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Sustained release acetaminophen dosage forms were prepared by microencapsulating acetaminophen with ethylcellulose (Chapter I). Drug release from microcapsules with a 2.5% ethylcellulose coat was extremely slow (15% acetaminophen released after 24 hours). Tablets or capsules containing microcapsules with 2.5 or 10% ethylcellulose coats provided prolonged in vitro drug release (time to 50% dissolution, $d_{50\%}$, $\geq$4.1 hr). Sustained acetaminophen release was achieved in one subject following administration of capsules containing 97.5% acetaminophen/2.5% ethylcellulose microcapsules.

Acetaminophen powder and pellets were spray coated with sustained release and/or enteric coats using aqueous-based film-forming dispersions (Chapter II). Tablets containing spray-coated acetaminophen powders

provided slow *in vitro* drug release when tested intact ($d_{50\%}$ of 5.4 to 22.6 hr) and rapid release when crushed ($d_{50\%}$ <2 hr). Acetaminophen release from ethylcellulose-coated pellets was extremely slow at coatings >4% with <25% of the drug released after 48 hours. In comparison, triple-coated acetaminophen pellets provided more rapid release ($d_{50\%}$ $\leq$48 hr). Compression of spray-coated pellets into tablets resulted in even faster drug release ($d_{50\%}$ of 7.8 to 25 hours). Sustained acetaminophen release was achieved in one subject following administration of tablets and capsules containing spray-coated acetaminophen powders which had slow *in vitro* drug release.

Saliva acetaminophen concentrations were determined in 15 subjects after administration of five different doses of commercial acetaminophen tablets (Chapter III). Saliva acetaminophen concentration-time profiles for individual subjects were adequately described with bi- or triexponential equations. Statistically significant differences ($p<0.05$) in elimination rate, mean residence time, and the ratio of area under the curve to dose were found between treatments (doses), suggestive of dose-dependent pharmacokinetics.

NEW PRODUCT FORMULATIONS

AND

PHARMACOKINETICS OF ACETAMINOPHEN

by Marie T. Borin

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CHAPTER I

MICROENCAPSULATED ACETAMINOPHEN:

FORMULATION OF SUSTAINED RELEASE DOSAGE FORMS

ABSTRACT

Sustained release acetaminophen dosage forms were prepared by microencapsulating acetaminophen with ethylcellulose using a nonaqueous phase-separation coacervation method. Drug release from microcapsules with only a 2.5% ethylcellulose coat was extremely slow in the rotating basket apparatus (15% acetaminophen released after 24 hours) due to lack of wetting when microcapsules are confined in the basket. Tablets and capsules containing microcapsules with 2.5 or 10% ethylcellulose coats provided prolonged *in vitro* drug release ($d_{50\%} \geq 4.1$ hr). Release patterns for acetaminophen microcapsules and dosage forms were complex and could not be described by any one process. Sustained acetaminophen release was achieved in one subject following administration of capsule dosage forms containing 97.5% acetaminophen/2.5% ethylcellulose microcapsules (saliva acetaminophen concentrations were maintained at 3 µg/ml for 6-16 hours post dosing). However, intact and chewed tablets did not provide sustained release *in vivo* with the latter saliva concentration-time profile being similar to that of an immediate release tablet product. With the exception of the intact tablet dosage form, *in vivo* results were in agreement with *in vitro* data.

INTRODUCTION

Statement of the Problem

The primary objective of this study was to develop a sustained release crushable and chewable acetaminophen tablet by microencapsulating acetaminophen and incorporating the microcapsules into tablets. During the course of this work, other sustained release oral dosage forms containing acetaminophen microcapsules, such as hard gelatin capsules and tablets (to be swallowed intact), were also developed and examined for purposes of comparison.

To date, no sustained release chewable tablet products are commercially available. The only novel oral sustained action product on the U.S. market which is not administered as intact tablets or capsules is Theo-Dur Sprinkle (Key Pharmaceuticals, Inc., Miami, FL). This dosage form contains microencapsulated theophylline and is ingested by mixing with soft food. However, the package insert states that the product should not be crushed or chewed prior to swallowing. The development of a sustained release chewable tablet poses quite a challenge since all known controlled or sustained release systems for oral administration are destroyed if masticated. Sustained release oral dosage forms have been reviewed by De Haan and Lerk (1984) and

others (Haenselmann and Voigt, 1971; Ritschel 1973; Garcia et al., 1978). These products can be classified as enteric coated preparations, repeat-action products, ion-exchange resins, slow release particles in tablets and capsules, matrices of waxes and fats, polymer matrices, and systems with drug release controlled by osmosis. The methods by which drug release is delayed in such dosage forms include diffusion, dissolution, erosion, leaching, and osmosis.

From a physiochemical point of view, acetaminophen was considered to be a challenging model compound for which to develop sustained release systems since it is fairly water soluble and has a short half-life (2-3 hours). The therapeutic rationale for development of an acetaminophen product, in particular, was to provide a convenient dosage form for pediatric or geriatric use which would not have to be swallowed whole and would extend the drug's antipyretic and analgesic activity, resulting in less frequent dosing.

