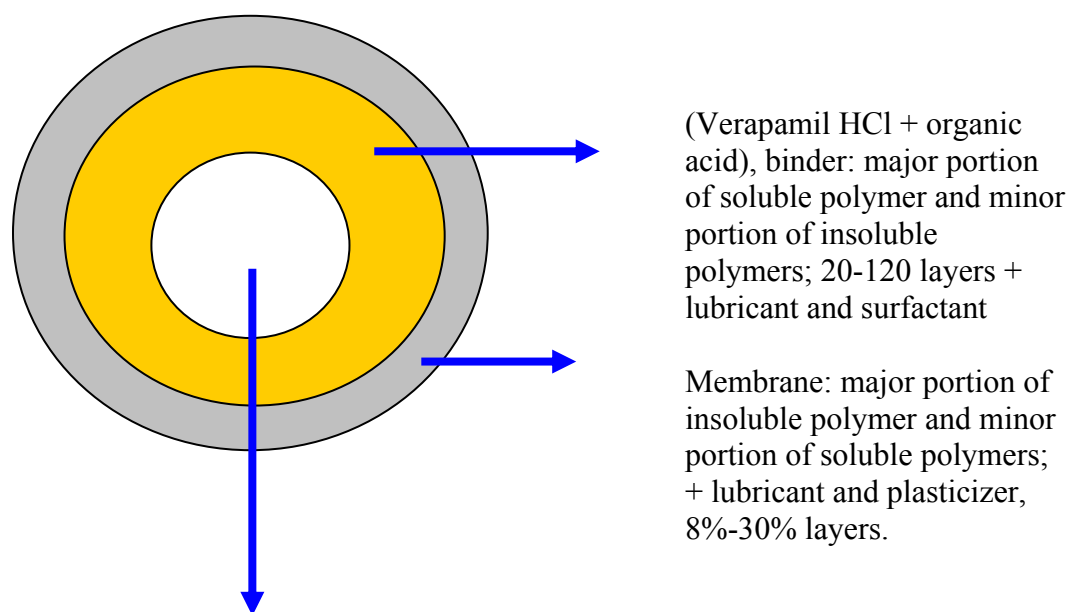
Sugar bead: 0.4-0.5 mm, non-pareil seed of sugar or starch

5.1a. Cross section of controlled absorption bead (Verelan PM bead)

Drug core**:** Verapamil HCl + Avicel pH 101 + Polyox Size: 1.0-1.41 mm

Controlled release membrane: Ethylcellulose + lactose
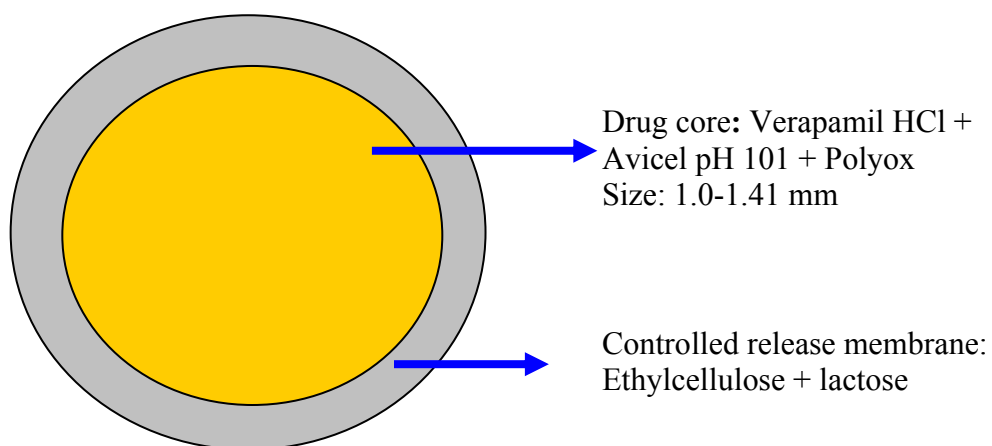
Figure 5.1b: Cross section of new bead formulation

Figure 5.1: Comparison of cross sections of Verelan PM and the new bead formulation

The goal of this study was to formulate a new and unique but simple to prepare multiple-beads in a capsule formulation that provides zero-order drug release, avoids the application of multiple alternating layers of drug and polymer as required in Verelan-PM, uses standard spray coating equipment rather than tedious and slow pan coating methods, and produces a product that is expected to be bioequivalent to Verelan-PM. The aims of this research include: 1. to investigate the effect of ratio of Surelease solid content and lactose in polymer coatings on drug release, 2. to evaluate the effect of coating weight gain on verapamil HCl release from coated beads. 3. to study the effect of tween 80 and Explotab® (Explotab) on drug release from coated beads. 4. to identify a novel formulation approach using FDA approved excipients and readily available processing equipment to produce "beads-in-a-capsule" that would provide nearly zero-order drug release, be relatively independent of dissolution media and stirring speeds (and gastrointestinal agitation and transit times), and equivalent to an established reference standard (Verelan PM capsule).

MATERIALS AND METHODS

Chemicals

Active drug used in the research was verapamil HCl, a gift from Teva Pharmaceuticals (Sellersville, PA). Surelease® (Surelease or ethylcellulose), formula No.: E-7-19010 with solids content of 25.0 % was a gift from Colorcon (West Point, PA). Avicel® (Avicel) pH 101 was a gift from FMC BioPolymer (Newark DE) and lactose monohydrate powder was purchased from Mallinckrodt Baker, Inc. (Phillipsburg, NJ). Tween® 80 (tween 80) was purchased from FisherBiotech (Fair Lawn, NJ). Natural transparent size 0 capsules were a free sample from Capsugel (Greenwood, SC). Polyethylene oxide W.M. 100000 (Polyox®) was purchased from Aldrich Chemical Company, Inc. (St. Louis, MO), and sodium starch glycolate pH 5.5-7.5 (Explotab®) was purchased from Edward Mendell Co., Inc. (Carmel, NY). Verelan-PM made by Schwarz Pharma, Inc. (Milwaukee, WI) was purchased from the OSU campus pharmacy.

Methods

Table 5.1 shows percentage weight compositions of different experimental bead formulations. Verapamil hydrochloride (HCl) is a model drug for this research, Polyethylene oxide weight molecular (W.M.) 100000 is a binder, Avicel pH 101 is a filler excipient. Explotab is a disintegrating agent and tween 80 is a surfactant agent.

Table 5.1: Percentage weight compositions of different experimental bead formulations

Ingredients	Formulations				
	F1	F2	F3	F4	F6
Verapamil hydrochloride	66.67%	66.67%	66.67%	66.67%	66.67%
Polyethylene oxide W.M. 100000	5%	5%	5%	5%	5%
Avicel pH 101	28.33 %	28.00%	27.67%	27.33 %	25.33 %
Explotab	0	0	0	1%	3%
Tween 80	0	0.33%	0.66%	0	0

Formulations were coated with Surelease/lactose with different ratios (see coating formulations in Table 5.2), with weight gains of 3, 5, 6.5, 8 and 10%.

Bead preparation:

Accurately weigh verapamil HCl, Avicel, Explotab, and Polyox for each formulation in Table 5.1 with the batch size of 100 g. Mix Polyox well with Avicel and Explotab, and then add verapamil HCl (equal amount to excipients). Sieve the mixture through screen size of 20 mesh (0.833 mm) twice. Remove 25% of powder mixture and set aside. Tween 80 (when used, see Table 5.1) was dissolved in 75% of estimated DI water needed. Gradually add 75% of estimated de-ionized (DI) water needed or all tween 80 solution to the remaining 75% powder. Rinse the beaker containing tween 80 with remaining DI water, then add to the wet paste until enough water is present to allow extrusion. Total liquid was about 40-45 ml for 100 g of beads. Push the mixture through

the extruder screen, and cut the extruded material into fragments of 3-6 mm. Take 20 g of damp extruded granules and gently mix with 4 to 5 grams of previous set-aside powder mixture. Spheronize this mixture for 2 minutes, then gently mix beads. Continue spheronizing for 4-5 more minutes, gently mix beads during spheronization to produce good beads. Dry beads at 37^0C for 16 hours. Note: with the small scale laboratory equipment, spheronization must be done in stages using small batches of 100 g.

Comment: Adding previously "set aside" powder helps dry beads and prevents their building into large beads in lab equipment. Gently mixing beads during spheronization produces good beads and assures that beads are not so wet that they "grow" and become too big in lab equipment. Note that extrusion of all powder as a single batch is anticipated using industrial scale equipment (which has a much larger spinning plate), and has now also been demonstrated in the lab equipment (see below).

The procedure for production in the lab equipment without using "set-aside" powder is as follows:

1. Mix Avicel pH 101 with Polyox, then add verapamil HCl using geometric dilution and mix well.

2. Sieve twice through screen mesh 20.

3. Make wet paste with de-ionized water (DI) (20-23 ml for 50 g of powder) until correct consistency (depends on operator experience).

4. Extrude damp paste, and cut 3-6 mm. Leave for 5-10 minutes.

5. Spheronize about 18 g of wet granules for 1 to 1.5 minutes. Take beads out for 15-25 minutes to allow drying in room temperature, then spheronize for another 2-3 minutes, gently mix one or two times when drying to promote drying.

Comment: It will be helpful to use moisture measurement equipment and optimize the water content of the extrusion mass, and employ a spheronizer equipped with drying controls. Dry beads were sieved to select appropriate size for spray coating.

Coating procedure

Table 5.2 shows the coating formulations used for coating beads. The description of coating dispersion preparation is below.

Table 5.2: Ratio of Surelease solid content and lactose in coating dispersions

Formulations	CF-1	CF-2	CF-3	CF-5
Surelease solid content	100 g	100 g	100 g	100 g
Lactose monohydrate	0 g	1 g	3 g	5 g
Water	400 g	400 g	400 g	400 g

Surelease, batch No.: E-7-19010, solids content: 24-26.0% (average 25%).

Surelease was accurately weighed into a beaker for each formulation (see Table 5.2). Then weighed DI water was added. Accurately weighed lactose was dissolved in the above dispersion for each corresponding formulation (see Table 5.2) and mixed well

for one hour. This dispersion was gently stirring while coating. Extruded drug beads of size between 0.833 and 1.41 mm (mesh size 12-20) or 1.0 mm and 1.41 mm (mesh size 12-18) were selected to coat. 55 g of drug beads were put into a laboratory Niro STREA spray coater, with the coating parameters: Nozzle needle 8 (air flow pressure valve), drying temperature: 55^0C, outlet air temperature: 45^0C, pressure: 5-15 psi, flow: 0.95 ml/minute. The pressure was kept low at 5 psi during the first 10 minutes to prevent bead breakage before bead surfaces become sealed. After 10 minutes the air pressure was increased to increase bead mixing and speed drying.

Coated beads were sieved through mesh size 20 to eliminate broken beads, if present. The percentage of broken beads was usually less than 1%.

Capsule filling

Coated beads were filled in natural transparent size 0 capsules. Each capsule contains 200 mg (100%) of verapamil HCl based on drug content assay of the beads

Process of making coated beads is described in Figure 5.2.

1. Mixing

2. Making a paste

3. Extrusion

4. Spheronization

5. Coating

Figure 5.2: Process of making coated beads

Verapamil hydrochloride Assay

Standard Curves of Verapamil hydrochloride

An exact amount (250 mg) of verapamil hydrochloride (HCl) was weighed and transferred to a 1000-ml volumetric flask. The sample was dissolved in either simulated gastric fluid (pH 1.4 ± 0.1) without pepsin, or pH 7.4 buffer (Na_3PO_4 + HCl), simulated intestinal fluid pH 6.8, or potassium chloride medium and adjusted to final volume. All stock solutions contained equal amount of verapamil HCl of concentration of 250μg/ml. A series of standard solutions with a concentration range of 4-250 μg/ml was prepared from the stock solution by dilution. UV absorbance of standard solutions was measured by UV spectrophotometer at 277 nm in pH 7.4 buffer, simulated intestinal fluid pH 6.8, and simulated gastric fluid pH 1.4, and at 278 nm in potassium chloride medium. Standard curves of verapamil HCl in media of simulated gastric fluid, pH 7.4 buffer and simulated intestinal fluid pH 6.8 superimposed over each other. Average curve was calculated for these media. Standard curve of absorbance versus verapamil HCl concentration in potassium chloride medium is seen in Figure 5.3. Standard curve of absorbance versus verapamil HCl concentrations in simulated gastric fluid, pH 7.4 buffer, and simulated intestinal fluid pH 6.8 is shown in Figure 5.4.

In Vitro Dissolution Testing of Formulations

Beads were put into transparent capsules size 0. Dissolution studies of drug released from the beads in capsules were performed according to the USP XXV

apparatus 1 and 2, using KCl medium, two-pH medium, and simulated gastric and intestinal fluid media and maintained at 37 ± 0.5^0C. For KCl medium, 1000 ml of medium at different rpm stirring speeds was used. For two-pH medium method, formulations were placed for the first 2 h in 750 ml of gastric fluid without pepsin, then 258 ml of 0.2 M Na_3PO_4 was added and pH was adjusted to 7.4 by 6N NaOH or concentrated HCl, as needed. For simulated gastric and intestinal fluid method, formulations were placed for the first 2 h in 900 ml of simulated gastric fluid without pepsin, then in 900 ml of simulated intestinal fluid pH 6.8 without pancreatin at different rpm stirring speeds (see results). 5-mL samples were filtered through flow filters (0.70 μm), and collected via an autosampler at predetermined time intervals for the 24-h dissolution study. Filtered solutions were centrifuged at 3000 rpm for 10 minutes, supernatants were measured to determine absorbance at 278 nm in KCl medium or 277 nm in other media. Dissolution drug concentrations were determined via standard curves (presented in Figures 5.3 and 5.4) in each medium and converted to percentage verapamil HCl released. Three or six runs of each dissolution experiment were performed and the mean ± standard deviation (S.D.) was calculated. Average drug released from beads and their standard deviations were calculated from replications in all dissolution experiments and compared to results obtained from Verelan PM capsules. Verapamil HCl dissolution profiles are presented as percent drug release versus time curves.

<u>Drug Content Assay</u>

Drug content assay was performed once for each uncoated bead formulation. An amount of uncoated beads equivalent to 100 mg of verapamil HCl was weighed and transferred to 100-ml volumetric flasks. Simulated gastric fluid was used to dissolve drug using a stirring bar to facilitate the dissolution for 5 hours. Then samples were filtered through a 45 μm diameter membrane. Filtered solutions were diluted 10 times with simulated gastric fluid and diluted solution measured by UV spectrophotometer at 277 nm. Amount of verapamil HCl contained in each uncoated formulation was determined using an appropriate standard curve. This standard curve is presented in Figure 5.4.

Potassium chloride medium preparation:

Potassium chloride medium was prepared by adding 25 ml of 2M KCl to 900 ml of DI water, adjusted to pH 7.5 by 0.1 M NaOH, and then DI water was added to give a final volume of 1000 ml.

Simulated gastric fluid preparation

Add 8 grams of sodium chloride and 20 ml of concentrated hydrochloric acid to 1000 ml of DI water and mix well. Add 2950 ml of DI water and mix well. Adjust to pH 1.4 ± 0.1 with concentrated hydrochloric acid. DI water was added to give a final volume of 4000 ml.
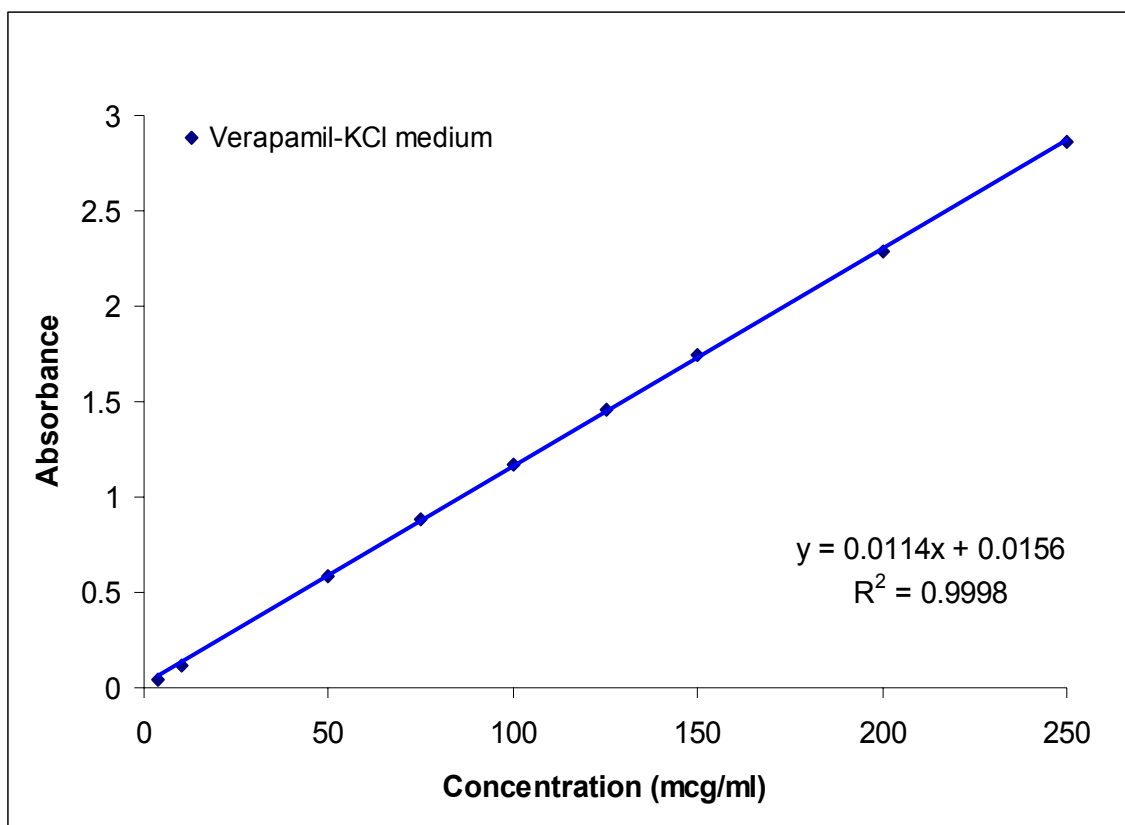
Figure 5.3: Standard curve of absorbance versus verapamil HCl concentration in potassium chloride medium (UV wavelength at 278 nm)
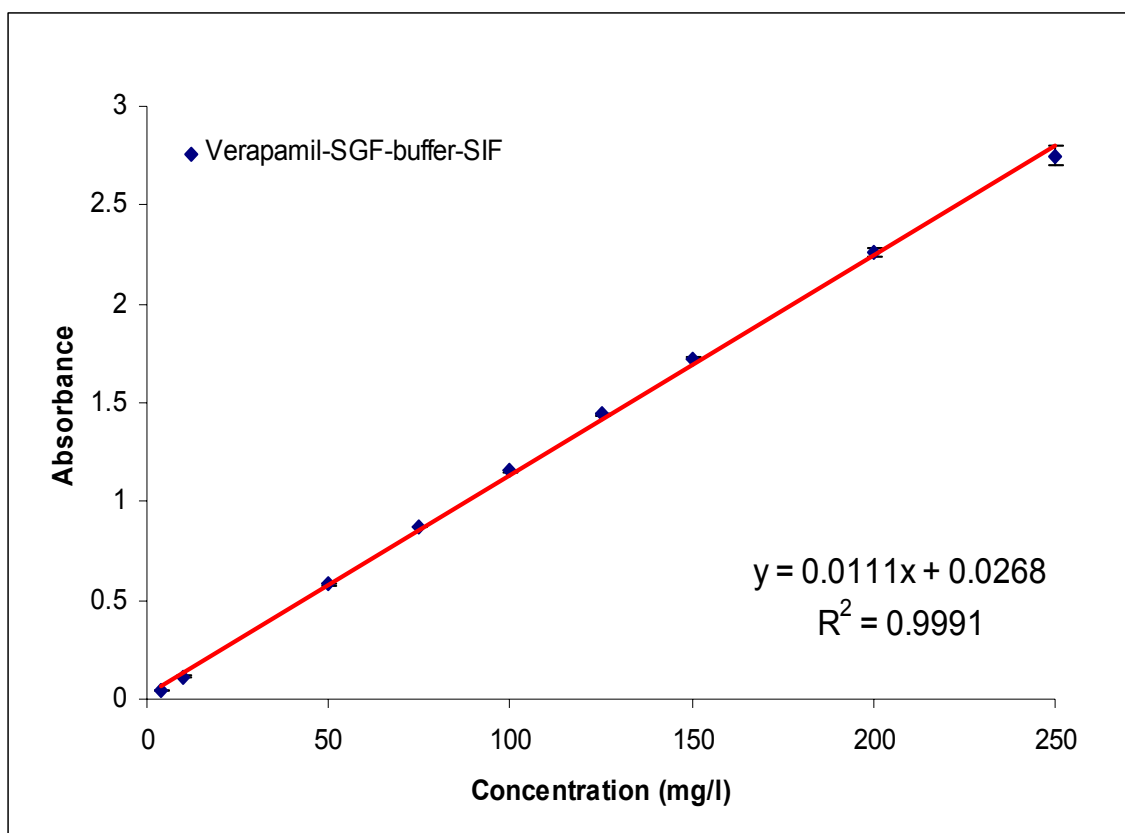
Figure 5.4: Standard curve of absorbance versus verapamil HCl concentration in simulated gastric fluid, pH 7.4 buffer, and simulated intestinal fluid pH 6.8 (UV wavelength at 277 nm)

Simulated intestinal fluid preparation

Dissolve 136.1 grams of KH_2PO_4 and 17.92 grams of NaOH in 19 liters of DI water. Adjust to pH 6.8 ± 0.05 with 3N NaOH. DI water was added to give a final volume of 20 liters.

Statistical analysis

Influence of various preparation parameters on drug release from beads

Investigations of the influence of ingredients in each layer, such as ratio of Surelease solids content to lactose, percentage of tween 80, percentage of Explotab, and coating weight gain on dissolution rate constants were performed.

To obtain information on the most influential preparation or formulation parameters on drug dissolution rate constants, the response variable was evaluated by several statistical methods using S-plus 7.0 statistical software multiple linear regression. Every experiment was performed in either triplicate or six replications. The significance level was set at $\alpha = 0.05$.

To compare dissolution rate constants between produced formulations and Verelan PM capsules, two-way ANOVA was used. Differences between groups were evaluated by multiple comparisons using the Tukey method. Intervals excluding 0 flagged by '****' are considered "significant differences". Residual plots were used to check the assumption of constant variance and normal quantile quantile (QQ) plots were

used to check the assumption of normality. The Tukey assumptions are an ideal normal model with equal spreads and equal sample sizes in all groups.

The release rate$_{14}$ was used as a response variable. Release rate$_{14}$ is calculated as follows:

$$\text{Release rate}_{14} = \frac{\%release14h - \%release0.0833h}{14 - 0.0833}$$

Influence of basket and paddle speeds on dissolution rate constants

An analysis of variance model (ANOVA) using S-plus 7.0 statistical software was used to identify the influence of paddle speeds and basket speeds on dissolution rate constants. Table 5.3 summarizes the factors and levels studied. Every experiment was performed in triplicate or six replications. The significance level was set at $\alpha = 0.05$.