Microencapsulation is only one of many techniques used to achieve sustained or prolonged release of drug in vivo. Microencapsulation of acetaminophen with ethylcellulose using a phase separation coacervation procedure was used in this study because sustained release of dyphylline from crushed tablets containing ethylcellulose microcapsules was unexpectedly achieved

in vivo following administration to pigs (Chang, 1984).

Results from *in vitro* dissolution testing and a preliminary *in vivo* study were used to assess release patterns of drug from oral dosage forms containing acetaminophen microcapsules in order to determine whether they would provide sustained drug release. The *in vivo* study was performed with one human subject and involved monitoring saliva acetaminophen concentrations. Saliva was chosen instead of plasma since it can be collected by non-invasive techniques and because saliva and serum acetaminophen levels have been shown to be correlated with mean saliva to serum concentration ratios ranging from 1.0 to 1.4 (Glynn and Bastain, 1973; Ahmed and Enever, 1981; Adithan and Thangam, 1982). This preliminary *in vivo* data was viewed only as a tool which may be useful to supplement the *in vitro* dissolution results.

Microencapsulation

Microencapsulation is a means of applying thin film-forming coatings to small particles of solids, droplets of liquids, or dispersions. Microcapsules provide a means of converting liquids to solids, altering colloidal and surface properties, providing environmental protection, and controlling release characteristics or availability of coated materials. Microencapsulation technology is highly diversified and

has been applied in many fields other than pharmacy and medicine. Industries such as those which supply paints, cosmetics, adhesives, pesticides, detergents, and foods have all found useful applications for microencapsulation (Untersee, 1963; Raun and Jackson, 1966; Herbig, 1967; Rindt et al., 1968; Schwarzkopf, 1969; Charle et al., 1970a, 1970b; Suffis et al., 1970; Todd, 1970; Hollinshead, 1971; National Cash Register Corporation, 1971; Fanger, 1974; Sliwka, 1975).

Microencapsulation techniques have also been widely used for pharmaceutical applications. The most common uses are development of sustained release medications, taste-masked tablets, powders and suspensions, single layer tablets containing incompatible ingredients, and new formulations for creams, ointments, aerosols, dressings, plasters, suppositories, and injectables (Bakan and Anderson, 1976).

For encapsulation of a particular material, consideration must be given to the physical and chemical characteristics of the core material and the coating material, as well as the intended use and character of the final product. Microcapsules can be made in sizes ranging from a few microns to several thousand microns, with coatings varying in amount from 1 to 70% by weight, although normal commercial applications require 2 to 30% (Bakan, 1980). This corresponds to a dry film thickness

of 0.1 to 200 µm, depending on the surface area of the core material and other physical characteristics of the system (Bakan, 1980). Capsule size and size distribution can be predetermined by appropriate processing controls and are usually highly reproducible. The encapsulated product may be isolated as a free flowing powder or in the form of a slurry. The material to be coated (core material) can be a liquid, either dissolved or dispersed, or a solid. Physical and chemical properties of the core material should be considered first when choosing an appropriate encapsulation system. Water soluble substances are usually microencapsulated in organic vehicles while water insoluble materials are microencapsulated in aqueous vehicles. Selection of the coating material is based on product objectives and requirements. In general, the coating material must be capable of forming a film that is cohesive with the core material, is chemically compatible and nonreactive with the core material, and provides the desired coating properties, such as strength, flexibility, impermeability, optical properties and stability (Bakan and Anderson, 1976). Some typical coating materials are celluloses, gelatins, polyvinylalcohol, waxes, and shellac.

Release of core material from microcapsules can occur by 1) disruption of the coating by pressure,

sheer, or abrasion forces; 2) enzymatic permeability changes; or 3) release from inert coatings by diffusion or leaching of a permeant fluid (Bakan, 1980). In the latter case, the release rate is a function of permeability of the coating to extraction fluid and permeability of the coating to the core material solute, the rate of dissolution of the core material, the coating thickness, and the concentration gradient across the coating membrane. The intended route of administration will, to a great extent, dictate the type of release desired which in turn can be achieved by selection of an appropriate coating material.

Several methods have been proposed and successfully used for microencapsulation of pharmaceuticals. These can be classified in the following categories: 1) coacervation-phase separation, 2) air suspension, 3) multiorifice centrifugal, 4) pan coating, 5) spray drying and congealing, 6) interfacial polymerization, and 7) electrostatic and vacuum deposition techniques.