Table 5.3: Factors and levels studied for the influence of paddle speeds and basket speeds on dissolution rate constant

Factors	Code of factors	Levels
Basket speeds	rpm	75 and 200
Paddle speeds	rpm	50, 75, 100, and 200

The dissolution rate constants:

The first-order, square root, and zero order rate constants were determined as follows. The first-order model equation (5.1), square root of time (SRT) model equation (5.2), and zero-order model equation (5.3):

$$C = Cn(1 - \exp(-k_1 t)) \qquad (5.1)$$

$$C = k_2 t^{0.5} \qquad (5.2)$$

$$C = k_0 t \qquad (5.3)$$

C is the percentage of drug released at time t, Cn is the percentage of total drug that is released by the first-order mechanism, k_1 is the first-order rate constant, k_2 is the SRT rate constant, and k_0 is the zero-order rate constant. Estimates for k_2 were obtained from the slope of a linear SRT plot (C vs. $t^{0.5}$) using S-plus software. Equations (5.2) and (5.3) were fitted in S-plus software program using linear regression with the intercept set at zero (without intercept fitting) to estimate k_2 and k_0. Estimates for Cn were obtained from the y-intercept of the plot of dC/dt versus C. The equation dC/dt = k_1C was used to estimate k_1. The slope (dC/dt) of the curve was divided by the concentration [C] to obtain the estimate of k_1. Both C_n and k_1 were estimated first based on the above method. Then, non-linear regression fitting in S-plus software program was used to refit data based on the draft-obtained C_n and k_1 from the above method. The estimated C_n and k_1 presented in here were from non-linear regression fitting in S-plus software program. Values for the AIC (Akaike criteria) were used as basis of comparison (equation 5.4). The best models are the ones with the smallest AIC.

$$AIC = n \bullet \log(\widehat{\sigma}^2) + 2p \qquad (5.4)$$

Convolution:

Convolution was performed to simulate plasma concentrations time curves for Verelan PM capsules and OSU2 using Kinetica 2000. Although simulated data are not always close to real data, convolution is still a good tool to predict the relative fate of drug in the body from multiple drug formulations. Convolution was completed with the following assumptions. The first assumption is that the drug after being instantly absorbed, is only eliminated via first order elimination. The second assumption is that no absorption phase is considered; the drug is treated like a series of IV bolus injections with appropriate adjustment of bioavailability. For the third assumption, absorption rate constant is greater than dissolution rate constant. Finally, verapamil follows linear pharmacokinetics.

RESULTS AND DISCUSSION

Figure 5.5 shows dissolution profiles of the starting formulation F-1 overcoated with various incremental weight gains of ethylcellulose (Surelease) used as a controlled release polymer membrane. Arwidsson et al. (1991) studied the influence of coating process factors when using aqueous dispersions and concluded that the mechanical properties of Surelease films are influenced by many process factors, such as air pressure, drying temperature, flow rate, plasticizer level, spraying distance, and concentration of solids. Surelease coating process was reported to be more sensitive to small variations in processing conditions, irrespective of plasticizer content, than Aquacoat ECD-30 films. Thus, conditions for Surelease coating were kept critically constant throughout the current study.

Diameter of all beads in Figure 5.5 was between 0.833 and 1.41 mm. With a 3% and 10% coating weight gain, about 70% and 20% of drug was released after 24 hrs, respectively. Dissolution profiles in Figure 5.5 of F1 formulation coated with various incremental weight gains of Surelease alone are lower than the dissolution profile of Verelan PM. As expected, the greater the outer coating weight gain, the slower the drug release.
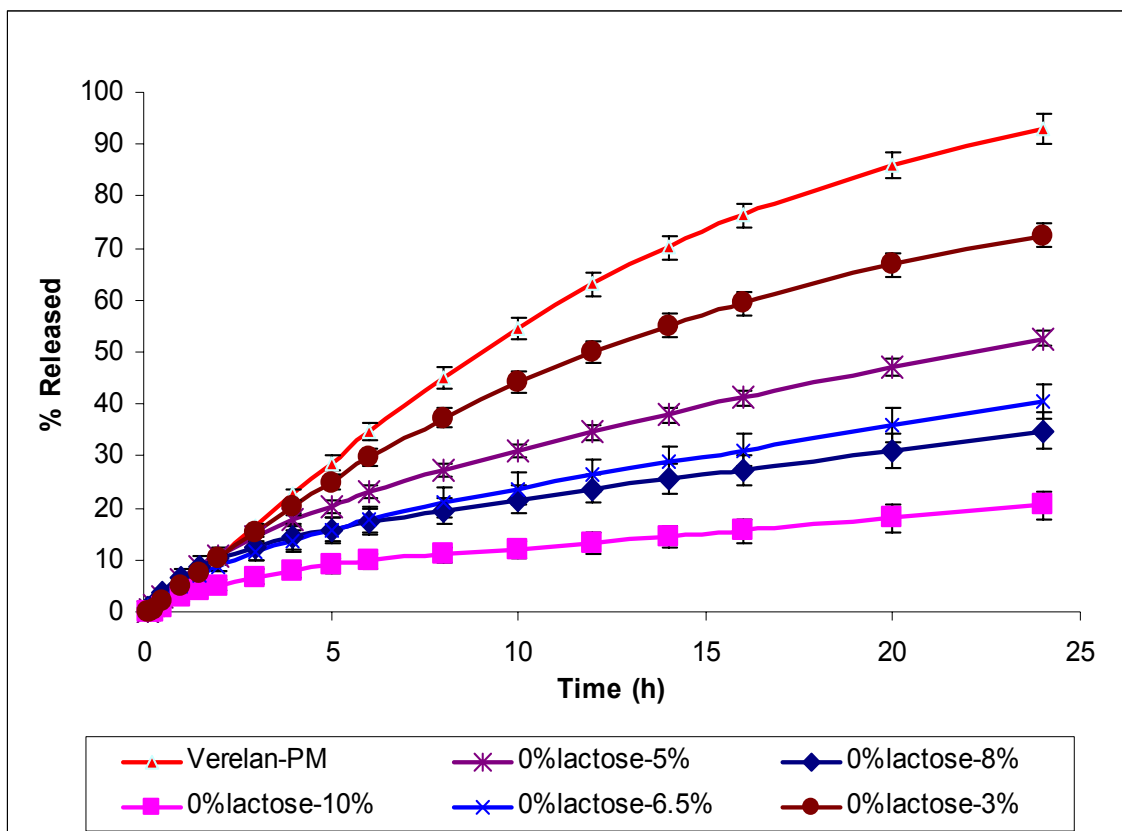
Figure 5.5: Dissolution profiles of verapamil HCl: Effect of 0% lactose (F1 beads coated with Surelease), KCl medium at 75 rpm basket speed

Verelan-PM = Verelan PM capsules.

0%lactose-5% = F1 coated with Surelease, 5% weight gain.

0%lactose-8% = F1 coated with Surelease, 8% weight gain.

0%lactose-10% = F1 coated with Surelease, 10% weight gain.

0%lactose-6.5% = F1 coated with Surelease, 6.5% weight gain.

0%lactose-3% = F1 coated with Surelease, 3% weight gain.

Drug beads were made by extrusion spheronization method in this study. In extrusion spheronization method, amounts of granulating fluid and binder are critical. The amount of granulating fluid has a major influence on the properties of beads including drug release, shape, size distribution, internal porosity, and mechanical strength (Habib et al., 2002). For a given batch, the more water added, the larger the pellets became. The most notable effect was that the product shape was sensitive to plate spin speed, with higher speeds creating the most spherical shape (Mount et al., 1996). Spheronized granulations had slightly higher granule densities than hand-formed granulations. In extrusion spheronization method, microcrystalline cellulose was considered the most appropriate excipient from among other ingredients considered. Dibasic calcium phosphate dehydrate, lactose monohydrate, starch, and pregelatinized starch were unsuitable as single components for sphere production (Mount et al., 1996).

Size of beads is one important factor to control drug release and to obtain polymer coating efficiency. In the current study, initially the size of the beads was selected from 0.833 to 1.41 mm, mesh size 12-20, due to coating efficiency. Beads smaller than 0.833 mm coated with Surelease were more easily fractured during coating. Smaller beads were sensitive to basket rotation speeds as will be shown in Figure 5.13. Bechard et al. (1992), and Altaf et al. (1998) showed that at the same coating amount, smaller pellets were more fragile than larger pellets. Coating film thickness was found to be about 15 μm for 40/60 mesh pellets, as opposed to 20-25 μm for 20/30 or 30/40 mesh pellets (Bechard and Leroux, 1992). Reduced film thickness on smaller pellets was attributed to their larger surface area (Bodmeier, 1997; Altaf et al., 1998). Since drug release is proportional to

surface area and inversely proportional to film thickness of the coated beads, smaller pellets require more coating to obtain the same drug release profiles (Ragnarsson, 1988). When reducing particle diameter to half of its original value, the amount of coating solution must be doubled to obtain the same film thickness (at the same density and content and for a thin coating layer) and to maintain equivalent release properties (Ragnarsson, 1988).

Beads size 1.41 to 1.68 mm, mesh 10-12, worked well for coating herein, but beads larger than 2.362 mm (mesh 8) were not used for coating because these larger beads were easily broken. Ideally, for the laboratory scale equipment, beads ranging from 1.0 to 1.41 mm were used to obtain good uniform coating. Coated beads were sieved through mesh size 20 to eliminate broken beads. The relatively uniform size beads recovered from sieving provided somewhat superior straightened drug release profiles (more zero-order).

Effect of Tween 80:

As mentioned before, dissolution profiles of the all coating weight gains of F1 formulation coated with Surelease only are lower than the dissolution profile of Verelan PM (Figure 5.5). To increase drug release from coated beads, based on data from Rakkanka's study (2003) in this laboratory, it was hypothesized that adding tween 80 inside beads (mixed into the beads formulation) would promote verapamil HCl dissolution. Figures 5.6 and 5.7 show effects for addition of 0.33% tween 80 (0.5%

compared with drug content) and 0.66% tween 80 (1% compared with drug content), respectively.

Inclusion of tween 80 (0.66%) in the extruded drug core increased rate and extent of drug release significantly with all weight gains of coating over 0% tween 80 in the bead core (compare Figure 5.5 and Figure 5.7). Drug release from the formulation of 5% coating weight gain for 0.66% tween 80 in the core is close to Verelan PM up to 6 h, and then differs from Verelan PM 10-23% at other times (Figure 5.7). For 6.5, 8 and 10% coating weight gain of 0.66% tween 80 (Figure 5.7) and all weight gains of 0.33% tween 80 in the core formulations (Figure 5.6), the rate and extent of drug release was still too low compared with Verelan PM. For example, the dissolution profile of 5% coating weight gain of 0.33% tween 80 in the core formulation was lower than the dissolution profile of Verelan PM (Figure 5.6). As expected, the higher the concentration of tween 80, the faster the release rate (compare Figure 5.6 and Figure 5.7).

Multiple linear regression analysis of the effects of addition of tween 80 and weight gain on release rate$_{14}$ versus coating weight gain (weight gain), tween 80, weight gain squared, tween 80 squared, and the interaction term between weight gain squared and tween 80 squared are summarized in Table 5.4.
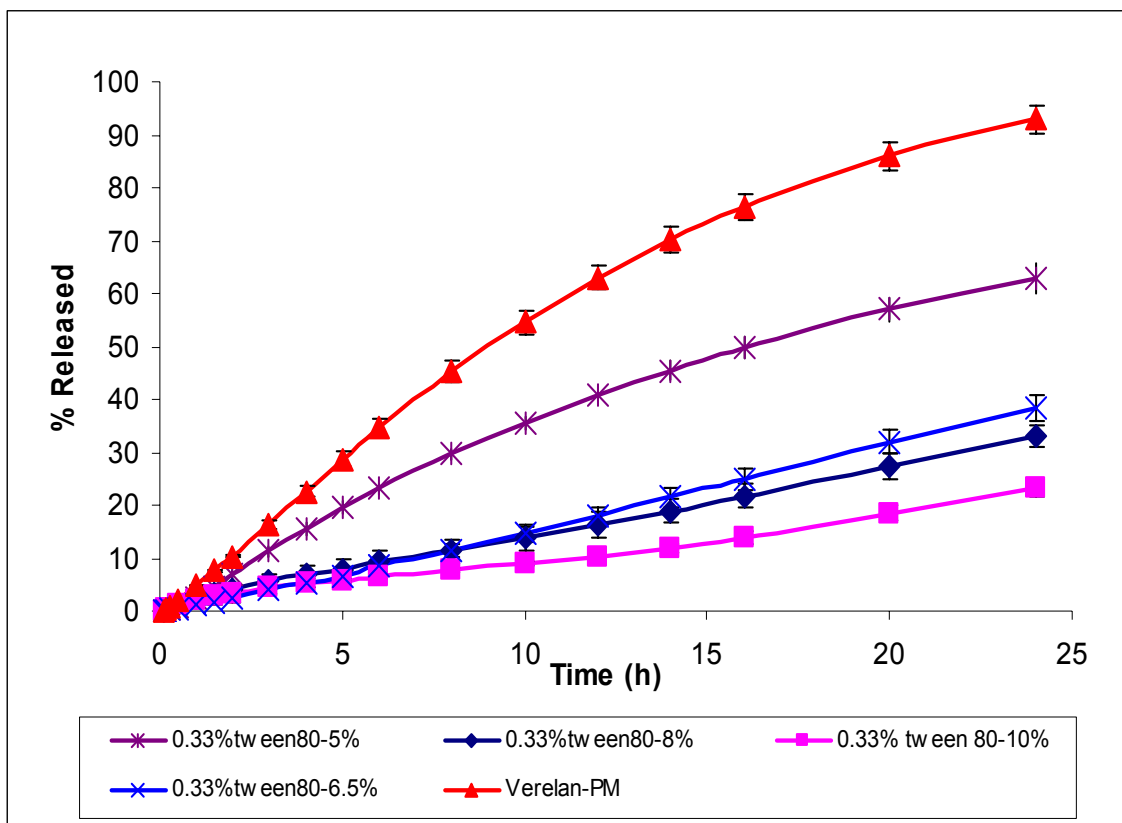
Figure 5.6: Dissolution profiles of verapamil HCl: Effect of addition 0.33% tween 80, KCl medium at 75 rpm basket speed

0.33%tween80-5% = F2 coated with Surelease, 5% weight gain.

0.33%tween80-8% = F2 coated with Surelease, 8% weight gain.

0.33%tween80-10% = F2 coated with Surelease, 10% weight gain.

0.33%tween80-6.5% = F2 coated with Surelease, 6.5% weight gain.

Verelan PM = Verelan PM capsules.
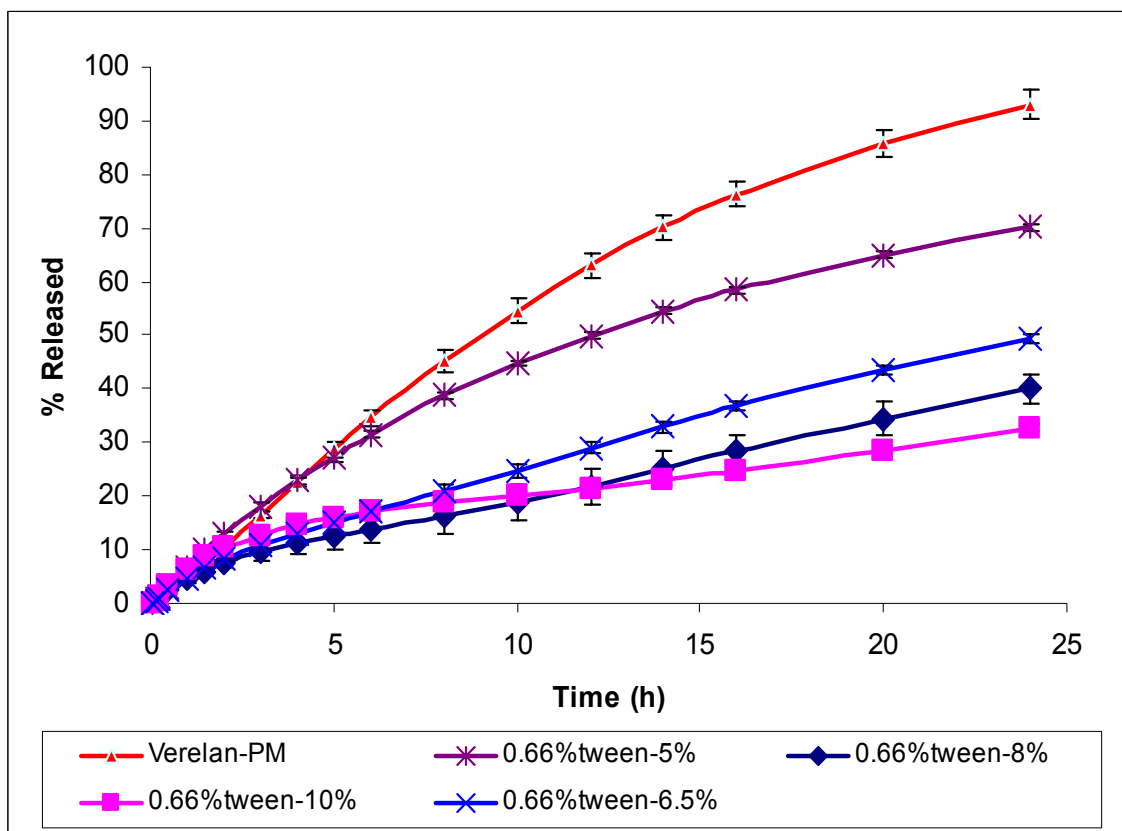
Figure 5.7: Dissolution profiles of verapamil HCl: Effect of addition 0.66% tween 80, KCl medium at 75 rpm basket speed

Verelan PM = Verelan PM capsules.

0.66%tween-5% = F3 coated with Surelease, 5% weight gain.

0.66%tween-8% = F3 coated with Surelease, 8% weight gain.

0.66%tween-10% = F3 coated with Surelease, 10% weight gain.

0.66%tween-6.5% = F3 coated with Surelease, 6.5% weight gain.

Table 5.4: Effect of Tween 80 and weight gain on drug release rate$_{14}$

	DF	Sum of square	Mean square	F value	Pr (F)
Model 5.1: release rate$_{14}$ ~ tween80 + weight gain					
tween80	1	1.654	1.654	8.713	0.006
weight gain	1	19.663	19.663	103.602	< 0.001
Residuals	33	6.263	0.190		
Model 5.2: release rate$_{14}$ ~ tween80 + weight gain + weight gain^2+ tween80^2					
tween80	1	1.654	1.654	19.711	< 0.001
weight gain	1	19.663	19.663	234.385	< 0.001
weight gain^2	1	2.340	2.340	27.891	< 0.001
tween80^2	1	1.322	1.322	15.764	< 0.001
Residuals	31	2.601	0.084		
Model 5.3: release rate$_{14}$ ~ tween80 + weight gain + weight gain^2+ tween80^2 + weight gain:tween80 + weight gain^2: tween80^2					
tween 80	1	1.654	1.654	23.769	< 0.001
weight gain	1	19.663	19.663	282.632	< 0.001
tween80^2	1	1.322	1.322	19.009	< 0.001
weight gain^2	1	2.340	2.340	33.636	< 0.001
weight gain:tween80	1	0.247	0.247	3.552	0.069
weight gain^2: tween80^2	1	0.336	0.336	4.830	0.036
Residuals	29	2.018	0.070		

(% weight gain and % tween 80 in linear regression models were treated as continuous factors, e.g. 5, 6.5, 8, and 10 for % weight gain, and 0, 0.33 and 0.66 for % tween 80).

The residual plot of model 5.1 suggested quadratic forms should be added to the model. Since the quadratic forms of tween 80 and weight gain are significant in model 5.2 (P-values < 0.001) (the relationship between release rate$_{14}$ and weight gain squared and tween 80 squared is significant), the interaction of quadratic forms of tween 80 and weight gain was added and is shown in model 5.3. Model 5.3 is the final model which contains all appropriate independent parameters. There is moderate evidence that the interaction term between weight gain squared (weight gain^2) and tween 80 squared (tween 80^2) affects release rate$_{14}$ (model 5.3, P-value = 0.036). Since the interaction term between weight gain squared and tween 80 squared is significant, the interaction term between weight gain and tween 80 is kept in the model. The effect of coating weight gain on release rate$_{14}$ depends on tween 80. There is strong evidence of an association of tween 80 and release rate$_{14}$ (P-value < 0.001, model 5.3). Model 5.3 has a multiple R-squared = 0.9268. The coefficients of model 5.3 are seen in Table 5.5. The residual plot of model 5.3 (shown in Figure A.4, Appendix 6) looks O.K. The normal QQ plot for model 5.3 (Figure A.5, Appendix 6) exhibits normality.

Based on the coefficients of model 5.3 in Table 5.5, the relationship between mean release rate$_{14}$ and percent of tween 80 at 5% weight gain is presented in equation A.1 (Appendix 6). Increasing tween 80 by 0.33% over a range 0 to 0.66% of tween 80 in the beads at 5% weight gain is associated with increasing 0.252 of release rate$_{14}$ (based on equation A.1, see Appendix 6).

Table 5.5: Coefficients of model of effect of coating weight gain and tween 80 on release rate[14]

Coefficients:	Value	Std. Error	t value	Pr(>|t|)
(Intercept)	8.385	0.963	8.708	< 0.001
tween80	4.208	2.291	1.837	0.077
weight gain	-1.497	0.256	-5.853	< 0.001
$(tween80^2)$	0.066	1.876	0.035	0.972
$(weight\ gain^2)$	0.079	0.016	4.796	< 0.001
tween80:weight gain	-0.797	0.300	-2.654	0.013
$(tween80^2):(weight\ gain^2)$	0.063	0.029	2.198	0.036

Effect of Lactose in coating layer:

Drug release from the formulation of 5% coating weight gain with 0.66% tween 80 in the core is close to Verelan PM up to 6 h, and then differs from Verelan PM 10-23% at later times (Figure 5.7). The percentage of tween 80 in the bead core may be increased to more than 0.66%. However, increasing tween 80 to more than 0.66% in the bead core may increase the drug release rate at the beginning. The increase in drug release rate at the beginning may lead to an increased maximum drug concentration in the body when the formulation is taken by mouth, which is not preferred. Besides, addition of tween 80 to more than 0.66% in the core made the bead preparation difficult (especially, in the spheronization process). Thus, addition of tween 80 increases drug release rate but is not beneficial for the purposes of this specific study and was ommitted from future formulations.

It was felt that inclusion of lactose within the Surelease coating might create channels which, coupled with ethylcellulose coating effects, may result in more zero-order release than is seen with Surelease alone while increasing the release rate of verapamil. Figures 5.8 to 5.11 show the effects of the addition of lactose. The more lactose the higher the drug release rate and extent of drug release (compare Figures 5.8, 5.9, and 5.11). In contrast, increasing weight gain of the outer coating of Surelease and lactose is associated with decreasing the drug release rate (Figures 5.8, 5.9, and 5.11).

The effect of lactose and weight gain on release $rate_{14}$ was modeled using multiple linear regression models. Linear and quadratic models are summarized in Table 5.6. The residual plot of model 5.4 suggested the quadratic forms should be added to the model. Since the quadratic forms of lactose and weight gain are significant in model 5.5, the interaction of quadratic forms of lactose and weight gain was checked and is shown in model 5.6. Model 5.6 was adopted to represent data (P-values-add <0.01, see Appendix 7). Coefficients of model 5.6 are shown in Table 5.7. Sample size was 48 with 4 levels of weight gain, and 4 levels of lactose.
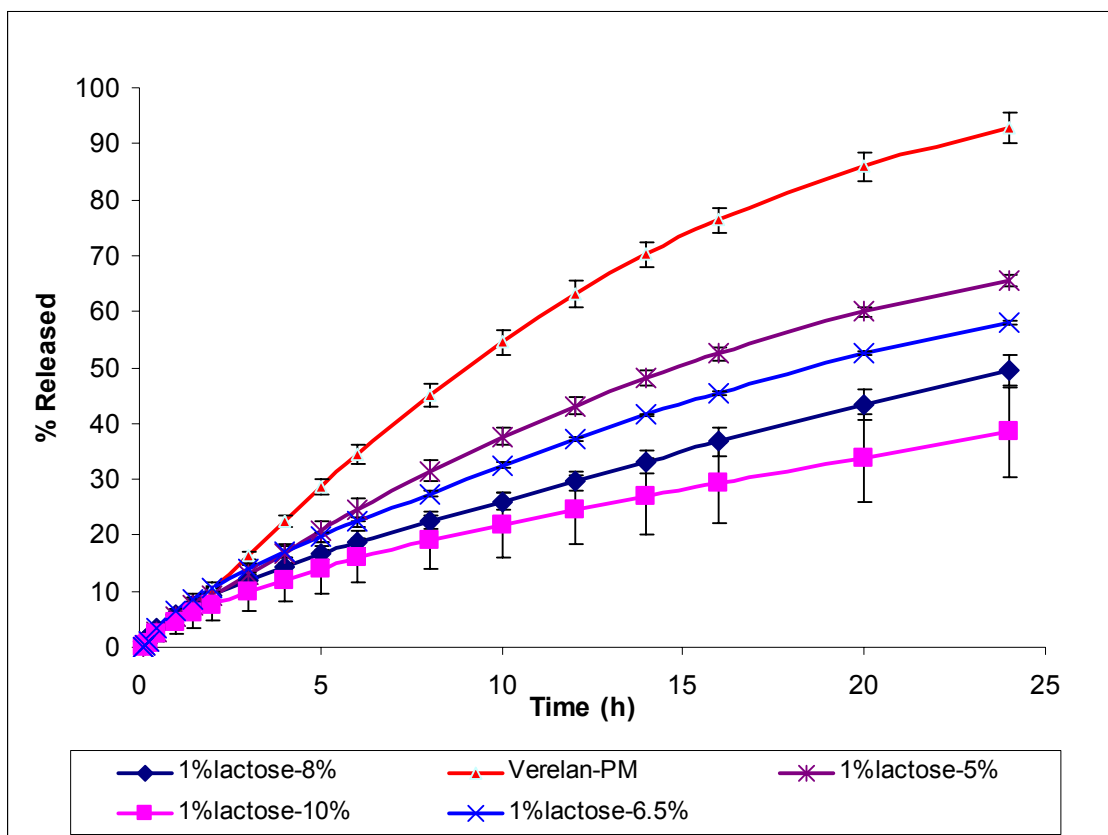
Figure 5.8: Dissolution profiles of verapamil HCl: Effect of 1% lactose in Surelease layer on drug release, KCl medium at 75 rpm basket speed

1%lactose-8% = F1 coated with Surelease:lactose = 100:1, 8% weight gain.

Verelan-PM = Verelan PM capsules.

1%lactose-5% = F1 coated with Surelease:lactose = 100:1, 5% weight gain.

1%lactose-10% = F1 coated with Surelease:lactose = 100:1, 10% weight gain.

1%lactose-6.5% = F1 coated with Surelease:lactose = 100:1, 6.5% weight gain.

(Surelease: lactose = Surelease solid content:lactose).
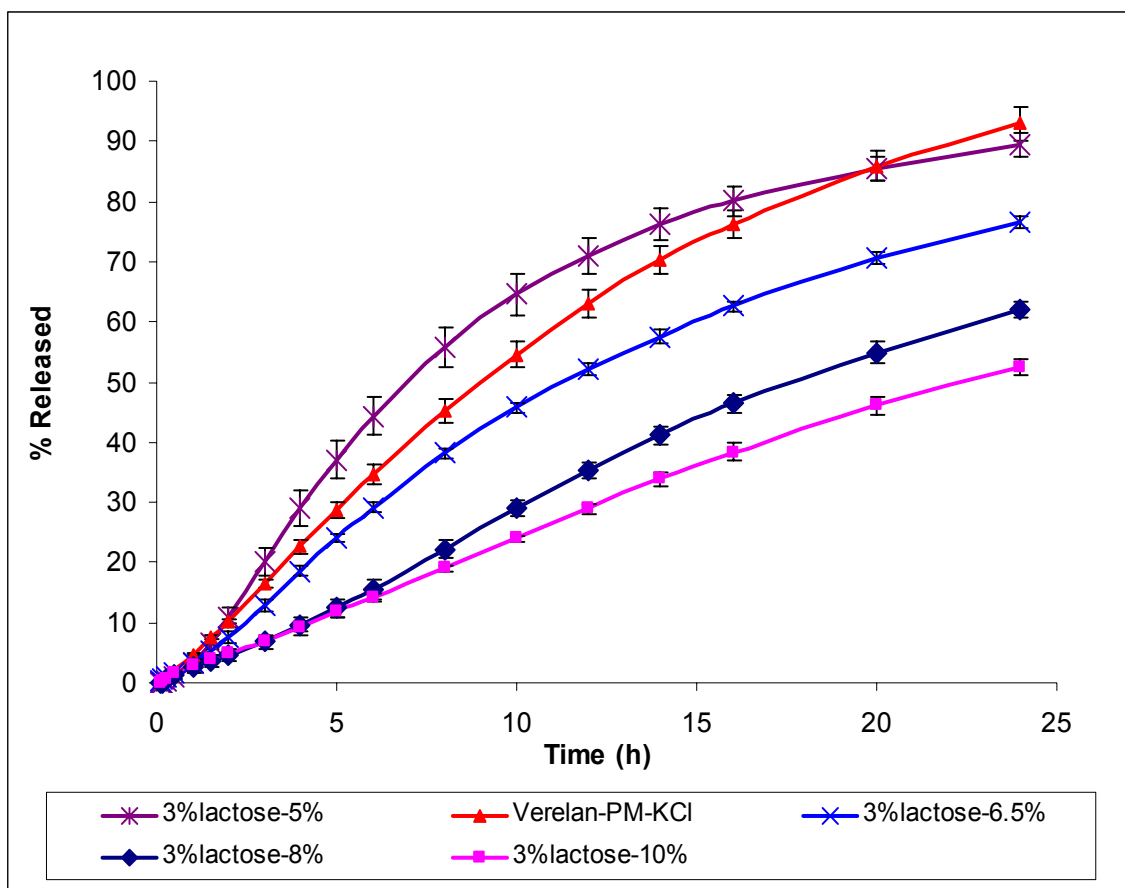
Figure 5.9: Dissolution profiles of verapamil HCl: Effect of 3% lactose in Surelease layer on drug release, KCl medium at 75 rpm basket speed

3%lactose-5% = F1 coated with Surelease:lactose = 100:3, 5% weight gain.

Verelan PM-KCl = Verelan PM capsules.

3%lactose-6.5% = F1 coated with Surelease:lactose = 100:3, 6.5% weight gain.

3%lactose-8% = F1 coated with Surelease:lactose = 100:3, 8% weight gain.

3%lactose-10% = F1 coated with Surelease:lactose = 100:3, 10% weight gain.

Table 5.6: Table III sum of squares results of model of effect of lactose and weight gain on release rate$_{14}$

	DF	Sum of square	Mean square	F value	Pr (F)
Model 5.4: release rate$_{14}$ ~ weight gain + lactose					
weight gain	1	32.031	32.031	185.707	< 0.001
lactose	1	34.035	34.035	197.323	< 0.001
Residuals	45	7.762	0.172		
Model 5.5: release rate$_{14}$ ~ weight gain + lactose + weight gain^2 + lactose^2					
weight gain	1	32.031	32.031	285.312	< 0.001
lactose	1	34.035	34.035	303.158	< 0.001
weight gain^2	1	0.526	0.526	4.684	0.036
lactose^2	1	2.408	2.408	21.452	< 0.001
Residuals	43	4.827	0.112		
Model 5.6: release rate$_{14}$ ~ weight gain + lactose + weight gain^2 + lactose^2 + weight gain:lactose + lactose^2:weight gain^2					
weight gain	1	32.031	32.031	465.507	< 0.001
lactose	1	34.035	34.035	494.624	< 0.001
weight gain^2	1	0.526	0.526	7.642	0.009
lactose^2	1	2.408	2.408	35.001	< 0.001
weight gain:lactose	1	1.643	1.643	23.874	< 0.001
lactose^2:weight gain^2	1	0.364	0.364	5.283	0.027
Residuals	41	2.821	0.069		

(% coating weight gain and % lactose were treated as continuous factors, e.g. 5, 6.5, 8, and 10 for % weight gain, and 0, 1, 3 and 5 for % of lactose)

There is moderate evidence that the interaction term between weight gain squared and lactose squared affects release rate$_{14}$ (model 5.6 in Table 5.6, P-value = 0.027). The linear effect of lactose on release rate$_{14}$ strongly depends on coating weight gain (P-value <0.001). There is statistically significant evidence that both lactose and coating weight gain influence release rate$_{14}$ (P values <0.01 for both coefficients of lactose and weight gain in model 5.6, Table 5.7). The residual plot for model 5.6 (not shown) appears random and validates the assumptions of the model. The residual normal QQ plot for model 5.6 (not shown) exhibits normality.

Table 5.7: Coefficients of model 5.6

Coefficients	Value	Std. Error	t value	Pr(>|t|)
(Intercept)	5.420	0.839	6.460	< 0.001
weight gain	-0.692	0.221	-3.134	0.003
lactose	1.883	0.294	6.413	< 0.001
(weight gain^2)	0.027	0.014	1.938	0.060
(lactose^2)	-0.151	0.032	-4.760	< 0.001
weight gain:lactose	-0.137	0.039	-3.563	< 0.001
(weight gain^2):(lactose^2)	0.001	0.0005	2.299	0.027

Close examination of Figure 5.9 suggests a linear relationship between coating weight gain and release rate$_{14}$ from formulation F1 coated with Surelease:lactose = 100:3. Thus, the effect of weight gain and weight gain square on release rate$_{14}$ from formulation

F1 coated with Surelease:lactose = 100:3 was modeled (model 5.7) and is shown in Table 5.8.

Table 5.8: Table III sum of squares results of model of effect of coating weight gain on release rate$_{14}$ for 3% lactose

	DF	Sum of square	Mean square	F value	Pr (F)
Model 5.7: release rate$_{14}$ ~ weight gain + weight gain^2					
weigh gain	1	15.313	15.313	918.437	< 0.001
weight gain^2	1	1.032	1.032	61.921	< 0.001
Residuals	9	0.150	0.017		

There is statistically significant evidence that weight gain and weight gain squared influence release rate$_{14}$ (model 5.7 in Table 5.8, P values < 0.01). The model 5.7 was adopted as the final model. The relationship between mean release rate$_{14}$ discussed in model 5.7 of Table 5.8 and weight gain is as follows.

Release rate$_{14}$ = 13.784 - 2.176*weight gain + 0.104*(weight gain)^2 (Eq 5.5)
          (0.720)   (0.200)   (0.013)
(The numbers in parenthesis are the standard errors for each corresponding coefficient.)

The interest was to determine the weight gain of Surelease:lactose = 100:3 at a 5.041 release rate$_{14}$ of Verelan PM. The 5.041 release rate$_{14}$ was inserted into equation (Eq 5.5). Solving for this quadratic equation, the Surelease:lactose = 100:3 outer coating weight gain was approximated at 5.5% from this calculation.

It can also be seen from Figure 5.9 that with an average outer coating weight gain between 5% and 6.5 % with 3% lactose in the coating will give a dissolution curve close

to the reference (Verelan-PM). Following up on this, the production and dissolution testing of the formulation containing 3 % lactose in the controlled release membrane and 5.8% outer coating weight gain confirmed this hypothesis with simulated and real dissolution profiles being different by less than 5% at all time points (see Figure 5.10).

Figure 5.11 shows dissolution curves of verapamil HCl beads coated with Surelease containing 5% lactose, with different weight gains. The formulation of 5 % lactose, 6.5% outer coating weight gain, and size 12-20 mesh extruded beads gave a dissolution curve that was closest to reference product Verelan PM, especially for the first 10 hours which is the portion of the curve most predictive of Cmax *in vivo*.

Effect of sodium starch glycolate (Explotab) and bead size:

It is well known that dissolution curves from ethylcellulose coated beads usually have a distinctive convex curvature, i.e., drug release deviates from a zero-order drug release due to a slowing down in dissolution rate as time progresses. To increase the rate of drug release at later times and increase total extent of drug release over the 24 hours of dissolution, a disintegrant (Explotab) was added into the core (at 1% and 3% levels) and the range of bead size was narrowed. This disintegrant may have no effect initially but then act overtime to expand and "stretch" or "open" channels for drug dissolution created by lactose. Dissolution profiles for formulations containing Explotab in the core and the effect of bead size are shown in Figures 5.12 and 5.13. Statistics table III presents sum of squares results of the effect of Explotab on drug release rate[14] in Table 5.9.
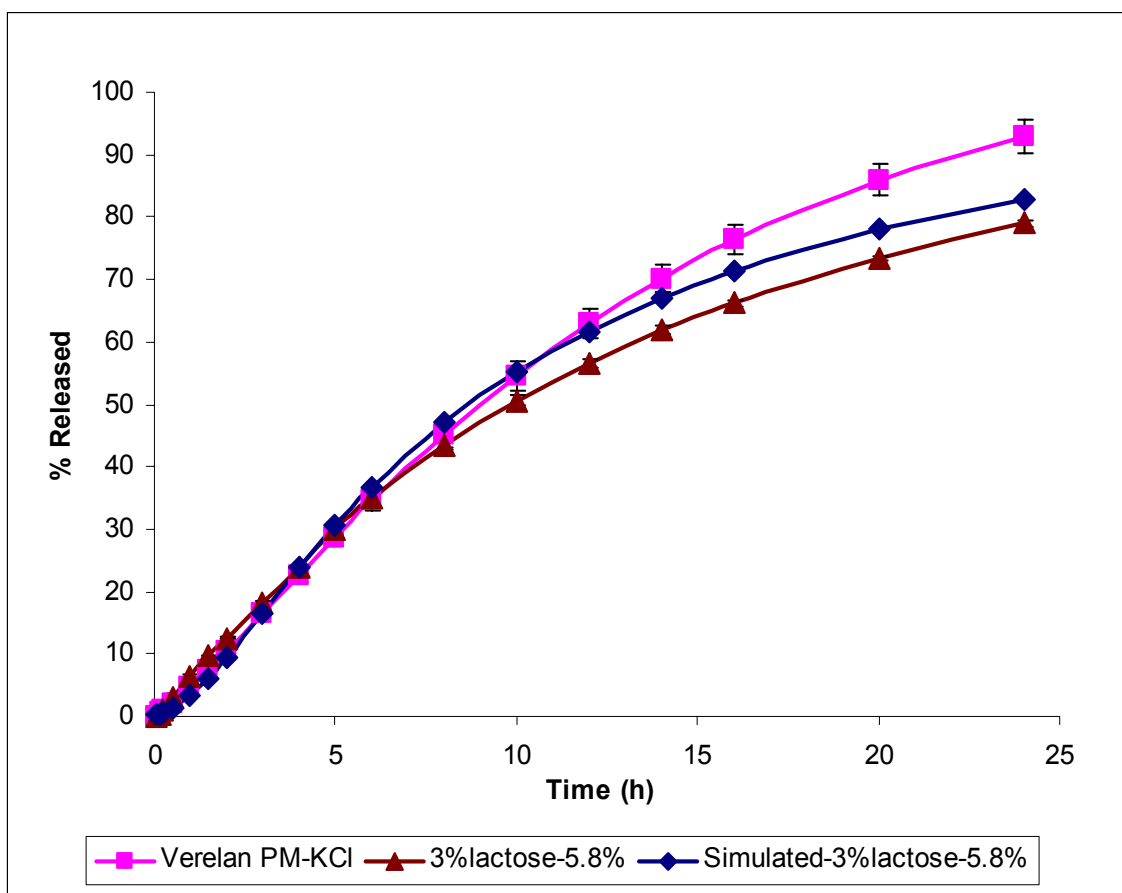
Figure 5.10: Simulated and real dissolution profiles of verapamil HCl 3% lactose, 5.8% weight gain, KCl medium at 75 rpm basket speed

Verelan PM-KCl = Verelan PM capsules.

3%lactose-5.8% = F1 coated with Surelease:lactose=100:3, 5.8% weight gain.

Simulated-3%lactose-5.8% = Simulated data of F1 (coated with Surelease:lactose = 100:3, 5.8% weight gain), using Eq 5.5 based on model 5.7 in Table 5.8.
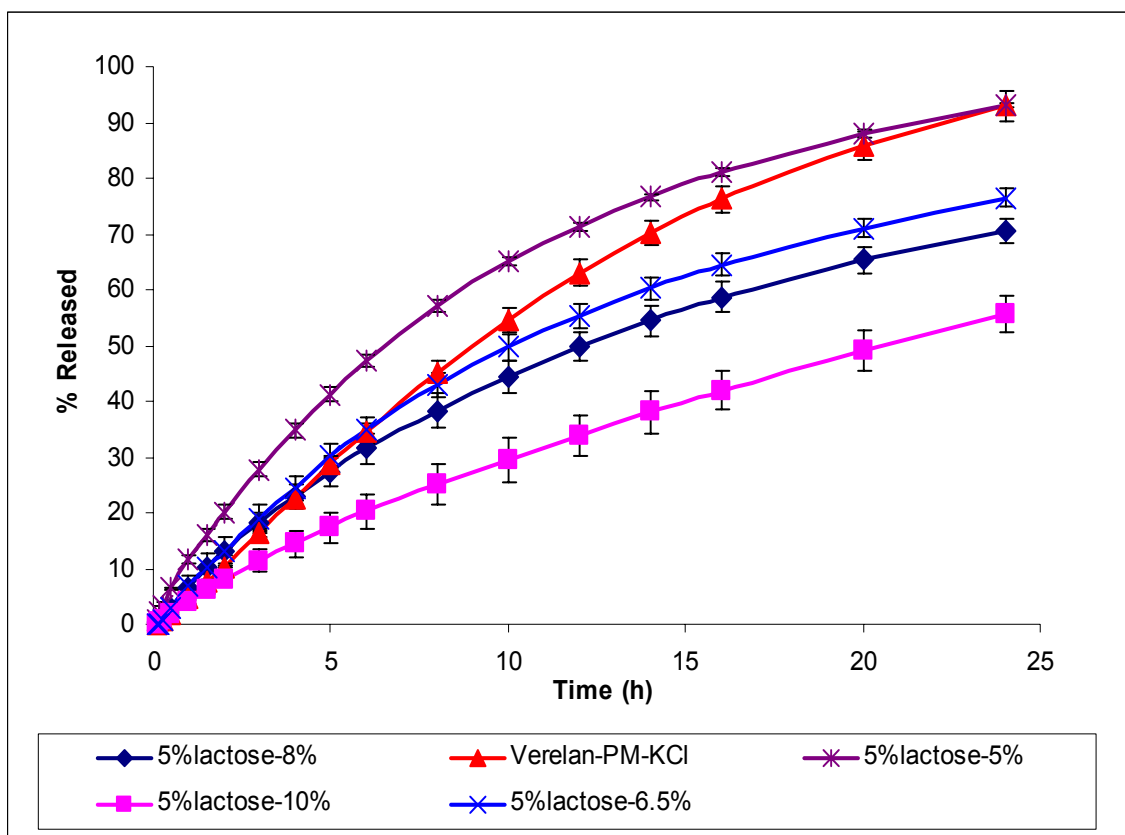
Figure 5.11: Dissolution profiles of verapamil HCl: Effect of 5% lactose in Surelease layer on drug release, KCl medium at 75 rpm basket speed

5%lactose-8% = F1 coated with Surelease:lactose=100:5, 8% weight gain.

Verelan-PM-KCl = Verelan PM capsules.

5%lactose-5% = F1 coated with Surelease:lactose=100:5, 5% weight gain.

5%lactose-10% = F1 coated with Surelease:lactose=100:5, 10% weight gain.

5%lactose-6.5% = F1 coated with Surelease:lactose=100:5, 6.5% weight gain.
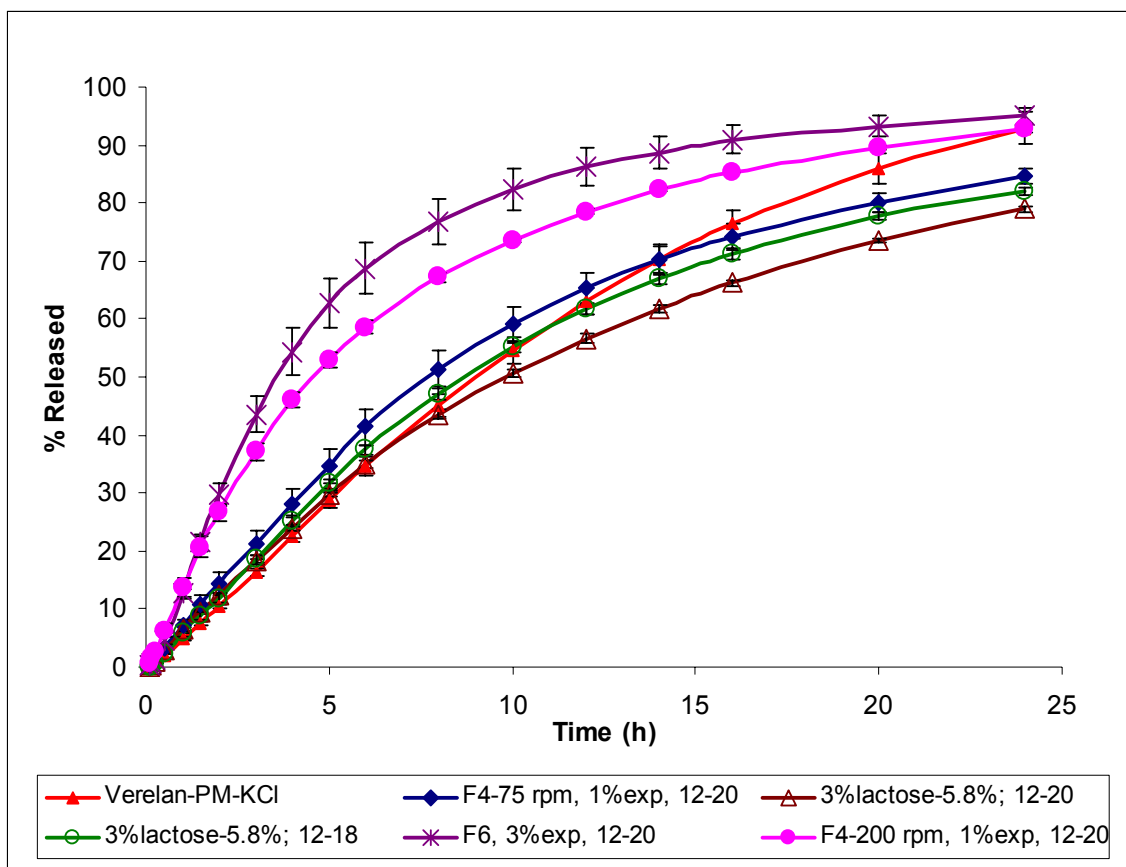
Figure 5.12: Effect of disintegrant (Explotab) in the bead core and bead size on verapamil HCl dissolution versus time, KCl medium using basket method

Verelan-PM-KCl = Verelan PM capsules.

F4-75 rpm, 1%exp, 12-20 = F4 (1% Explotab) coated with Surelease:lactose=100:3, 5.8% weight gain, mesh size = 12-20, 75 rpm.

3%lactose-5.8%; 12-20 = F1 coated with Surelease:lactose=100:3, 5.8% weight gain, mesh size = 12-20, 75 rpm.

3%lactose-5.8%; 12-18 = F1 coated with Surelease:lactose=100:3, 5.8% weight gain, mesh size 12-18, 75 rpm.

F6, 3%exp, 12-20 = F6 (3% Explotab) coated with Surelease:lactose=100:3, 5.8% weight gain, mesh size = 12-20, 75 rpm.

F4-200 rpm, 1%exp, 12-20 = F4 (1% Explotab) coated with Surelease:lactose=100:3, 5.8% weight gain, mesh size = 12-20, 200 rpm.
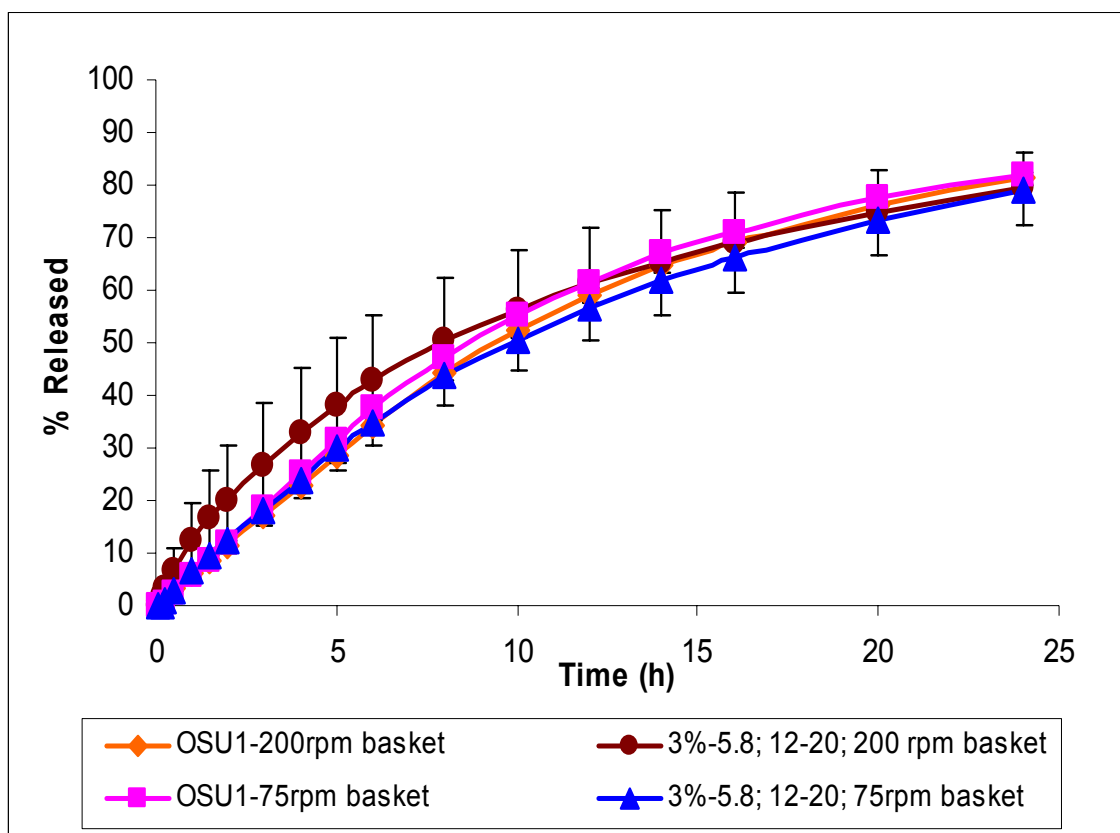
Figure 5.13: Effect of bead size on verapamil HCl dissolution versus time, KCl medium at 75 rpm and 200 rpm basket method

OSU1-200rpm basket = OSU1 formulation (F1 coated with Surelease:lactose = 100:3, 5.8% weight gain, mesh size 12-18), 200 rpm basket.

3%-5.8; 12-20; 200 rpm basket = F1 coated with Surelease:lactose=100:3, 5.8% weight gain, mesh size: 12-20, 200 rpm basket.

OSU1-75 rpm basket = OSU1 formulation, 75 rpm basket.

3%-5.8; 12-20; 75 rpm basket = F1 coated with Surelease:lactose=100:3, 5.8% weight gain, mesh size: 12-20, 75 rpm basket.

Table 5.9: Table III sum of squares results of model of effect of Explotab on release rate$_{14}$

	DF	Sum of square	Mean square	F value	Pr (F)
Model 5.8: release rate$_{14}$ ~ Explotab					
Explotab	1	5.729	5.729	256.660	< 0.001
Residuals	7	0.156	0.022		

(% Explotab was treated as a continuous variable, e.g. 0, 1, and 3 for % Explotab)

A linear model was first fit to these data. A lack of fit test was done to test the adequacy of the model (see Appendix 8). The results indicated that a linear model (model 5.8 in Table 5.9) is adequate to relate release rate$_{14}$ to percent of Explotab in the bead core formulations. Explotab strongly influences release rate$_{14}$ when increased from 0% to 3% (P-value < 0.001). The relationship between mean release rate$_{14}$ and percent of Explotab presented in model 5.8 of Table 5.9 is shown in equation 5.6.

Release rate$_{14}$ =   4.422   +   0.640*%Explotab   (5.6)
                          (0.073)   (0.040)
(The numbers in parenthesis are the standard errors for each corresponding coefficient.)

Increasing Explotab by 1% over a range 0 to 3% of Explotab in the beads is associated with increasing 0.640 of release rate$_{14}$ (95% confidence interval is 0.562 - 0.718, based on equation 5.6).

Figure 5.12 shows that including 1% of Explotab in the bead core increased both the rate and extent of release only a small amount compared with no Explotab in the bead

core (brown curve). Including 3% Explotab in the bead core increased the release rate sharply compared with no Explotab in the bead core.

Beads containing 1% Explotab did not rupture over 24 h but beads with 3% Explotab ruptured after only 2 hours. That may be a reason why beads containing 3% Explotab released drug faster than beads containing 1% Explotab. In addition, the 1% Explotab in the bead core formulation at 200 rpm basket speed (the pink curve in Figure 5.12) released drug faster than the 1% Explotab-formulation at 75 rpm basket speed (the blue curve in Figure 5.12). These results with Explotab were not considered outstanding for this specific project but provide useful guidance for some effects of inclusion/omission of a disintegrant inside coated beads.

Bead size 12-18 and 12-20 had a strong effect (P-value = 0.001, two sample t-test, Appendix 9) on release rate$_{14}$ for the formulation of 3% lactose, 5.8% coating weight gain. However, bead size 12-18 and 12-20 had a moderate effect (P-value = 0.010, two sample t-test, Appendix 9) for the formulation of 5% lactose, 6.5% coating weight gain.

Selection of beads size 12-18 was as follows. First, before coating, dried uncoated sphere beads were selected between mesh sizes 12 and 18, and then coated beads were sieved through 12 and 18 mesh size to eliminate broken beads or agglomerated particles after coating. The process was different from the selection of size range of 12-20 mesh, which eliminated broken beads after coating only. Thus, the real bead size between 18 (opening size 1.0 mm) and a little smaller than 12 mesh sizes (opening size 1.41 mm) was chosen. Rejected coated beads, smaller than mesh size 18 and greater than mesh size 12,

was less than 1% of the production batch. Dissolution profiles of verapamil from formulations of bead size 12-18 were closer to Verelan PM at later times (Figures 5.14 and 5.15). This may not be due only to the size of beads because distribution of bead sizes was not studied. Within this size range, beads were more uniform and their size range (1.0 to 1.41 mm) was appropriate.

Additionally, the formulation F1 with bead size 12-20 released drug slightly faster up to 10 h at 200 rpm basket stirring speed compared with that at 75 rpm basket stirring speed in KCl medium (Figure 5.13). Formulation F1 coated with 3% lactose, 5.8 weight gain, size 12-18 (OSU1) released drug consistently at 75 rpm and at 200 rpm basket stirring speeds (Figure 5.13). The size of the bead affected the robustness of drug release.

Effect of stirring speeds and method in KCl medium:

OSU1 and OSU2 (F1 coated with Surelease:lactose = 100:5, 6.5% weight gain, mesh size = 12-18) formulations were tested at different speeds of paddle and basket in KCl medium (see Methods) to evaluate the robustness of these formulations. Results are shown in Figures 5.14 and 5.15. Two-way ANOVA was used to test the effect of stirring speeds (75 rpm and 200 rpm) and dissolution method (paddle method and basket method), and results are presented in Tables 5.10 and 5.11.

Table 5.10: Sum of squares results of model of effect of speed and method on OSU1 drug release in KCl medium, two-way ANOVA

	DF	Sum of squares	Mean square	F value	Pr (F)
Model 5.9: release rate$_{14}$ ~ Speed + Method + Speed:Method					
Speed	1	1.299	1.299	256.804	< 0.001
Method	1	2.792	2.792	551.825	< 0.001
Speed:Method	1	2.312	2.312	456.845	< 0.001
Residuals	8	0.040	0.005		

Table 5.10 shows both stirring speed (P-value < 0.001) and dissolution method (P-value <0.001) influence release rate$_{14}$ of OSU1. The influence of stirring speed on release rate$_{14}$ also depends on dissolution method, paddle or basket method, (P-value < 0.001). The multiple comparisons (Tukey method) show 95% confidence interval of differences between mean of "high speed" groups (200 rpm stirring speed) and mean of "low speed" groups (75 rpm stirring speed) at the same method (paddle or basket method) are positive (see Appendix 10). In other words, increasing stirring speed in the dissolution test by either paddle or basket method is associated with increasing release rate$_{14}$.

The effect of paddle stirring on OSU1 was more pronounced than basket stirring as seen in Figure 5.14. This effect of stirring speed is well known and is related to hydrodynamic effects caused by dissolution medium rushing over the bead surface and carrying away dissolved drug. Generally, the faster the stirring the faster drug is removed.

Table 5.11: Sum of squares results of model of effect of speed and method on OSU2 drug release (Method: 2 levels, Speeds: 2 levels), KCl medium

	DF	Sum of square	Mean square	F value	Pr (F)
Model 5.10: release rate$_{14}$ ~ method + speed					
method	1	0.002	0.002	0.051	0.823
speed	1	0.429	0.429	11.640	0.003
Residuals	18	0.663	0.037		

Model 5.10 is adequate since there is little evidence that the interaction term between method and speed affect release rate$_{14}$ (see Appendix 11). Table 5.11 shows that the dissolution methods, paddle and basket, do not affect release rate$_{14}$ from OSU2 (P-value = 0.823). Although there is strong evidence that stirring speed influences OSU2 release rate$_{14}$ (P-value = 0.003), the multiple comparison shows that the OSU2 release rate$_{14}$ at 200 rpm basket stirring speed differs from the OSU2 release rate$_{14}$ at 75 rpm basket stirring speed (see Appendix 11) but the differences at all time points are smaller than 5% (see Figure 5.15).

Verelan PM capsules released drug consistently with little differences in the dissolution profiles at 75 and 200 rpm basket stirring speeds (Figure 5.15) in KCl medium. Aforementioned, OSU1 released drug consistently at 75 rpm and at 200 rpm basket stirring speeds (Figure 5.14). However, OSU1 did not release drug at 200 rpm and 75 rpm paddle speeds in a similar profile (Figure 5.14).

It was found that OSU2 did release drug relatively consistently with small differences in the dissolution profiles at 75 rpm and 200 rpm stirring speeds for both basket method and paddle method in KCl medium (Figure 5.15). Thus, the size of drug bead in the formulation between 1.0 and less than 1.41 mm is preferable for both coating and drug release to achieve minimal variation in drug release profiles with both paddle and basket methods.

Comparison of Verelan PM and OSU2 in KCl medium:

The difference of drug release rate$_{14}$ between Verelan PM and OSU2 in KCl medium was evaluated using two-way ANOVA with multiple comparisons using the Tukey adjustment. The summary is presented in Tables 5.12 and 5.13 and Appendices 16 and 17.
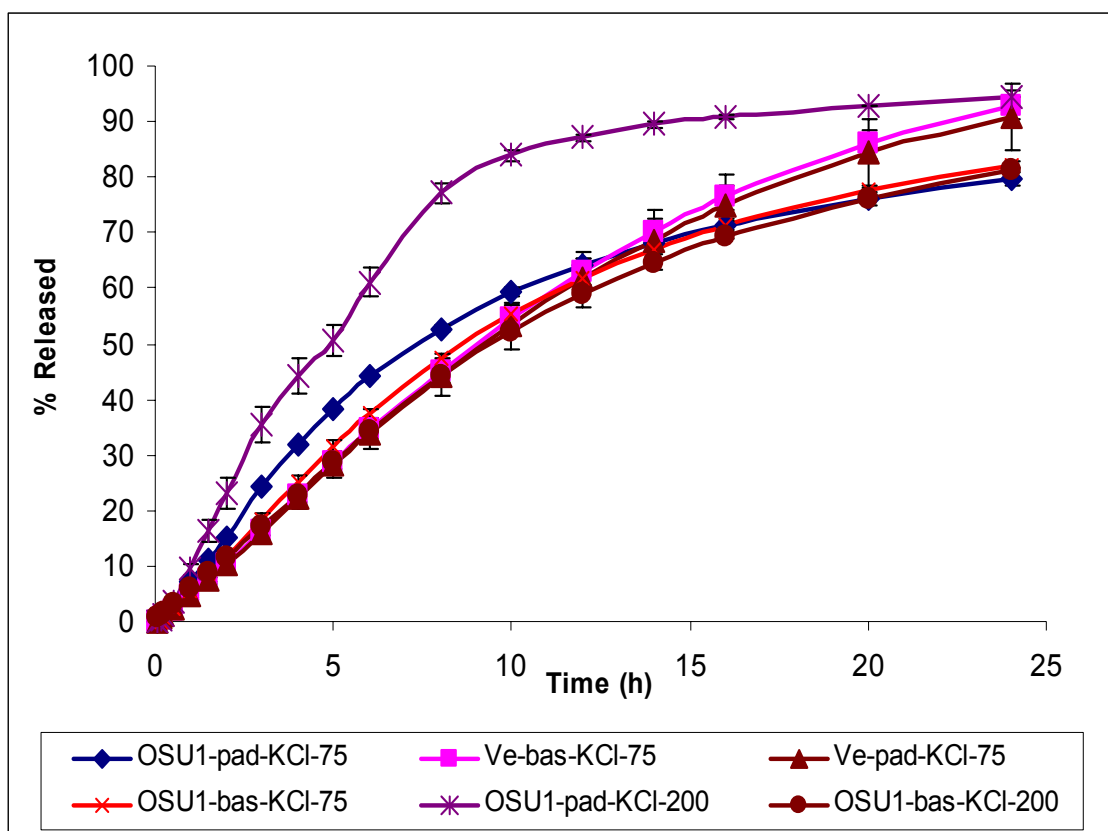
Figure 5.14: Effect of basket and paddle stirring speeds on verapamil HCl release from OSU1, KCl medium

OSU1-pad-KCl-75 = OSU1 formulation, 75 rpm paddle method.

Ve-bas-KCl-75 = Verelan PM capsules, 75 rpm basket method.

Ve-pad-KCl-75 = Verelan PM capsules, 75 rpm paddle method.

OSU1-bas-KCl-75 = OSU1 formulation, 75 rpm basket method.

OSU1-pad-KCl-200 = OSU1 formulation, 200 rpm paddle method.

OSU1-bas-KCl-200 = OSU1 formulation, 200 rpm basket method.
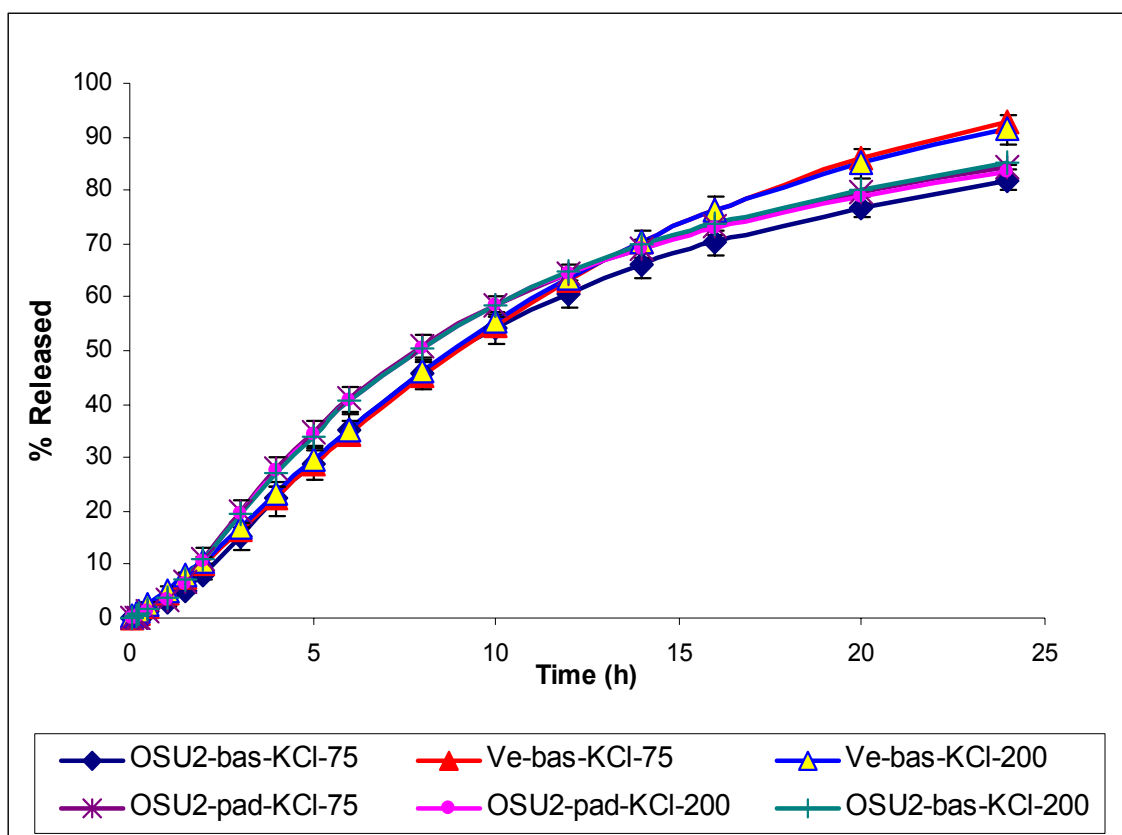
Figure 5.15: Effect of basket and paddle stirring speeds on verapamil HCl release from OSU2, KCl medium

OSU2-bas-KCl-75 = OSU2 formulation, 75 rpm basket method.

Ve-bas-KCl-75 = Verelan PM capsules, 75 rpm basket method.

Ve-bas-KCl-200 = Verelan PM capsules, 200 rpm basket method.

OSU2-pad-KCl-75 = OSU2 formulation, 75 rpm paddle method.

OSU2-pad-KCl-200 = OSU2 formulation, 200 rpm paddle method.

OSU2-bas-KCl-200 = OSU2 formulation, 200 rpm basket method.

Table 5.12: Table III sum of squares of model comparing Verelan PM and OSU2 drug release rates, paddle method, KCl medium, two-way ANOVA

	DF	Sum of square	Mean square	F value	Pr (F)
Model 5.11: release rate$_{14}$ ~ Paddle speed + Ve-OSU2 + Speed* Ve-OSU2					
Paddle speed	1	0.260	0.260	1.721	0.211
Ve-OSU2	1	0.180	0.180	1.190	0.294
Speed* Ve-OSU2	1	0.010	0.010	0.064	0.804
Residuals	14	2.111	0.151		
Model 5.12: release rate$_{14}$ ~ Paddle speed + Ve-OSU2					
Paddle speed	1	0.260	0.260	1.836	0.195
Ve-OSU2	1	0.180	0.180	1.270	0.278
Residuals	15	2.121	0.141		

Ve-OSU2: Verelan PM and OSU2, 2 levels.   Speeds: 2 levels

Speed* Ve-OSU2 is Paddle speed* Ve-OSU2

3 replications in 2 combinations; 6 replications in 2 other combinations; sample size = 18.

Table 5.12 shows there is little evidence the effect of paddle speeds depends on tested capsules, Verelan PM or OSU2 (P-value = 0.804, model 5.11). The interaction term was dropped in model 5.12. There are no differences on release rate$_{14}$ between Verelan PM and OSU2 (P-value = 0.278, model 5.12). The speed of paddle also did not affect release rate$_{14}$ (P-value = 0.195, model 5.12) in the dissolution test using KCl medium.

Table 5.13: Table III sum of squares of model comparing Verelan PM and OSU2 drug release rates, basket method, KCl medium, two- way ANOVA

	DF	Sum of square	Mean square	F value	Pr (F)
Model 5.13: release rate$_{14}$ ~ Ve-OSU2 + Basket speed + Speed* Ve-OSU2					
Ve-OSU2	1	0.077	0.077	2.929	0.109
Basket speed	1	0.120	0.120	4.552	0.051
Speed* Ve-OSU2	1	0.127	0.127	4.819	0.046
Residuals	14	0.368	0.026		

Ve-OSU2: Verelan PM and OSU2, 2 levels.   Speeds: 2 levels

Speed* Ve-OSU2 is Basket speed* Ve-OSU2

3 replications in 2 combinations; 6 replications in 2 other combinations; sample size = 18.

From model 5.13 presented in Table 5.13, there is moderate evidence that the effect of basket speeds on the drug release rate$_{14}$ depends on Verelan PM or OSU2 (P-value = 0.046). The multiple comparisons (Tukey method) shows that only OSU2 at the 200 rpm basket speed differed in drug release rate$_{14}$ from OSU2 at the 75 rpm basket speed in the dissolution test using KCl medium (Appendix 17).

Effect of two pH media and osmotic pressures:

In vivo, drug is exposed in the GI tract to pH: ranging from 1 to 8. To investigate drug behavior in various media, Verelan PM, OSU1 and OSU2 were tested in two-medium dissolution method (see Method part for the detail of two-medium dissolution method). The results are represented in Figure 5.16.
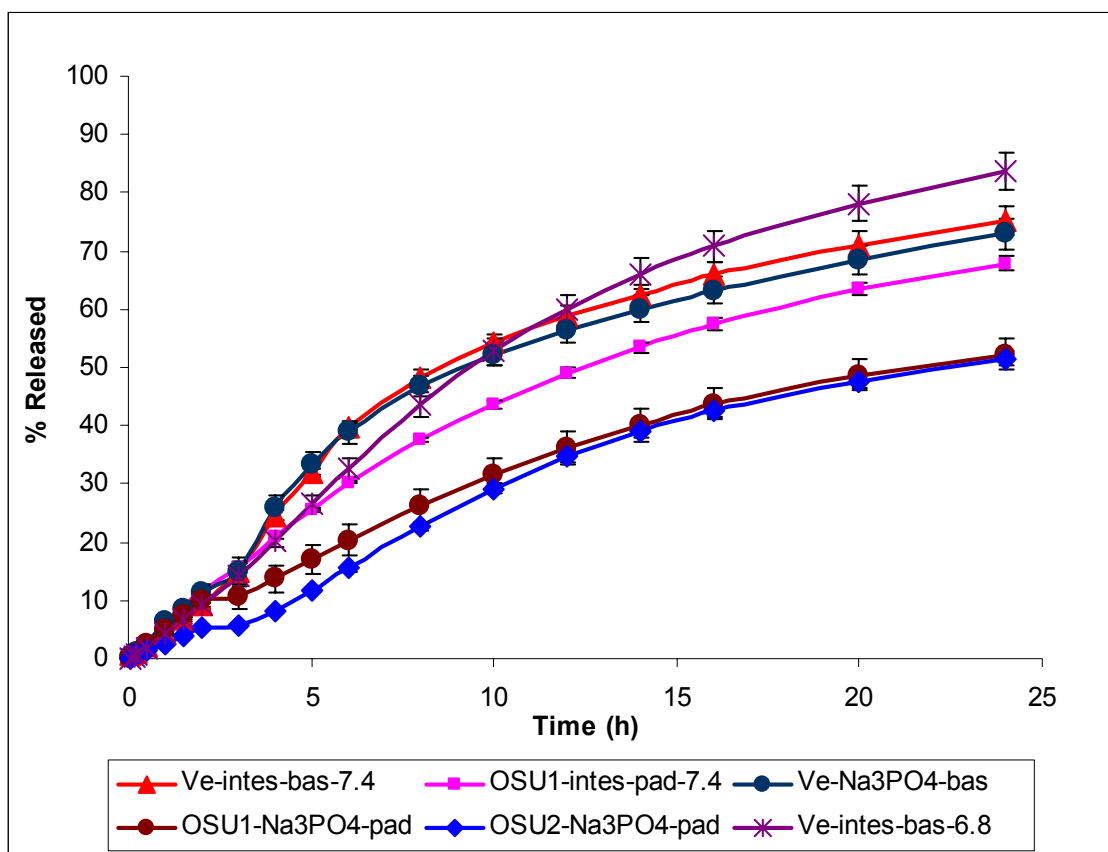
Figure 5.16: Effect of medium on verapamil HCl release from OSU1 and OSU2; the first 2 h in simulated gastric fluid, then other media, at 75 rpm stirring speed

Ve-intes-bas-7.4 = Verelan PM capsules, basket method, simulated intestinal medium pH 7.4.

OSU1-intes-pad-7.4= OSU1 formulation, paddle method, intestinal medium pH 7.4.

Ve-Na3PO4-bas = Verelan PM capsules, basket method, Na_3PO_4 buffer pH 7.4.

OSU1-Na3PO4-pad= OSU1 formulation, paddle method, Na_3PO_4 buffer pH 7.4.

OSU2-Na3PO4-pad= OSU2 formulation, paddle method, Na_3PO_4 buffer pH 7.4.

Ve-intes-bas-6.8 = Verelan PM capsules, basket method, simulated intestinal medium pH 6.8.

Figure 5.16 shows that alkaline pH affected dissolution from Verelan-PM, OSU1 and OSU2. Verelan-PM was the least affected by pH change. The dissolution profile of OSU2, paddle method (the light blue curve), was much lower than the dissolution profile of Verelan PM, basket method (the blue curve), in Na_3PO_4 buffer pH 7.4 medium (Figure 5.16). Interestingly, at the same pH 7.4, but different concentrations of solutes, there is a significant difference of release rate$_{14}$ of OSU1 in intestinal fluid pH 7.4 and in Na_3PO_4 buffer pH 7.4 (Figure 5.16). There may be a difference between osmotic pressure in these two media. In intestinal fluid pH 7.4, where solute concentration is more diluted, release rate$_{14}$ of OSU1 was higher than OSU1 release rate$_{14}$ in Na_3PO_4 buffer pH 7.4.

The effect of media on drug release from Verelan-PM was evaluated using one way ANOVA as shown in Table 5.14.

Table 5.14: Table III sum of squares of model of Verelan PM in different media

	DF	Sum of square	Mean square	F value	Pr (F)
Verelan-Medium	2	0.312	0.156	5.650	0.042
Residuals	6	0.166	0.028		

Table 5.14 shows sum of squares table of one way ANOVA to compare release rate$_{14}$ in 3 different media: simulated intestinal fluid pH 6.8, simulated intestinal fluid pH 7.4, and Na_3PO_4 buffer pH 7.4 using the basket method at a 75 rpm stirring speed. The only significant comparison was Na_3PO_4 buffer pH 7.4 medium versus simulated intestinal fluid pH 6.8 medium (multiple comparisons, see Appendix 13).

Release rate$_{14}$ of Verelan PM in Na$_3$PO$_4$ buffer pH 7.4 is slightly less compared with Verelan PM release rate$_{14}$ in simulated intestinal fluid pH 7.4. There is a difference in the solute concentration upon comparison of Na$_3$PO$_4$ buffer pH 7.4 and simulated intestinal fluid pH 7.4, but both pH and solute concentration differ between Na$_3$PO$_4$ buffer pH 7.4 and simulated intestinal pH 6.8. The difference in solute concentration and pH may produce the differences seen in Verelan PM release rate$_{14}$ in Na$_3$PO$_4$ buffer pH 7.4 and in simulated intestinal pH 6.8. However, the decrease of Verelan PM release rate$_{14}$ was not as pronounced as with OSU1. The reason for the smaller differences may be that Verelan PM contains an organic acid buffer and a sugar core which contributes significant osmotic pressures (Ozturk et al., 1990), therefore the effects of dissolution medium's osmotic pressure and pH are reduced significantly. The hypothesis of effect of osmotic pressure agrees with Krämer and Henning's note (1994) that the concentration of buffering agent, and consequently the osmotic pressure of dissolution media was shown to have an impact on the dissolution behavior of verapamil extended-release products of various galenical types.

Biological availability of a drug is influenced by a variety of pathological, physiological and pharmaceutical factors. Important among the physiological factors are gastric residence time, intestinal transit (Davis et al., 1984) and pH. The human gastrointestinal (GI) tract can be divided into three distinct sections, namely the stomach, the small intestine and the colon. Each has its own physiological function and is highly varied in terms of pH, nature of its luminal contents, length and surface area (Yuen et al., 1993). The small intestine, pH 5-7 (fasted state) and 4-4.7 (fed state) (Gibson et al., 2002)

with its enormous absorption area of between 200 and 500 m^2 is invariably the principal site of drug absorption. In contrast, the stomach with pH from 1-2 (fasted state) to 2-5 (fed state) (Gibson et al., 2002), being a secretory rather than an absorptive organ, and the colon with pH of 5-7.8 (Gibson et al., 2002), because of its small absorptive area, usually play a small role in the absorption of drugs. Nevertheless, particularly in the case of sustained release preparations, the colon may play an important absorptive role (Yuen et al., 1993). The times for 50% gastric emptying of pellets were 119 ± 15 (light breakfast) and 285 ± 45 min (heavy breakfast) (Davis et al., 1984). The corresponding transit time of pellets through the small intestines was 204 ± 31 min, for colon transit time was up to 15-48 h (fasted state) and 72 h (fed state-Gibson et al., 2002). Yuen et al. (1993) studied gastrointestinal transit and absorption of theophylline from controlled-release pellets. They found that for both fed and fasted conditions, absorption of theophylline was fastest when the pellets were in the small intestine, followed by in the stomach, and was slowest when in the colon (Yuen et al., 1993). Total contact time of pellets with stomach and intestinal medium with pH lower than 7.0 is about 6 h (fasted state) to 12 h (fed state). Sink condition, surfactants, metabolized enzymes, and drug transporters in the GI tract also are critical factors in drug absorption.

Because sustained release formulations travel through the entire G.I. tract before releasing their entire drug contents, it is useful to know the effect of the G.I. tract pH on the drug release patterns. Sorasuchart et al. (1999) investigated the effects of pH on drug release from spray layered and coated drug-containing beads. It was shown that Ketoprofen (weak acid, pKa 4.8), and nicardipine-HCl (salt of weak organic base, pKa

8.6) provided different dissolution characteristics in enzyme-free stimulated gastric fluid (pH 1.4) and enzyme-free simulated intestinal fluid (pH 7.4), indicating the rate of drug release was pH dependent and related to drug ionization even though the solubility of the coating (ethylcellulose) is pH independent. Acetaminophen (very weak acid, pKa 9.7, not ionized at physiological pH) is relatively more soluble in water; therefore, the release rates were similar on both dissolution media and were not affected by degree of ionization (Sorasuchart et al., 1999).

Ratio of ionized to non-ionized forms of drug is described in Henderson and Hasselbalch's equations (Sorasuchart et al., 1999):

For weak acids: $\dfrac{Ionized}{Nonionized} = 10^{(pH - pKa)}$; For weak bases: $\dfrac{Nonionized}{Ionized} = 10^{(pH - pKa)}$

Verapamil-HCl (salt of weak organic base) is more ionized in acidic medium and is very soluble in acidic medium, but in higher pH medium its solubility is reduced since verapamil HCl may form its non-ionized base form, and be precipitated.

In the case of the dissolution profiles of verapamil presented in Figure 5.16, it was observed that for both OSU1, and OSU2, the beads began to clump and stick together when 0.2M Na_3PO_4 was added into simulated gastric medium in the dissolution study. The exposed surface area of beads when they clump together obviously reduces when compared with the beads in the KCl medium. The Verelan-PM beads remained separated in all dissolution media tested. All beads, including Verelan PM, released drug in two-pH medium method more slowly than KCl medium. "Sticking together" of beads as observed

in the dissolution study is not expected to occur *in vivo*. Further, for the Na_3PO_4 buffer pH 7.4 method, when 0.2M Na_3PO_4 was added into simulated gastric fluid has a higher concentration than USP simulated intestinal fluid pH 7.4, approximately 4 to 6 times higher. Thus, while many dissolution methods and media have been reported in the literature, it is important to consider a myriad of factors to select appropriate dissolution conditions in formulation development and testing. The differences in verapamil release for the formulations and methods reported above, along with the considerations presented show how complex the selection can become. In this case, the well known Na_3PO_4 buffer pH 7.4 method is not a good candidate to test verapamil HCl beads coated with ethylcellulose because the results are not expected to be predictive of drug release in the body for the reasons presented above. It was thus decided to evaluate the use of intestinal fluid (pH 6.8) as indicated in USP 25.

In test 1 for verapamil extended release tablets in USP 25, simulated gastric fluid without pepsin (simulated gastric fluid) for the first 1 h is suggested, followed by enzyme-free simulated intestinal fluid pH 6.8 (simulated intestinal fluid pH 6.8). Verelan-PM and OSU2 were tested using simulated gastric fluid pH 1.4 for the first 2 h, then simulated intestinal fluid pH 6.8. Dissolution profiles from this method are presented in Figures 5.17 and 5.18. Both Figures 5.17 and 5.18 show that OSU2 and Verelan-PM profiles were close, and drug release was minimally affected by the stirring speeds.

Figure 5.18 shows no effect of varying paddle speeds on verapamil HCl release from Verelan-PM (50 to 100 rpm) or OSU2 (50 to 200 rpm). However, Verelan PM at a

200 rpm paddle speed showed a slight increase in release rate over Verelan PM at other paddle speeds in the dissolution test of the two-medium method. More than 90% of drug was released from Verelan-PM after 30 h, while for OSU2 90% was released after 32 h, at 200 rpm paddle speed. All dissolution profiles were very close to each other.

The effect of paddle speeds on release rate$_{14}$ was evaluated using linear regression models (see Appendix 12). Table 5.15 presents the coefficients from an adopted model. Stirring speed using 50, 75, 100 and 200 rpm, was treated as a continuous variable.

Table 5.15: Effect of paddle speeds on OSU2 drug release rate$_{14}$, in intestinal fluid pH 6.8 method

Coefficients:	Value	Std. Error	t value	Pr(>|t|)
(Intercept)	4.373	0.054	81.165	< 0.001
Paddle speed	0.0006	0.0004	1.440	0.169

Table 5.15 shows no association between paddle speeds and release rate$_{14}$ (P-value = 0.169). The residual plot (Figure A.6 in Appendix 12) did not show any evidence of violation of the assumptions.
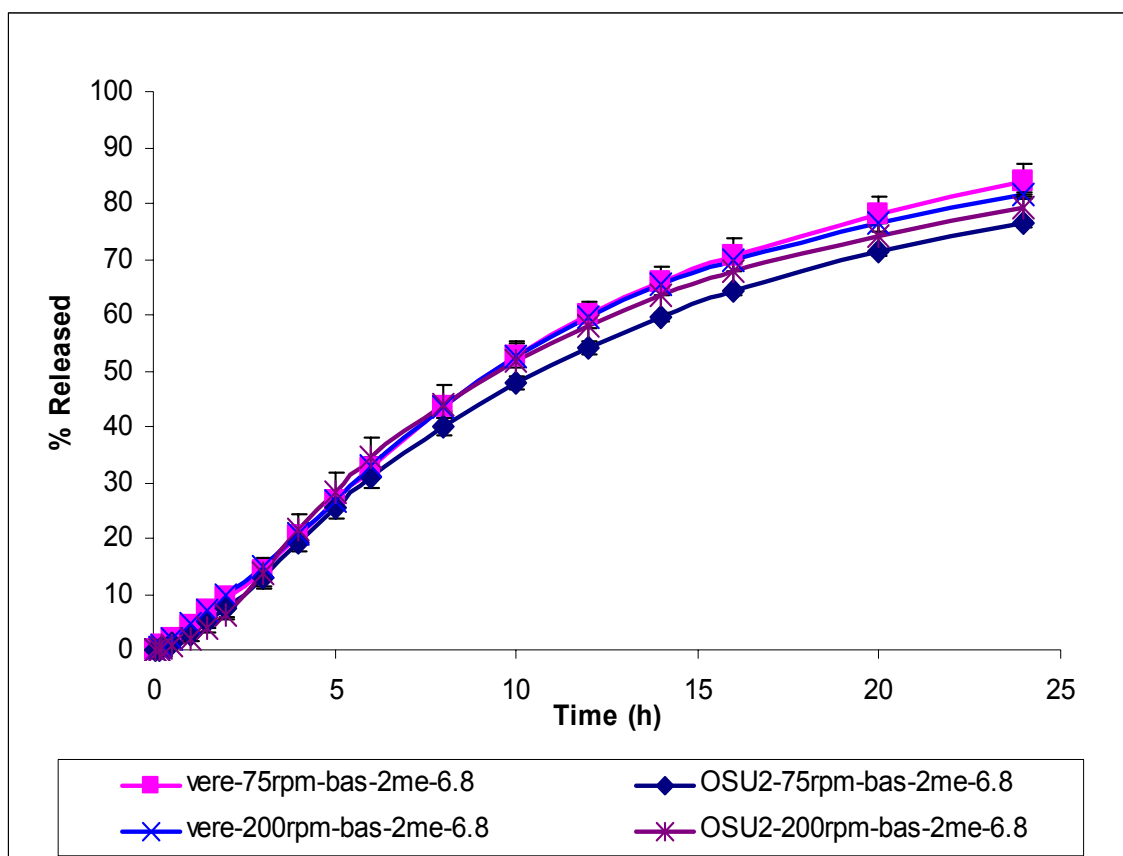
Figure 5.17: Dissolution profiles of Verelan PM and OSU2 in simulated gastric fluid pH 1.4 for the first 2h and then intestinal fluid pH 6.8 at 75 and 200 rpm basket method

vere-75rpm-bas-2me-6.8 = Verelan PM capsules, 75 rpm basket method.

OSU2-75rpm-bas-2me-6.8 = OSU2 formulation, 75 rpm basket method.

vere-200rpm-bas-2me-6.8 = Verelan PM capsules, 200 rpm basket method.

OSU2-200rpm-bas-2me-6.8 = OSU2 formulation, 200 rpm basket method.
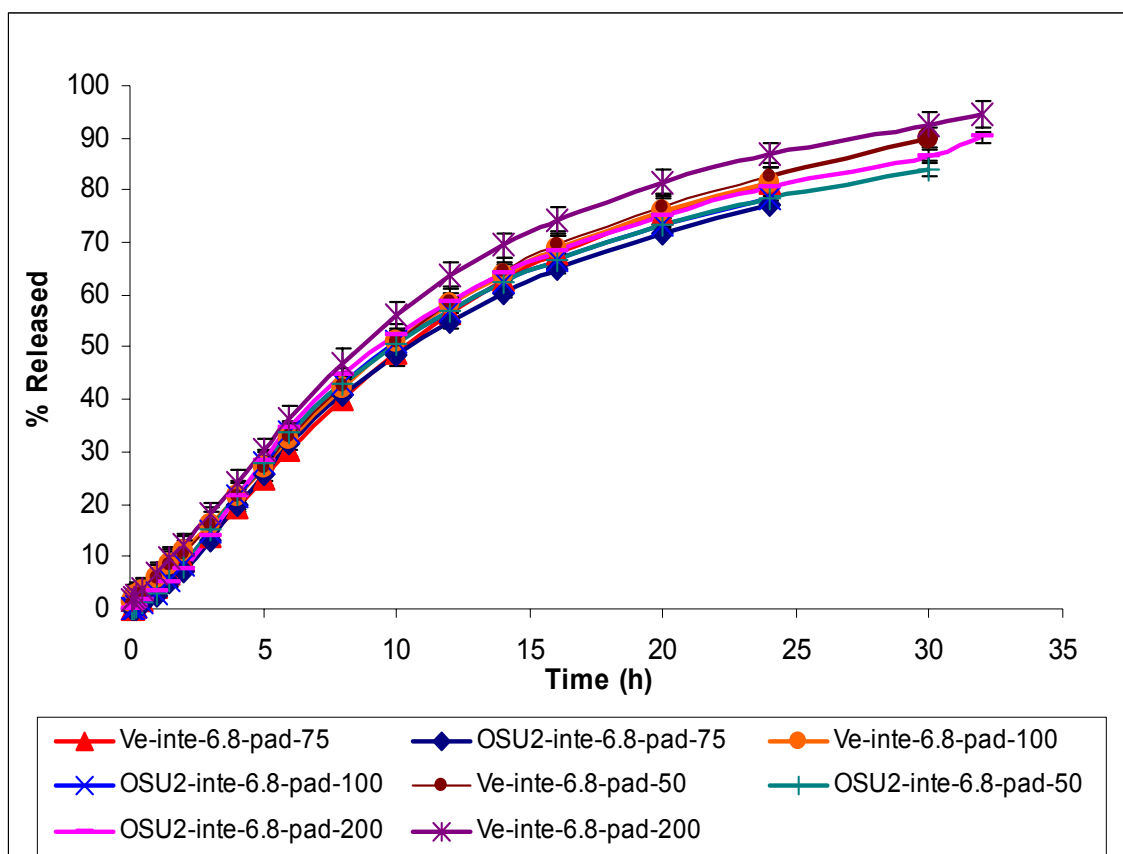
Figure 5.18: Dissolution profiles of Verelan PM and OSU2 in simulated gastric fluid pH 1.4 for the first 2 h and then intestinal fluid pH 6.8 at 50 to 200 rpm, paddle method

Ve-inte-6.8-pad-75 = Verelan PM capsules, 75 rpm paddle method.

OSU2-inte-6.8-pad-75 = OSU2 formulation, 75 rpm paddle method.

Ve-inte-6.8-pad-100 = Verelan PM capsules, 100 rpm paddle method.

OSU2-inte-6.8-pad-100 = OSU2 formulation, 100 rpm paddle method.

Ve-inte-6.8-pad-50 = Verelan PM capsules, 50 rpm paddle method.

OSU2-inte-6.8-pad-50 = OSU2 formulation, 50 rpm paddle method.

OSU2-inte-6.8-pad-200 = OSU2 formulation, 200 rpm paddle method.

Ve-inte-6.8-pad-200 = Verelan PM capsules, 200 rpm paddle method.

Comparison of release rate$_{14}$ between Verelan PM and OSU2 in two-medium test system:

Differences in release rate$_{14}$ between capsules, Verelan PM and OSU2, at various paddle speeds were evaluated for the two-medium method using the two-way ANOVA method. Tables 5.16 presents summaries of this analysis.

Table 5.16: Summaries type III sum of squares from two-way ANOVA, paddle stirring dissolution, two-medium method

	DF	Sum of square	Mean square	F value	Pr (F)
Model 5.14: release rate$_{14}$ ~ Ve-OSU2 + Paddle speed + Speed* Ve-OSU2					
Ve-OSU2	1	0.130	0.130	12.001	0.003
Paddle speed	3	0.125	0.042	3.852	0.030
Speed* Ve-OSU2	3	0.244	0.081	7.504	0.002
Residuals	16	0.173	0.011		

Speed* Ve-OSU2 is Paddle speed* Ve-OSU2;   Ve-OSU2: capsules have two levels.

Model 5.14 in Table 5.16 demonstrates there is strong evidence the effect of paddle speeds on release rate$_{14}$ depends on tested capsules, Verelan PM or OSU2 (P-value = 0.002). Multiple comparisons (Tukey method) show differences only existed between Verelan PM at 200 rpm paddle speed with Verelan PM at 50, 75, and 100 rpm paddle speeds, and between Verelan at PM 200 rpm paddle speed with OSU2 at 50, 75, 100, 200 rpm paddle speeds (herein Verelan PM at 50, 75, and 100 rpm paddle speeds, and OSU2 at 50, 75, 100, 200 rpm paddle speeds are named as other groups, see Appendix 14). Otherwise, there were no differences between Verelan PM at stirring

speeds of 50, 75, and 100 rpm with OSU2 at all paddle speeds. Even though statistically significant differences exist between Verelan PM at the 200 rpm stirring speed, paddle method and other groups, these differences at all time points are between 0 and 8%.

Figure 5.17 shows that Verelan PM capsules released drug consistently with little differences in the dissolution profiles at 75 and 200 rpm basket stirring speeds in two-medium method. OSU2 also released relatively consistently with small differences at 75 and 200 rpm basket stirring speeds in two-medium method (Figure 5.17). However, dissolution profiles of Verelan PM at 75 and 200 rpm basket stirring speeds were a little higher than dissolution profile of OSU2 at 75 rpm. Even though small differences exist between dissolution profiles Verelan PM at 75 and 200 rpm basket speeds and OSU2 at 75 rpm basket speed, the differences at all time points between Verelan PM and OSU2 at 75 rpm and 200 rpm basket are between 0 and 7% (Figure 5.17). Multiple comparisons among these groups (Verelan PM and OSU2 at 75 rpm and 200 rpm basket) are shown in Appendix 15.

These statistical dissolution comparisons are useful in product formulation optimization but because of physiological variations within and among people, less than 10% differences in dissolution time point results for different formulations do not result in statistical or clinical differences in bioavailability. That is, such formulations are expected to give essentially identical effects in people.

Release rate is equal to the slope of the dissolution curve if dissolution curve is a straight line (zero order drug release). To evaluate if drug released from ethylcellulose

coated beads follows square root order, first order, or zero order models (all common drug dissolution profiles), the dissolution rate constants in each model were calculated and simulated dissolution profiles using these models were generated and plotted. These models were used regardless of dissolution mechanism to elucidate drug release from ethylcellulose coated beads. AIC was chosen to select the best model by selecting the smallest values of the AIC. Figures 5.19 and 5.20 show simulated and real dissolution profiles of Verelan PM and OSU2 for 14 hours.
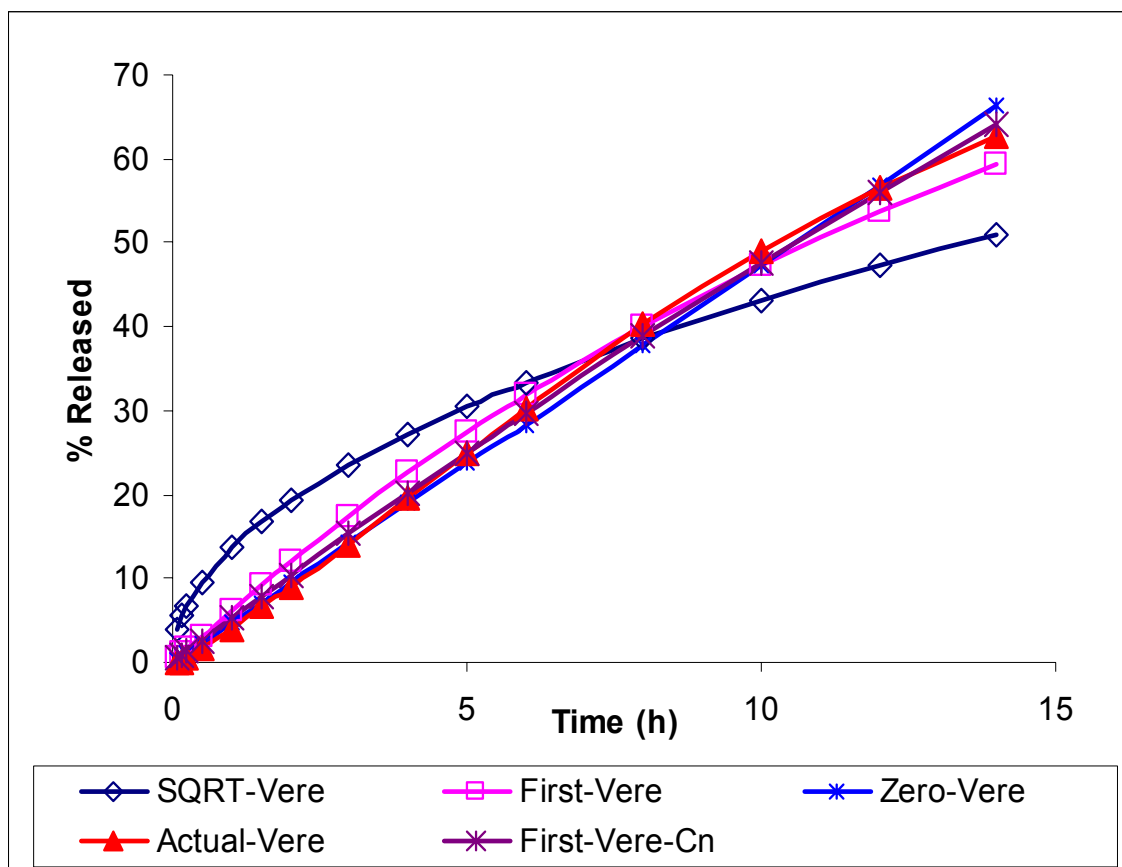
Figure 5.19: Simulated and real dissolution profiles of Verelan PM capsules based on two-medium method, 75 rpm paddle for 14 hours.

SQRT-Vere = Simulated dissolution curve from square root release model of Verelan PM for 14 h.

First-Vere = Simulated dissolution curve from first order release model of Verelan PM for 14 h with Cn =100.

Zero-Vere = Simulated dissolution curve from zero order release model of Verelan PM for 14 h.

Actual-Vere = real dissolution curve of Verelan PM for 14 h.

First-Vere-Cn = Simulated dissolution curve from first order release model of Verelan PM for 14 h with S-plus fitted Cn.
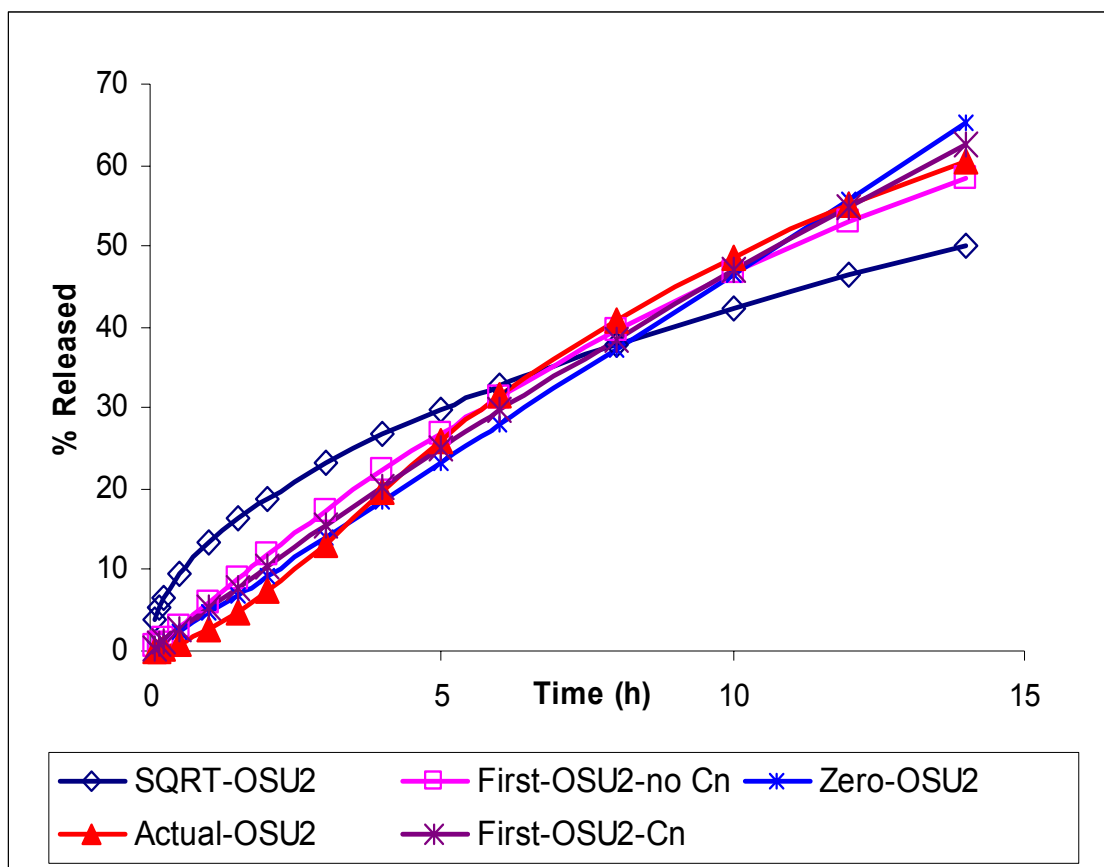
Figure 5.20: Simulated and real dissolution profiles of OSU2 based on two- medium method, 75rpm paddle for 14 hours

SQRT-OSU2 = Simulated dissolution curve from square root release model of OSU2 for 14 h.

First-OSU2-no Cn = Simulated dissolution curve from first order release model of OSU2 for 14 h with Cn =100.

Zero-OSU2 = Simulated dissolution curve from zero order release model of OSU2 for 14 h.

Actual-OSU2 = real dissolution curve of OSU2 for 14 h.

First-OSU2-Cn = Simulated dissolution curve from first order release model of OSU2 for 14 h with S-plus fitted Cn.

Table 5.17: Summarized residual standard errors and AIC of three drug release models

	Square root model		First order model with Cn		First order model fixed Cn		Zero order model	
	OSU2	Verelan	OSU2	Verelan	OSU2	Verelan	OSU2	Verelan
24 h data, n = 54								
Res-SD24	8.135	8.490	2.334	2.510	2.384	2.939	6.418	6.068
# para.	1	1	2	2	1	1	1	1
AIC	100.320	102.320	**43.750**	**47.160**	42.754	52.557	89.199	86.569
16 h data, n = 48								
Res-SD16	8.198	8.291	2.067	1.929	2.520	2.804	3.026	2.625
# para.	1	1	2	2	1	1	1	1
AIC	89.716	90.186	**34.270**	**31.400**	**40.530**	44.985	48.163	**42.240**
14 h data, n = 45								
Res-SD14	8.031	7.939	1.969	1.694	2.574	2.655	2.346	1.948
# para.	1	1	2	2	1	1	1	1
AIC	83.429	82.979	**30.480**	**24.590**	38.956	40.161	**35.330**	**28.060**

Res-SD24 = Residual standard error calculated up to 24 h, 24 h data.

Res-SD16 = Residual standard error calculated up to 16 h, 16 h data.

Res-SD14 = Residual standard error calculated up to 14 h, 14 h data.

para.= number of parameters in a model.

Verelan = Verelan PM

Table 5.17 presents summaries of residual standard errors and the AICs from these models. Table 5.18 shows the fitted dissolution rate constants (K_1s) with the fitted percentages of total drug released (fitted C_ns) from the first order model. Table A.2

(Appendix 18) presents the fitted dissolution rate constants from the three models. Appendix 18 also presents the fitting results of the dissolution rate constants for three models.

Table 5.17 shows that the square root model is the least acceptable compared to the other models (AICs of SRQT model are the largest). For the entire period of time up to 24 h, the first order release models are the best to represent dissolution data of Verelan PM and OSU2 (the smallest AIC) for both the fitted C_n (based on equation 5.1) or the fixed C_n ($C_n = 100$, based on equation 5.7 below) as seen in Table 5.17. Figures A.7 and A.8 in Appendix 19 show the simulated and real dissolution profiles of Verelan PM and OSU2 based on these models up to 24 hours. The fitted dissolution rate constants and the fitted C_ns from the first order model (equation 5.1) for the 14 to 24 hours data are shown in Table 5.18.

Table 5.18: Fitted dissolution rate constants and fitted percentage of total drug released of first order model

	14 hours		16 hours		24 hours	
	K_1	C_n	K_1	C_n	K_1	C_n
OSU2	0.027	**200.784**	0.037	**149.716**	0.057	**106.910**
Verelan PM	0.020	**261.905**	0.029	**185.625**	0.050	**119.908**

Using Splus software program, the fitted C_ns in the first order model (equation 5.1 in the Method part) are greater than 100% (Table 5.18), but in reality they must be less than or equal to 100% because drug loaded content is 100% in each OSU2 or Verelan PM

capsule. Therefore, C_ns were not estimated and fixed at 100. The fixed percentage of total drug released, which is equal 100%, was used to replace the fitted percentage of total drug released using the following equation (equation 5.7).

$$C = 100 * (1 - \exp(-k_1 t)) \qquad (5.7).$$

When C_ns were not estimated, the column of "First order model with Cn" was excluded. Based on Table 5.17 with only three columns remaining ("Square root model", "First order model fixed Cn", and "Zero order model" columns), the zero order model is the best fit for OSU2 up to 14 hours, and the best fit for Verelan PM up to 16 hours (the smallest AIC).

Fitting results for all three common dissolution release patterns suggest that the release patterns for Verelan PM and OSU2 are the same over the entire drug release vs. time curves which is both desirable and quite surprising given the large differences in manufacturing processes and in the product bead structures (see Figure 5.1). When formulation structures are identical then drug release mechanisms and dissolution profiles are expected to be the same. When formulations structures differ, it is common for release mechanisms to also differ but drug dissolution profiles may be the same or different. In the current case, one would not <u>a priori</u> expect the release mechanisms from such different formulations to be the same. Note that a finding of essentially identical release patterns through the fitting methods used does not mean the drug release mechanisms are the same.

Release mechanism:

As seen in all figures, drug release profiles exhibit two phases. In the first phase (the constant release phase) the release rate approximately follows zero-order kinetics up to 14 or 16 hours for OSU2 or Verelan PM, respectively**.** In the second phase from 14 or 16 hours, solid drug in the core is most likely sufficiently depleted that the release rate decreases. The release mechanism for the new formulation not only is controlled by a diffusion process through bead's coated ethylcellulose itself but also through lactose channels in the ethylcellulose. Osmotically driven forces should be considered. The difference of osmotic pressure between the outside and inside of the polymer membrane might control drug release. The release of verapamil HCl from ethylcellulose coated beads was also affected by pH. This probably is because of the drug itself. Verapamil HCl is highly soluble in water and low pH medium. At pH media greater than 7.0 verapamil HCl solubility is quickly reduced and its' free base may form.

For Verelan PM both osmotic pressure and pH are expected to be important as well but the drug release mechanism is complicated by the organic acid in the core and the large number of alternating drug and HPMC layers. It is expected that the HPMC forms a viscous gel through which both liquid and drug must diffuse with these gel layers and drug being alternating and non-continuous.

Convolution results:

Using convolution calculations and assuming a linear relationship between dissolution and absorption for both Verelan-PM and OSU2, simulation was performed to

predict the drug concentrations versus time curves for these two products in a bioavailability study. Because different dissolution tests have been investigated, convolution was conducted for the USP basket method in KCl and the USP paddle method in two pH change media using simulated intestinal fluid pH 6.8 with another assumption being that bioavailability of verapamil HCl sustained-release beads is 0.2 based on bioavailability of verapamil intermediate release tablet that is about 20% (McAllister et al., 1982). Dissolution data were selected to represent the widest range of all results given dissolution testing methods considered appropriate. Table 5.19 summarizes T_{max}s and C_{max}s. The simulated verapamil plasma concentrations versus time curves are shown in Figures 5.21 and 5.22.

Table 5.19: Simulated T_{max} and C_{max} of Verelan PM and OSU2

		T max (h)		Cmax (mg/l)	
		Verelan	OSU2	Verelan	OSU2
Basket, KCl medium	75 rpm	10	10	45.861	44.361
	200 rpm	10	8	46.647	47.620
Paddle, 2 media, pH 6.8	50 rpm	10	10	42.684	42.239
	100 rpm	10	10	42.441	42.347
	200 rpm	10	10	46.286	43.955

Verelan = Verelan PM
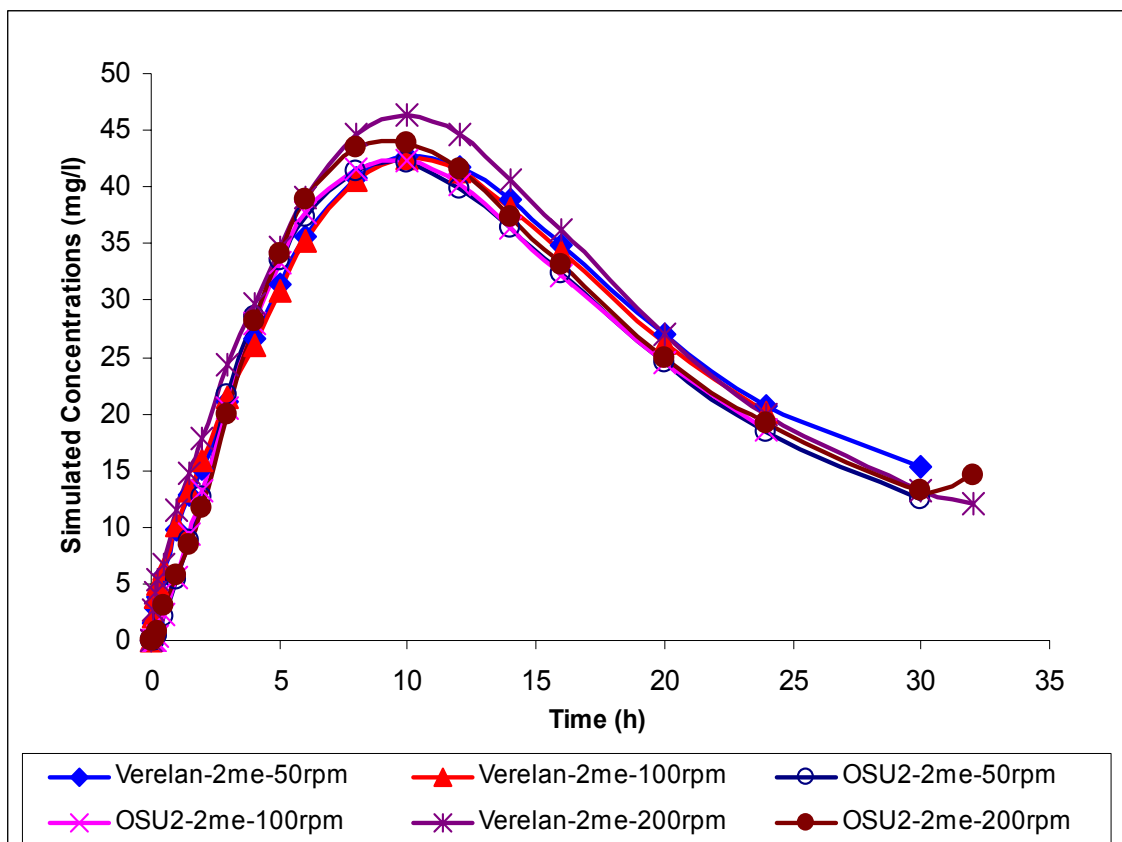
Figure 5.21: Simulated concentrations versus time curves of Verelan PM and OSU2 in simulated gastric fluid pH 1.4 for the first 2 h and then simulated intestinal fluid pH 6.8 at 50 to 200 rpm paddle stirring speeds

Verelan-2me-50rpm = Verelan PM capsules, 50 rpm paddle method.

Verelan-2me-100rpm = Verelan PM capsules, 100 rpm paddle method.

OSU2-2me-50rpm = OSU2 formulation, 50 rpm paddle method.

OSU2-2me-100rpm = OSU2 formulation, 100 rpm paddle method.

Verelan-2me-200rpm = Verelan PM capsules, 200 rpm paddle method.

OSU2-2me-200rpm = OSU2 formulation, 200 rpm paddle method.
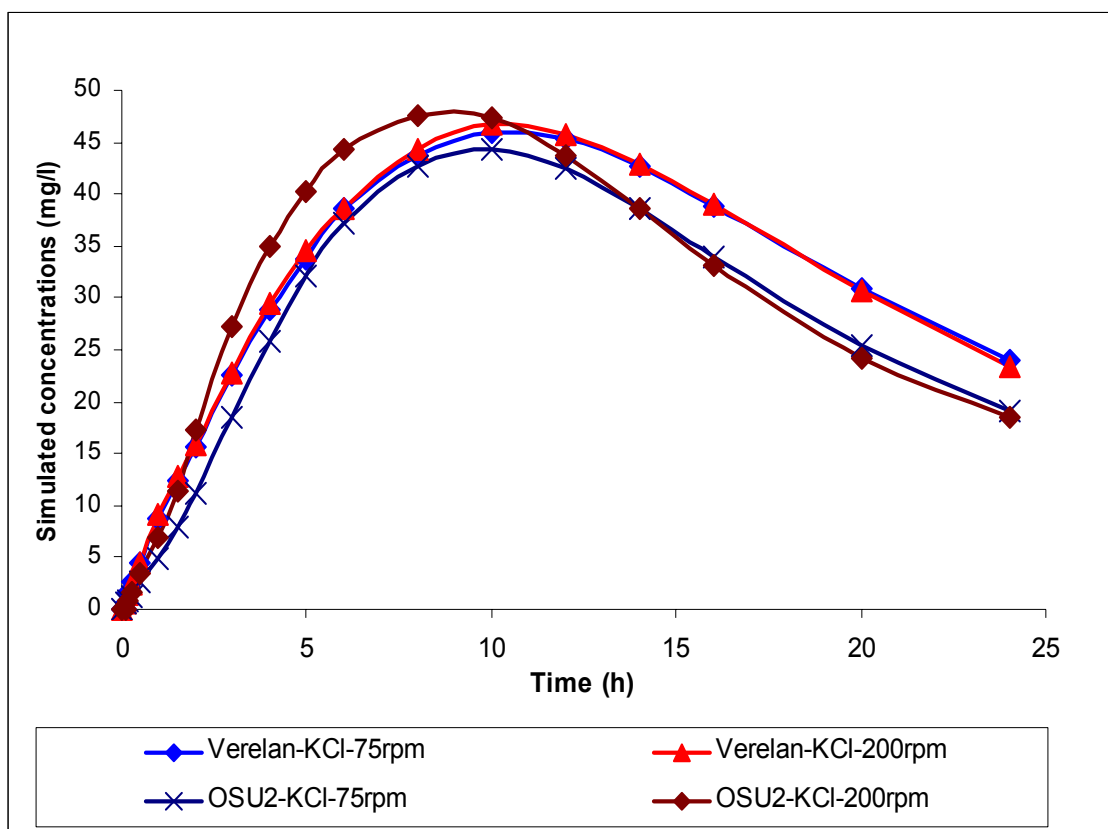
Figure 5.22: Simulated concentrations versus time curves of Verelan PM and OSU2 in KCl medium at 75 to 200 rpm basket stirring speeds

Verelan-KCl-75rpm = Verelan PM capsules, 75 rpm basket method.

Verelan-KCl-200rpm = Verelan PM capsules, 200 rpm basket method.

OSU2-KCl-75rpm = OSU2 formulation, 75 rpm basket method.

OSU2-KCl-200rpm = OSU2 formulation, 200 rpm basket method.

Figure 5.21 shows simulated plasma concentration curves versus time of Verelan PM and OSU2 in two-medium dissolution method using simulated gastric fluid pH 1.4 for the first 2 h and then simulated intestinal fluid pH 6.8; at 50, 100, and 200 rpm paddle speeds. Figure 5.22 shows simulated plasma concentration curves versus time of Verelan PM and OSU2 in KCl medium, 75 and 200 rpm basket speeds. The low stirring speeds of paddle and basket, at 50 and 75 rpm, respectively, represent administration in fasted state, while the high speed of paddle of 100 rpm and may be paddle of 200 rpm, and basket of 200 rpm, represent fed state. In all states, and all medium methods, simulated $C_{max}s$ of Verelan PM and OSU2 are not different by more than 10%. Furthermore, simulated verapamil plasma concentrations versus time curves of OSU2 are close to that of Verelan PM in each medium and each stirring speed, respectively, which implies that *in vivo* AUC of OSU2 is close to AUC of Verelan PM. In both cases, bioequivalence is predicted.

Aforementioned, OSU2 at 75 rpm basket speed differs (less than 5% at all time points) from OSU2 at 200 rpm basket speed, KCl medium, but convolution shows that simulated Cmax and AUC of OSU2 at 75 rpm basket speed, and 200 rpm basket speed are less than 10% differences. Thus, this difference is not of practical significance. Appendix 14 also shows statistically significant differences exist between Verelan PM at 200 rpm paddle speed and other groups (see page 248) at two-medium method, however convolution shows that simulated Cmax and AUC of Verelan PM at 200 rpm paddle speed differs less than 10% of those of other groups. Thus, these differences are not of practical significance.

CONCLUSIONS

A novel bead formulation of verapamil HCl has been developed comprising a combination of extrusion and spheronization to produce a relatively high drug load, followed by coating with an insoluble polymer (ethylcellulose) that contains a water soluble channeling agent (lactose), thus allowing a sufficiently thick coating to be uniform and robust without "shutting down" release of the relatively insoluble drug.

The effects of surfactant (tween 80), disintegrant (Explotab), channeling agent (lactose), and outer coating weight gain were investigated. Tween 80 influenced release $rate_{14}$ significantly (P-value < 0.001), with more tween 80 producing higher release $rate_{14}$. Also, the greater the outer coating weight gain the lower the release $rate_{14}$. Increasing the amount of Explotab in the bead core is strongly associated with release $rate_{14}$ (P-value <0.001). The effect of lactose on release $rate_{14}$ significantly depends on outer coating weight gain (P-value < 0.001).

Release mechanism and model for drug release during dissolution testing, and the rate constant for drug release were elaborated. Dissolution rate constants were fit using three models, first order release, square root order, and zero order models. From time zero to 24 h, a first order release model is best to represent dissolution data of new verapamil HCl coated beads. However, up to 14 h, a zero order release model is closer to real data than other models for new formulation beads. The release mechanism not only is controlled by a diffusion process through the barrier film itself, and lactose channels, but also depends on bead size. Osmotic pressure effects should also be considered for

inclusion in the mechanism of release from verapamil HCl beads coated with ethylcellulose.

OSU2 provided the unexpected benefit that by adjusting the coating thickness and ethylcellulose/lactose ratio, it is possible to obtain essentially a non-agitation sensitive and zero-order drug release of verapamil for up to 14 hours in either KCl or two pH media at stirring speeds of either 75 or 200 rpm with the USP basket or USP paddle stirring method. No references have been found of any other bead formulations with this unique set of characteristics.

OSU2, the preferred formulation for this study contains 200 mg of verapamil HCl, 85 mg of Avicel pH 101, 15 mg of Polyethylene oxide W.M. 100000, bead mesh size 12-18, extruded and spheronized to make beads, then coated with 6.5% weight gain with ratio of solids contents in Surelease:lactose =100:5. This formulation matched the dissolution pattern of Verelan-PM capsules with basket method and paddle method in KCl medium, and two-pH medium dissolution method at different speeds. OSU2 is predicted by convolution simulation to be bioequivalent to Verelan-PM *in-vivo*.

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CHAPTER 6: GENERAL CONCLUSION

GENERAL CONCLUSION

A novel hot-melt pan coating method was evaluated. Hot melt pan coating, which took 2-3 hours for 300 mg coating weight gain on capsules, and tamper-resistant coating, which took 30 minutes, is much faster than tedious sugar coating and allows greater coating weight gains in shorter times than spray-melt coating. Although hot-melt pan coating is promising, it needs modification for industrial scale-up and to provide more elegant formulations. Temperature jacketed ointment vats with side scrapers and mixing blades may be considered for larger scale production. Methods described herein are easy in a lab, can make sustained release formulations, pulse-release formulations, and tamper-resistant capsules. These approaches are recommended for researchers who want to quickly develop and test sustained release or pulse-release dosage forms. Industrial scale-up has not yet been undertaken.

Hot melt filling or solid matrix capsules were investigated. Dissolution of drug from solid matrix formulations made from a hot melt filling method is sensitive to stirring speeds. Hot-melt capsule filling is an especially appealing and simple way to make sustained release formulations in the lab and are suggested as an excellent approach for commercial application in underdeveloped or financially limited cases.

A novel formulation of glipizide also developed comprising compression of four-layer coated beads into tablets has advantages of providing a lag time before drug release, keeping sustained-release characteristics, providing approximately zero-order drug release, and drug release that is nearly independent of paddle speeds of 50 and 100 rpm.

The amount of binding and disintegrant ingredients can be adjusted to produce appropriate disintegration time for tablets and to release individually coated particulates. The role of the hardening layer, and the use of Surelease in the drug layer and controlled release layer were elucidated, along with the effects that compression pressures and paddle speeds had on drug release. It is possible to obtain essentially zero-order drug release in two pH media at stirring speeds of either 50 or 100 rpm with the USP paddle stirring method with glipizide from tablets made of four-layer coated beads. One of the new formulations, CH20 tablet, matched the dissolution pattern of Glucotrol-XL osmotic pump tablets in the USP paddle method in two pH medium method at 100 rpm. Also dissolution patterns of Glucotrol XL and CH20 tablets were very close to each other at 50, 150 and 200 rpm paddle speeds. This formulation is predicted by convolution simulation to be bioequivalent to Glucotrol-XL in-vivo.

A novel bead formulation of verapamil was also developed comprising a combination of extrusion and spheronization to produce a relatively high drug load, followed by coating with an insoluble polymer (ethylcellulose) that contains a water soluble channeling agent (lactose), thus allowing a sufficiently thick coating to be uniform and robust without "shutting down" release of the relatively insoluble drug. The effect of surfactant (Tween® 80), disintegrant (Explotab®), and weight gain are studied. Dissolution release constant model and release mechanism were proposed. A formulation, OSU2, provided the unexpected benefit that by adjusting the coating thickness and ethylcellulose/lactose ratio, it is possible to obtain essentially a non-agitation sensitive and zero-order drug release for up to 14 hours in either KCl or two pH

media at stirring speeds of either 75 or 200 rpm with the USP basket or USP paddle stirring method. This formulation matched the dissolution pattern of Verelan-PM capsules with basket method and paddle method in KCl medium, and two pH medium dissolution methods at different speeds and is predicted by convolution simulation to be bioequivalent to Verelan-PM *in-vivo*.

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APPENDICES

Table A.1: Individual weights of chlorpheniramine hot-melt coated capsules

Capsule number	F1 (112 mg weight gain)	F2 (152 mg weight gain)	F3 (172 mg weight gain)	F4 (192 mg weight gain)
1	170.2	205.1	242.6	285.1
2	144.1	219.6	216	262.8
3	172.2	230.4	221.3	301.3
4	157.0	212.3	262.5	291.3
5	144.6	215.5	238.7	253.9
6	159.8	216	229.4	257.8
7	162.7	214.9	240.4	259.4
8	168.4	277.6	254.7	226.2
9	145.8	268.8	242.7	237.9
10	168.8	225.9	228.7	275.9
11	147.9	204.5	248.1	310
12	144.1	235.6	263.8	288.9
13	167.7	212.4	252.5	240.5
14	156.5	246.7	216.6	269.2
15	165.9	229.9	249.2	269.5
16	148.5	264.7	221.6	241.7
17	182.1	266.5	239.9	230
18	153.3	305	273.9	214.4
19	151.0	222.4	228.3	222.6
20	139.9	207.6	244.4	223.5
Average	157.525	234.070	240.765	258.095
Standard deviation	11.793	28.213	16.152	28.203
CV	7.486	12.053	6.709	10.927

Appendix 1: Effect of binder/disintegrant layer on CH 6 formulation
Comparison simple linear regression and separate means models: Lack-of-fit F-test
Reduced model (Simple linear regression):
Release16 ~ CH6amount

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Amount	1	1049.286	1049.286	21.021	0.003
Residuals	7	349.411	49.916		

Full model (Separate mean model):
Release16 ~ groupCH6
Type III Sum of Squares

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
groupCH6	2	1169.758	584.879	15.328	0.004
Residuals	6	228.940	38.157		

$$F = \frac{(Sumsquare_{linear} - Sumsquare_{seperatemean})/(df_{LR} - df_{SM})}{\mathrm{Re}\,sidual_{SM}}$$

$$F = \frac{(349.411 - 228.940)/1}{38.157} = 3.157;\, \mathrm{p}\ (F_{1,7} > 3.157) > 0.1$$

%release16_CH6 ~ weight gain and square of weight gain

Weight gain	1	1049.286	1049.286	27.500	0.002
Weight gain ^{2}	1	120.472	120.472	3.157	0.126
Residuals	6	228.940	38.157		
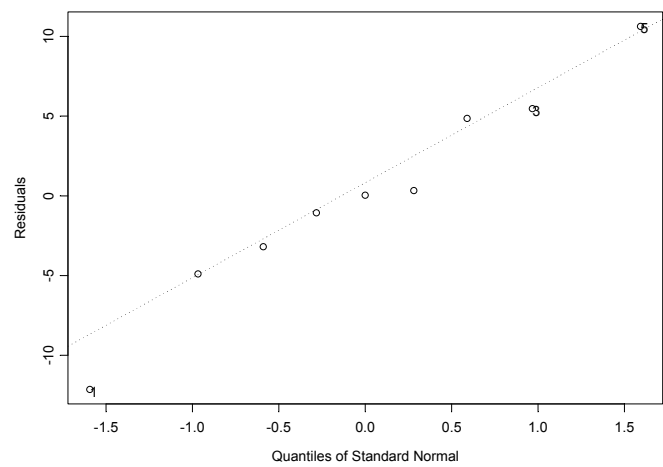
Figure A.1: Residual plot of %release16_CH6 ~ Weight gain

Appendix 2: Effect of compression pressures and paddle speed on %Release at 16 h of CH20
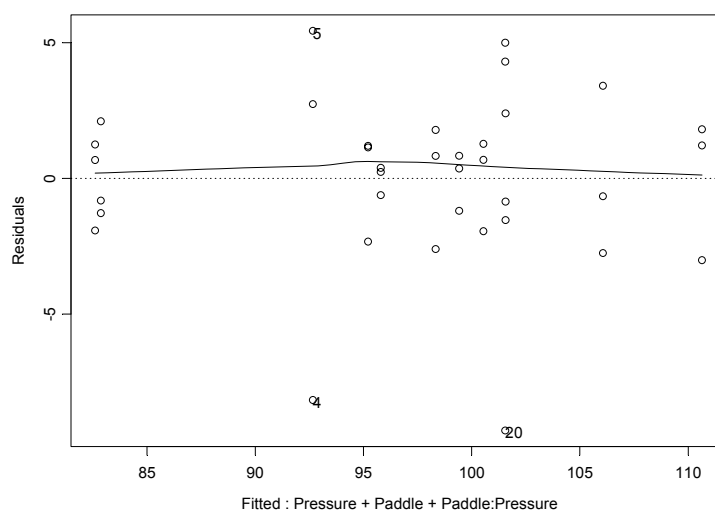
Figure A.2: Residual plot of Glipizide %Release 16~ Pressure+paddle+ Pressure*paddle of CH20 formulation

Appendix 3: Effect of compression pressures and paddle speed on Release rate of CH20
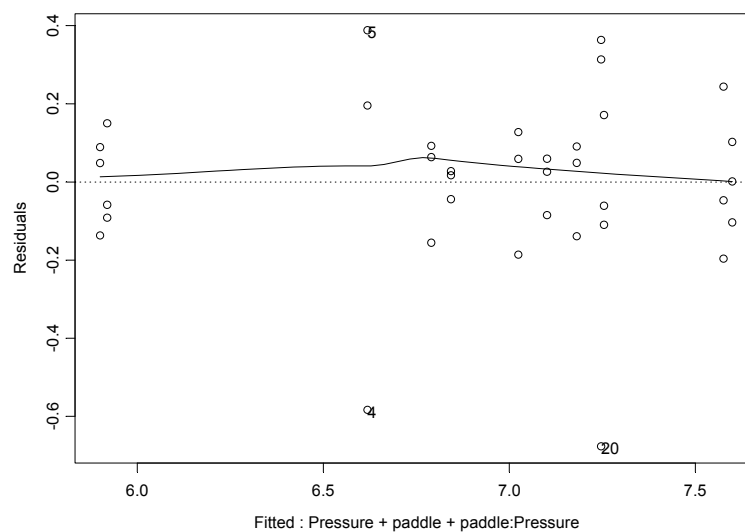
Figure A.3: Residual plot of Glipizide release rate~ Pressure+paddle+ Pressure*paddle of CH20 formulation

Appendix 4: Comparison of Glucotrol XL and CH20-1500 lbs on Rate release
2-way ANOVA, paddle
<u>Release rate ~ Gluco-CH20 + Speed</u>
95 % non-simultaneous confidence intervals for specified linear combinations, by the Fisher LSD method
Intervals excluding 0 are flagged by '****'

	Estimate	Std.Error	Lower Bound	Upper Bound
Gluco-CH20	-0.143	0.140	-0.435	0.150

Appendix 5: Comparison of Glucotrol XL and CH20 on %Release at 16 h
2-way ANOVA, balance
<u>%Release 16 ~ Speed + Gluco-CH20</u>
Estimated effects are balanced
95 % non-simultaneous confidence intervals for specified linear combinations, by the Fisher LSD method
intervals excluding 0 are flagged by '****'

	Estimate	Std.Error	Lower Bound	Upper Bound
CH20for-Glucotrol	-4.060	2.060	-8.360	0.246

Appendix 6: Effect of tween 80 and weight gain on Verapamil HCl release (F2 and F3 coated with Surelease only)
Release rate$_{14}$ ~ tween80 + weight gain + weight gain^2 + tween80^2 + weight gain:tween80 + weight gain^2:tween80^2

Fitted : tween80 + weight.gain + tween80^2 + weight.gain^2 + tween80:weight.gain +
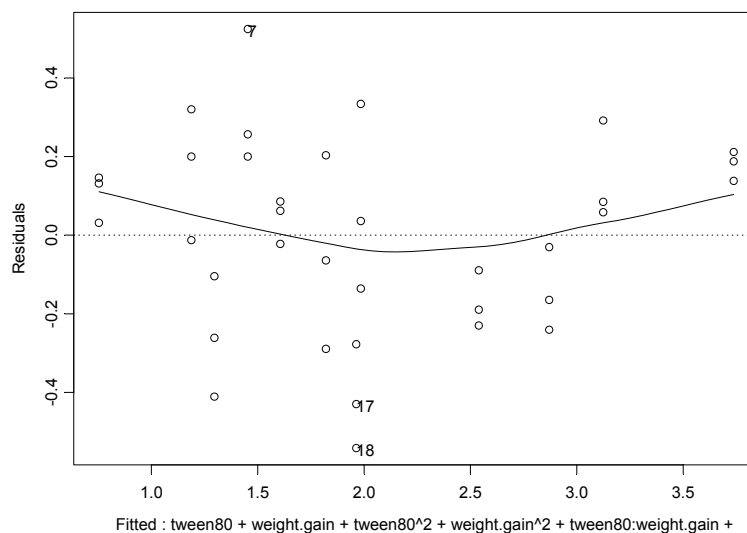
Figure A.4: Residual plot of Verapamil HCl release rate$_{14}$ ~ tween80 + weight gain + weight gain^2 + tween80^2 +weight gain:tween80 + weight gain^2:tween80^2
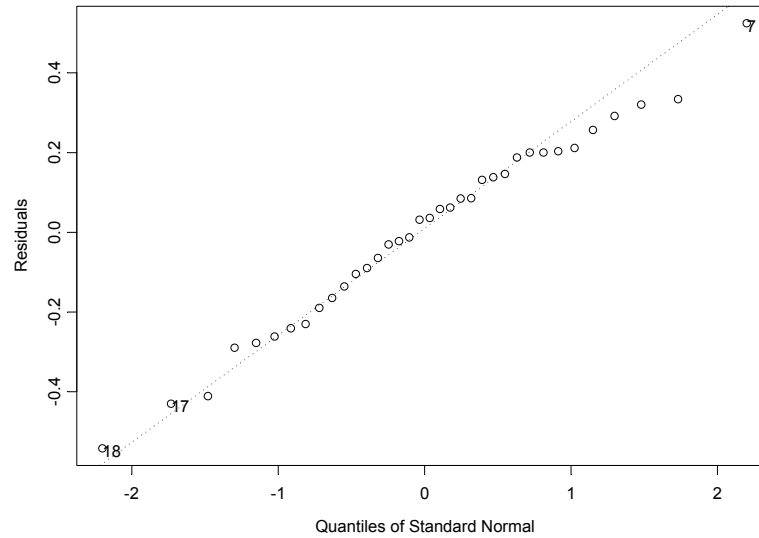
Figure A.5: Normal QQ plot of Verapamil HCl release rate$_{14}$ ~ tween80+weight gain + weight gain^2 + tween80^2 +weight gain:tween80 + weight gain^2:tween80^2

Relationship between tween 80 and release rate$_{14}$ at 5% weight gain based on Table 5.5:

Release rate$_{14}$ = 8.385 + 4.208*tween80 -1.497*5 + 0.066*tween80^2 + (0.079*5)^2 –
    0.797*5*tween80 + 0.063*(5*tween80)^2 (Equation A.1)

Change in release rate$_{14}$ when increasing 0.33% tween 80 at 5% weight gain
= 4.208*0.33 + 0.066*0.33^2 - 0.797*5*0.33 + 0.063*(5*0.33)^2 = 0.252

Appendix 7: Effect of Lactose and weight gain on Verapamil HCl release

$$F = \frac{(Sumsquare_{reduced} - Sumsquare_{full})/\text{\# parameter}}{\mathrm{Re}\,sidual_{full}}$$

- *Comparison Model 5.4 and 5.5: effect of quadratic term:*

$$F = \frac{(7.76168 - 4.82748)/2}{0.11227} = 13.068 \text{ ; P } (F_{2,43} > 13.07) < 0.01$$

- *Comparison Model 5.5 and 5.6: effect of interaction term:*

$$F = \frac{(4.82748 - 2.82117)/2}{0.06881} = 14.579 \text{ ; P } (F_{2,41} > 14.58) < 0.01$$

Release rate$_{14}$ ~ Weight gain:lactose + Weight gain^2+ Lactose^2

Weight gain	1	32.031	32.031	422.427	< 0.001
Lactose	1	34.035	34.035	448.849	< 0.001
Weight gain^2	1	0.526	0.526	6.935	0.012
Lactose^2	1	2.408	2.408	31.762	< 0.001
Weightgain:lactose	1	1.643	1.643	21.665	< 0.001
Residuals	42	3.185	0.076		

Appendix 8: Explotab effect on Verapamil release rate, Lack of fit test
Full model (Separate mean model)
Releaserate (eplotab)~ group
Residual standard error: 0.159628

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
group	2	5.732	2.866	112.476	< 0.001
Residuals	6	0.153	0.025		

$$F = \frac{(Sumsquare_{linear} - Sumsquare_{seperatemean})/(df_{LR} - df_{SM})}{\mathrm{Re}\,sidual_{SM}}$$

Comparison Simple linear regression and separate means models

$$F = \frac{(0.156241 - 0.152887)/1}{0.025481} = 0.132$$

Check quadratic term of Explotab
Model 5.11: release rate ~ Explotab + Explotab^2

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Explotab	1	5.729	5.729	224.821	< 0.001
Explotab^2	1	0.003	0.003	0.132	0.729
Residuals	6	0.153	0.025		

Appendix 9: Effect of bead size on Verapamil release rate.
Comparison: 3% lactose, 5.8% weight gain, mesh 12-18 and 12-20; KCL
x: rate release with 3% lactose, 5.8% weight gain; mesh size = 12-18.
y: rate release with 3% lactose 5.8% weight gain; mesh size = 12-20.
t = 8.771;   degree of freedom = 4;   p-value = 0.001;   n = 6
Alternative hypothesis: difference in means is not equal to 0
95 percent confidence interval: 0.251 to 0.483.
Sample estimates:

Mean of x	Mean of y
4.806	4.439

Comparison: 5% lactose, 6.5% weight gain, mesh 12-18 and 12-20; KCL
x: release rate with 5% lactose 6.5% weight gain; mesh size = 12-20.
y: release rate with 5%lactose 6.5% weight gain; mesh size = 12-18 .
t = -3.495;   degree of freedom = 7;   p-value = 0.010;   n = 9
Alternative hypothesis: difference in means is not equal to 0
95 percent confidence interval: -0.635   to -0.122.
Sample estimates:

Mean of x	Mean of y
4.321	4.700

Appendix 10: Comparison of paddle and basket method for OSU1, KCl medium
OSU1-Release rate$_{14}$ ~ formula-OSU1
95 % simultaneous confidence intervals for specified linear combinations, by the Tukey method
intervals excluding 0 are flagged by '****'

	Estimate	Std.Error	Lower Bound	Upper Bound
O1/200/ba - O1/75/ba	0.220	0.058	0.034	0.406 ****
O1/75/ba - O1/200/pa	-1.620	0.058	-1.810	-1.440 ****
O1/75/ba - O1/75/pa	-0.087	0.058	-0.273	0.099
O1/200/ba - O1/200/pa	-1.840	0.058	-2.030	-1.660 ****
O1/75/pa - O1/200/ba	-0.307	0.058	-0.493	-0.121 ****
O1/200/pa - O1/75/pa	1.540	0.058	1.350	1.720 ****

O1/75/ba= OSU1, 75 rpm basket;   O1/200/ba= OSU1, 200 rpm basket;
O1/75/pa= OSU1, 75 rpm paddle;   O1/200/pa= OSU1, 200 rpm paddle.

Appendix 11: Comparison of paddle and basket method for OSU2, KCl medium
OSU2 release rate$_{14}$-KCl ~ Method + Speed + Method:Speed

Type III Sum of Squares

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Method	1	0.006	0.006	0.148	0.705
Speed	1	0.372	0.372	9.911	0.006
Method:Speed	1	0.025	0.025	0.674	0.423
Residuals	17	0.638	0.038		

Release rate$_{14}$ ~ OSU2 group
95 % simultaneous confidence intervals for specified linear combinations, by the Tukey method
intervals excluding 0 are flagged by '****'

	Estimate	Std.Error	Lower Bound	Upper Bound
O2/200/ba-O2/75/ba	0.351	0.112	0.033	0.669 ****
O2/200/ba-O2/pa/200	0.107	0.137	-0.283	0.496
O2/200/ba-O2/pa/75	0.312	0.112	-0.006	0.630
O2/75/ba-O2/pa/200	-0.244	0.137	-0.634	0.145
O2/75/ba-O2/pa/75	-0.039	0.112	-0.356	0.279
O2/pa/200-O2/pa/75	0.206	0.137	-0.184	0.595

O2/75/ba= OSU2, 75 rpm basket.
O2/200/ba= OSU2, 200 rpm basket.
O2/pa/75= OSU2, 75 rpm paddle.
O2/pa/200= OSU2, 200 rpm paddle.

Appendix 12: Effect of Paddle speed on OSU2 pH 6.8 (paddle –continuous factor)

OSU2 paddle release rate$_{14}$ ~ paddle speed + paddle speed^2

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
paddle speed	1	0.023	0.023	1.980	0.180
I(paddle speed^2)	1	0.003	0.003	0.289	0.599
Residuals	15	0.175	0.012		
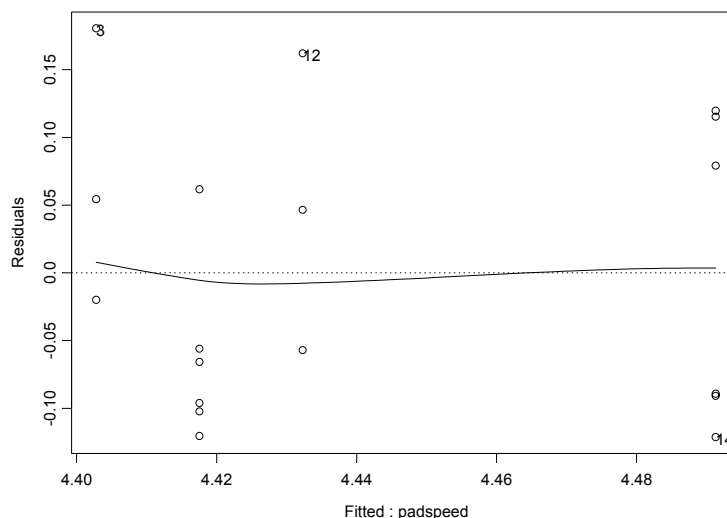
Figure A.6: Residual plot of OSU2 Verapamil HCl Release rate14~ paddle speed, two-medium method, simulated intestinal fluid pH 6.8

OSU2 paddle release rate$_{14}$ ~ paddle speed

Multiple R-Squared: 0.1147

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
paddle speed	1	0.023	0.023	2.072	0.169
Residuals	16	0.178	0.011		

Appendix 13: Effect of Medium on Verelan PM Release

meverelan ~ verelan

95 % simultaneous confidence intervals for specified linear combinations, by the Tukey method

intervals excluding 0 are flagged by '****'

	Estimate	Std.Error	Lower Bound	Upper Bound
V75/74ba-V75/Na/ba	0.140	0.136	-0.276	0.557
V75/74ba-Ve75/68ba	-0.306	0.136	-0.722	0.110
V75/Na/ba-Ve75/68ba	-0.446	0.136	-0.863	-0.030 ****

V75/74ba = Verelan PM, simulated intestinal fluid pH 7.4, 75 rpm basket.
V75/Na/ba = Verelan PM, (Na$_3$PO$_4$+HCl) medium pH 7.4, 75 rpm basket.
Ve75/68ba = Verelan PM, simulated intestinal fluid pH 6.8, 75 rpm basket.

Appendix 14: Comparison release rate between OSU2 and Verelan PM, two medium pH 6.8, paddle
2-way ANOVA
Release rate$_{14}$ pad ~ Ve.OSU2 + Speed paddle + Ve.OSU2:Speed paddle
95 % non-simultaneous confidence intervals for specified linear combinations, by the Fisher LSD method
intervals excluding 0 are flagged by '****'

	Estimate	Std.Error	Lower Bound	Upper Bound
OSU2-Verelan	-0.147	0.043	-0.237	-0.057 ****

Multiple comparisons
95 % simultaneous confidence intervals for specified linear combinations, by the Tukey method
intervals excluding 0 are flagged by '****'

	Estimate	Std.Error	Lower Bound	Upper Bound
O2/68/10p-O2/68/20p	0.092	0.085	-0.202	0.386
O2/68/10p-O2/68/50p	-0.113	0.085	-0.408	0.181
O2/68/10p-O2/68/75p	0.085	0.085	-0.209	0.380
O2/68/10p-V100/68pa	-0.022	0.085	-0.316	0.273
O2/68/10p-V200/68pa	-0.395	0.085	-0.689	-0.100 ****
O2/68/10p-V50/68pa	-0.088	0.085	-0.382	0.207
O2/68/10p-V75/68pa	-0.021	0.085	-0.315	0.273
O2/68/20p-O2/68/50p	-0.205	0.085	-0.500	0.089
O2/68/20p-O2/68/75p	-0.007	0.085	-0.301	0.288
O2/68/20p-V100/68pa	-0.114	0.085	-0.408	0.181
O2/68/20p-V200/68pa	-0.487	0.085	-0.781	-0.192 ****
O2/68/20p-V50/68pa	-0.180	0.085	-0.474	0.115
O2/68/20p-V75/68pa	-0.113	0.085	-0.407	0.181
O2/68/50p-O2/68/75p	0.198	0.085	-0.096	0.493
O2/68/50p-V100/68pa	0.092	0.085	-0.203	0.386
O2/68/50p-V200/68pa	-0.282	0.085	-0.576	0.013
O2/68/50p-V50/68pa	0.026	0.085	-0.269	0.320
O2/68/50p-V75/68pa	0.092	0.085	-0.202	0.387
O2/68/75p-V100/68pa	-0.107	0.085	-0.401	0.187
O2/68/75p-V200/68pa	-0.480	0.085	-0.774	-0.186 ****
O2/68/75p-V50/68pa	-0.173	0.085	-0.467	0.122
O2/68/75p-V75/68pa	-0.106	0.085	-0.400	0.188
V100/68pa-V200/68pa	-0.373	0.085	-0.667	-0.079 ****
	Estimate	Std.Error	Lower Bound	Upper Bound
V100/68pa-V50/68pa	-0.066	0.085	-0.360	0.228
V100/68pa-V75/68pa	0.001	0.085	-0.294	0.295
V200/68pa-V50/68pa	0.307	0.085	0.013	0.602 ****
V200/68pa-V75/68pa	0.374	0.085	0.080	0.668 ****

V50/68pa-V75/68pa   0.067   0.085   -0.228   0.361

O2/68/50p = OSU2, simulated intestinal fluid pH 6.8, 50 rpm paddle.
O2/68/10p = OSU2, simulated intestinal fluid pH 6.8, 100 rpm paddle.
O2/68/75p = OSU2, simulated intestinal fluid pH 6.8, 75 rpm paddle.
O2/68/20p = OSU2, simulated intestinal fluid pH 6.8, 200 rpm paddle.
V50/68pa = Verelan PM, simulated intestinal fluid pH 6.8, 50 rpm paddle.
V75/68pa = Verelan PM, simulated intestinal fluid pH 6.8, 75 rpm paddle.
V100/68pa = Verelan PM, simulated intestinal fluid pH 6.8, 100 rpm paddle.
V200/68pa = Verelan PM, simulated intestinal fluid pH 6.8, 200 rpm paddle.

Appendix 15: Comparison release rate between OSU2 and Verelan PM, two medium pH 6.8, basket
2-way ANOVA, Basket
Basket release rate$_{14}$ ~ Ve.OSU2 + Speed basket
Type III Sum of Squares

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Ve.OSU2	1	0.272	0.272	8.700	0.016
Speed basket	1	0.041	0.041	1.310	0.282
Residuals	9	0.282	0.031		

95 % non-simultaneous confidence intervals for specified linear combinations, by the Fisher LSD method
intervals excluding 0 are flagged by '****'

	Estimate	Std.Error	Lower Bound	Upper Bound
OSU2-Verelan	-0.301	0.102	-0.532	-0.070 ****

Multiple comparisons
95 % simultaneous confidence intervals for specified
linear combinations, by the Tukey method

intervals excluding 0 are flagged by '****'

	Estimate	Std.Error	Lower Bound	Upper Bound
O2/68/20ba-O2/68/75ba	0.280	0.130	-0.135	0.695
O2/68/20ba-Ve20/68/ba	-0.138	0.130	-0.553	0.277
O2/68/20ba-Ve75/68/ba	-0.184	0.130	-0.599	0.231
O2/68/75ba-Ve20/68/ba	-0.418	0.130	-0.833	-0.003 ****
O2/68/75ba-Ve75/68/ba	-0.465	0.130	-0.880	-0.050 ****
Ve20/68/ba-Ve75/68/ba	-0.047	0.130	-0.462	0.369

O2/68/20ba = OSU2, simulated intestinal fluid pH 6.8, 200 rpm basket;
O2/68/75ba = OSU2, simulated intestinal fluid pH 6.8, 75 rpm basket;
Ve20/68/ba = Verelan PM, simulated intestinal fluid pH 6.8, 200 rpm basket;
Ve75/68/ba = Verelan PM, simulated intestinal fluid pH 6.8, 75 rpm basket.

Appendix 16: Comparison between Verelan PM and OSU2, KCL
2-way ANOVA, paddle
Type III Sum of Squares

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Paddle Speed	1	0.260	0.260	1.836	0.195
VeOSU2	1	0.180	0.180	1.270	0.278
Residuals	15	2.121	0.141		

95 % non-simultaneous confidence intervals for specified linear combinations, by the Fisher LSD method
intervals excluding 0 are flagged by '****'

	Estimate	Std.Error	Lower Bound	Upper Bound
OSU2-Verelan PM	-0.212	0.188	-0.613	0.189

Multiple Comparison Verelan PM and OSU2, KCl medium, Paddle method
95 % simultaneous confidence intervals for specified linear combinations, by the Tukey method
response variable: paddlrate
intervals excluding 0 are flagged by '****'

	Estimate	Std.Error	Lower Bound	Upper Bound
O2/pa/200-O2/pa/75	0.206	0.275	-0.592	1.000
O2/pa/200-Ve200/pad	-0.261	0.275	-1.060	0.537
O2/pa/200-Ve75/pad	0.043	0.317	-0.879	0.965
O2/pa/75-Ve200/pad	-0.467	0.224	-1.120	0.185
O2/pa/75-Ve75/pad	-0.163	0.275	-0.961	0.635
Ve200/pad-Ve75/pad	0.304	0.275	-0.494	1.100

O2/pa/200 = OSU2, simulated intestinal fluid pH 6.8, 200 rpm paddle.
O2/pa/75 = OSU2, simulated intestinal fluid pH 6.8, 75 rpm paddle.
Ve75/pad = Verelan PM, simulated intestinal fluid pH 6.8, 75 rpm paddle.
Ve200/pad = Verelan PM, simulated intestinal fluid pH 6.8, 200 rpm paddle.

Appendix 17: Multiple Comparisons between Verelan PM and OSU2, KCl medium, Basket method
95 % simultaneous confidence intervals for specified linear combinations, by the Tukey method
response variable: basketrate
intervals excluding 0 are flagged by '****'

	Estimate	Std.Error	Lower Bound	Upper Bound
O2/200/ba-O2/75/ba	0.351	0.094	0.079	0.623 ****
O2/200/ba-Ve200/ba	0.039	0.115	-0.294	0.372
O2/200/ba-Ve75/bas	0.034	0.115	-0.299	0.367
O2/75/ba-Ve200/ba	-0.312	0.115	-0.645	0.022
O2/75/ba-Ve75/bas	-0.317	0.115	-0.650	0.017

Ve200/ba-Ve75/bas   -0.005   0.132   -0.390   0.380
O2/200/ba = OSU2; simulated intestinal fluid pH 6.8, 200 rpm basket.
O2/75/ba = OSU2; simulated intestinal fluid pH 6.8, 75 rpm basket.
Ve75/bas = Verelan PM, simulated intestinal fluid pH 6.8, 75 rpm basket.
Ve200/ba = Verelan PM, simulated intestinal fluid pH 6.8, 200 rpm basket.

Appendix 18: Dissolution rate constant fitting

Table A.2: Fitted dissolution rate constants from three models

	k_{sqrt}		k_0		$K_1, (C_n=100)$	
	OSU2	Verelan	OSU2	Verelan	OSU2	Verelan
14 h constants	13.372	13.622	4.652	4.734	0.063	0.064
16 h constants	13.923	14.261	4.475	4.586	0.063	0.065
24 h constants	14.612	15.115	3.888	4.033	0.063	0.066

First order 0-24 hours of OSU2 with Cn
Formula: OSU2 ~ Cn * (1 - exp(- k1 * Time))
Parameters:
          Value   Std. Error   t value
Cn   106.910   4.293   24.902
k1   0.057   0.004   15.846
Residual standard error: 2.334 on 52 degrees of freedom
Correlation of Parameter Estimates:
     Cn
k1 -0.98

First order 0-24 hours of OSU2 without Cn:
OSU2 ~ 100 * (1 - exp(- k1 * Time))
Parameters:
          Value   Std. Error   t value
k1   0.063   0.001   74.330
Residual standard error: 2.384 on 53 degrees of freedom

First order 0-24 hours of Verelan PM with Cn
Verelan ~ Cn * (1 - exp(- k1 * Time))
Parameters:
          Value   Std. Error   t value
Cn   119.908   5.751   20.850
k1   0.050   0.004   13.905
Residual standard error: 2.510 on 52 degrees of freedom
Correlation of Parameter Estimates:

Cn
k1 -0.985

First order 0-24 hours of Verelan PM without Cn
Formula: Verelan ~ 100 * (1 - exp(- k1 * Time))
Parameters:

	Value	Std. Error	t value
k1	0.066	0.001	60.795

Residual standard error: 2.938 on 53 degrees of freedom

First order 0-16 hours of OSU2 with Cn
Formula: OSU2 ~ Cn * (1 - exp(- k1 * Time))
Parameters:

	Value	Std. Error	t value
Cn	149.716	17.501	8.555
k1	0.037	0.005	6.845

Residual standard error: 2.067 on 46 degrees of freedom
Correlation of Parameter Estimates:
        Cn
k1 -0.997

First order 0-16 hours of OSU2 without Cn
Formula: OSU2 ~ 100 * (1 - exp(- k1 * Time))
Parameters:

	Value	Std. Error	t value
k1	0.063	0.001	61.846

Residual standard error: 2.520 on 47 degrees of freedom

First order 0-16 hours of Verelan PM with Cn
Formula: Verelan ~ Cn * (1 - exp(- k1 * Time))
Parameters:

	Value	Std. Error	t value
Cn	185.625	25.676	7.230
k1	0.029	0.005	6.053

Residual standard error: 1.929 on 46 degrees of freedom
Correlation of Parameter Estimates:
        Cn
k1 -0.998

First order 0-16 hours of Verelan PM without Cn
Formula: Verelan ~ 100 * (1 - exp(- k1 * Time))
Parameters:

	Value	Std. Error	t value
k1	0.065	0.001	56.139

Residual standard error: 2.804 on 47 degrees of freedom

First order 0-14 hours of Verelan PM with Cn
Formula: Verelan ~ Cn * (1 - exp(- k1 * Time))
Parameters:

	Value	Std. Error	t value
Cn	261.905	62.882	4.165
k1	0.020	0.005	3.743

Residual standard error: 1.694 on 43 degrees of freedom
Correlation of Parameter Estimates:

	Cn
k1	-0.999

First order 0-14 hours of Verelan PM WITHOUT Cn
Formula: Verelan ~ 100 * (1 - exp(- k1 * Time))
Parameters:

	Value	Std. Error	t value
k1	0.064	0.001	53.874

Residual standard error: 2.655 on 44 degrees of freedom

First order 0-14 hours of OSU2 with Cn
Formula: OSU2 ~ Cn * (1 - exp(- k1 * Time))
Parameters:

	Value	Std. Error	t value
Cn	200.784	42.132	4.766
k1	0.027	0.006	4.140

Residual standard error: 1.969 on 43 degrees of freedom
Correlation of Parameter Estimates:

	Cn
k1	-0.999

First order 0-14 hours of OSU2 without Cn
Formula: OSU2 ~ 100 * (1 - exp(- k1 * Time))
Parameters:

	Value	Std. Error	t value
k1	0.063	0.001	55.086

Residual standard error: 2.574 on 44 degrees of freedom

Verelan: fitting data: Zero order model: 24 hours
Verelan ~ Time + (-1)
Coefficients:

	Value	Std. Error	t value	Pr(>|t|)
Time	4.033	0.082	49.233	< 0.001

Multiple R-Squared: 0.979

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Time	1	89257.640	89257.640	423.864	< 0.001
Residuals	53	1951.700	36.820		

Verelan: fitting data: square root model: 24 hours:

Verelan~Squaretime + (-1)

Coefficients:

	Value	Std. Error	t value	Pr(>|t|)
Squaretime	15.115	0.434	34.818	< 0.001

Multiple R-Squared: 0.958

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Squaretime	1	87388.760	87388.760	1212.276	< 0.001
Residuals	53	3820.590	72.090		

OSU: fitting data: Zero order model: 24 hours:

OSU2 ~ Time + (-1)

Coefficients:

	Value	Std. Error	t value	Pr(>|t|)
Time	3.888	0.087	44.888	< 0.001

Multiple R-Squared: 0.974

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Time	1	82989.470	82989.470	2014.968	< 0.001
Residuals	53	2182.880	41.190		

OSU2: fitting data: square root model: 24 hours:

OSU2 ~ Squaretime + (-1)

Coefficients:

	Value	Std. Error	t value	Pr(>|t|)
Squaretime	14.612	0.416	35.130	< 0.001

Multiple R-Squared: 0.959

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Squaretime	1	81665.090	81665.090	1234.081	< 0.001
Residuals	53	3507.260	66.170		

Verelan: fitting data: Zero order model: 16 hours:

Verelan ~ Time + (-1)

Coefficients:

	Value	Std. Error	t value	Pr(>|t|)
Time	4.586	0.052	88.416	< 0.001

Multiple R-Squared: 0.994

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Time	1	53852.040	53852.040	7817.348	< 0.001
Residuals	47	323.770	6.890		

Verelan: fitting data: square root model: 16 hours:
Verelan ~ Squaretime + (-1)
Coefficients:

	Value	Std. Error	t value	Pr(>|t|)
Squaretime	14.261	0.524	27.225	< 0.001

Multiple R-Squared: 0.940

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Squaretime	1	50945.320	50945.320	741.198	< 0.001
Residuals	47	3230.490	68.730		

OSU2: fitting data: Zero order model: 16 hours:
OSU2 ~ Time + (-1)
Coefficients:

	Value	Std. Error	t value	Pr(>|t|)
Time	4.475	0.060	74.844	< 0.001

Multiple R-Squared: 0.992

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Time	1	51286.030	51286.030	5601.614	< 0.001
Residuals	47	430.310	9.160		

OSU2: fitting data: square root model: 16 hours:
OSU2 ~ Squaretime + (-1)
Coefficients:

	Value	Std. Error	t value	Pr(>|t|)
Squaretime	13.923	0.518	26.880	< 0.001

Multiple R-Squared: 0.939

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Squaretime	1	48557.700	48557.700	722.532	< 0.001
Residuals	47	3158.630	67.200		

Verelan: fitting data: Zero order model: 14 hours:
Verelan ~ Time + (-1)
Coefficients:

	Value	Std. Error	t value	Pr(>|t|)
Time	4.734	0.046	102.919	< 0.001

Multiple R-Squared: 0.996

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Time	1	40180.170	40180.170	10592.300	< 0.001
Residuals	44	166.910	3.790		

Verelan: fitting data: Square root order model: 14 hours: Verelan~Squaretime + (-1)
Coefficients:

	Value	Std. Error	t value	Pr(>|t|)
Squaretime	13.622	0.558	24.416	< 0.001

Multiple R-Squared: 0.931

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Squaretime	1	37573.790	37573.790	596.134	< 0.001
Residuals	44	2773.280	63.030		

OSU2: fitting data: Zero order model: 14 hours:
OSU2 ~ Time + (-1)
Coefficients:

	Value	Std. Error	t value	Pr(>|t|)
Time	4.652	0.055	83.981	< 0.001

Multiple R-Squared: 0.994

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Time	1	38804.540	38804.540	7052.776	< 0.001
Residuals	44	242.090	5.500		

OSU2: fitting data: Square root order model: 14 hours:
OSU2 ~ Squaretime + (-1)
Coefficients:

	Value	Std. Error	t value	Pr(>|t|)
Squaretime	13.372	0.564	23.695	< 0.001

Multiple R-Squared: 0.927

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Squaretime	1	36209.090	36209.090	561.473	< 0.001
Residuals	44	2837.530	64.490		

Appendix 19: Simulated and real dissolution profiles of Verelan PM and OSU2
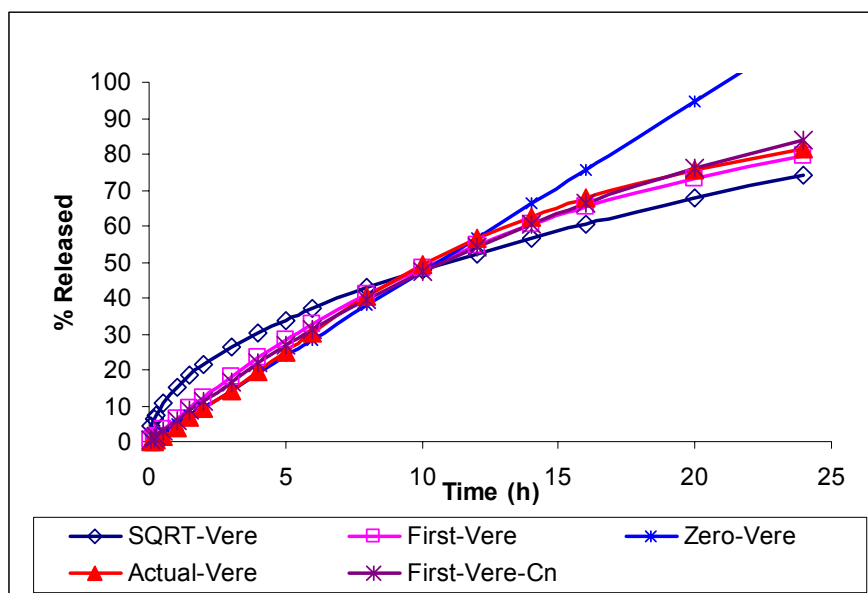
Zero: k from 14 h, others: k from 24 h.

Figure A.7: Simulated and real dissolution profiles of Verelan PM based on two-medium method, 75rpm paddle for 24 hours
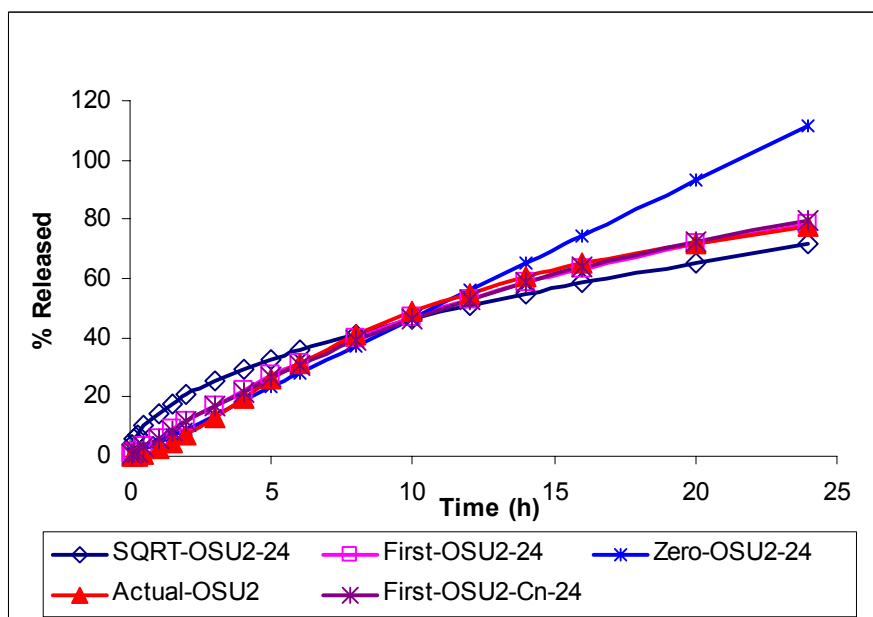
Zero: k from 14 h, others: k from 24 h.

Figure A.8: Simulated and real dissolution profiles of OSU2 based on two- medium method, 75rpm paddle for 24 hours