Microencapsulation by coacervation-phase separation is generally attributed to the National Cash Register Corporation (1963) and the patents of Green (1955, 1960) and others (Green and Schleicher, 1956, 1957; Miller and Anderson, 1964; Heistand et al., 1966; Brynko et al., 1967; Miller et al., 1967). Coacervation can be defined as salting out or phase separation of lipophilic

colloids into liquid droplets rather than solid aggregates. The process consists of three steps which are carried out under continuous agitation (Bakan, 1980). The first step is the formation of three, immiscible chemical phases: a liquid manufacturing vehicle phase, a core material (drug) phase, and a coating material phase. The core material is dispersed in a solution of the coating material, the solvent for the polymer being the liquid vehicle. The coating material phase is formed by changing the temperature of the polymer solution; by adding a salt, nonsolvent, or incompatible polymer to the polymer solution; or by inducing a polymer-polymer interaction. These are all methods of phase-separation coacervation and detailed descriptions can be found in the literature (Bakan and Anderson, 1976). The second step in the process is deposition of the coating. This is accomplished by controlled, physical mixing of the coating material in the vehicle. Deposition of the liquid polymer coating around the core material will occur if the polymer is adsorbed at the interface between the core material and the liquid vehicle phase. Continued deposition of the coating material is promoted by a reduction in the total free interfacial energy of the system which is brought about by decreases in the coating material surface area during coalescence of liquid polymer droplets. The

final step is rigidization of the coating which is accomplished by thermal, crosslinking, or desolvation techniques to give a self-sustaining microcapsule. Because core materials are encapsulated in a liquid vehicle, subsequent drying by spray-drying, freeze-drying, fluid bed drying, or tray-drying may be required.

Phase separation techniques can be classified into two categories: aqueous phase separation and nonaqueous phase separation. The aqueous system consists of a dispersion of a polymeric or macromolecular wall material in water. Wall formation occurs when the wall material is caused to separate into liquid coacervate droplets by addition of a hydrophilic material or by adjustment of pH. The coacervation process can further be broken down into two types: simple coacervation and complex coacervation (Bungenberg de Jong, 1949). In simple coacervation, a strongly hydrophilic substance is added to a less hydrophilic colloidal dispersion. This results in the formation of two layers, one rich in colloidal droplets and the other deficient in these droplets. Complex coacervation depends primarily on pH and deals with systems containing more than one colloid in the continuous phase of the fluid system. Two oppositely charged colloids discharge with each other to produce a coacervate. In nonaqueous phase separation

the continuous wall-containing phase is organic or hydrophobic in nature, and the core material is water miscible.

In the air suspension process, finely divided particles of the core material are suspended by a vertical current of air and spray-coated with the wall material solution. This air stream also dries the product, resulting in a solid shell of the wall material being deposited around each particle. Proper adjustment of air flow, temperature, and fluid application rate are critical to successful operation of this process. Wurster (1953, 1957, 1966) developed a special air suspension method which is now known as the Wurster process. It is carried out in chambers containing vertical pipes around which the core material circulates by an ascending air current. The particles move upward through the interior of the vertical pipe section while being sprayed and then descend outside the pipe section while the coating dries. During each pass through the coating zone, the core material receives an increment of coating material. The process is repeated until the desired coating thickness is obtained.

The multiorifice-centrifugal method is a mechanical process which uses centrifugal forces to hurl a core material particle through an enveloping microencapsulation membrane, thereby effecting

microencapsulation (Heistand et al., 1970; Bakan and Anderson, 1976).

Microencapsulation of solid particles greater then 600 µm can be achieved by pan coating. Coating material can be applied as a solution or atomized spray to the desired solid core material in a coating pan. To remove the coating solvent, warm air is passed over the coated materials and final solvent removal is accomplished in a drying oven.

Spray drying and spray congealing both involve dispersing the core material in a liquid coating substance and then spraying or introducing the core-coating mixture into some environmental condition whereby rapid solidification of coating occurs. The two processes differ in the means by which solidification occurs. In spray drying, the solvent in which the coating material is dissolved or dispersed is rapidly evaporated, thereby solidifying the coating. In spray congealing, a molten coating material is thermally congealed or a dissolved coating is solidified by introducing the coating-core material mixture into a nonsolvent. Removal of the solvent or nonsolvent is accomplished by sorption, extraction, or evaporation (Hecker and Hawks, 1964).

Microencapsulation by interfacial polymerization involves bringing two reactants together at the

interface existing between a core material substance and a continuous phase in which the core material is dispersed. The reaction produces a continuous film of the formed polymer around the dispersed phase. This method is mainly used to prepare microcapsules with nylon coatings (Chang and MacIntosh, 1964; Chang, 1964, 1965, 1966; Chang et al., 1966).

In electrostatic microencapsulation the wall material and core material are brought together in aerosol form. The process is described in detail in several patents (Langer and Yamate, 1964, 1966; Berger et al., 1965). Vacuum encapsulation involves enveloping a solid, nonvolatile core material under high vacuum. The wall material is volatilized in vacuum and condensed on the colder particles which are in rotary motion. Specific applications and processes can be found in the patent literature (Brynko, 1961; Brynko and Scarpelli, 1961; Orsino et al., 1964; Orsino and Mandel, 1964; Gorham and Chappaqua, 1967; Vandegaer and Meier, 1969, 1971).

No single microencapsulation process is adaptable to all core materials or product applications. Difficulties such as incomplete and discontinuous coating, inadequate stability or shelf-life of sensitive products, and economic limitations are often encountered in attempts to microencapsulate a substance for a

particular purpose. Bakan and Anderson (1976) have classified several microencapsulation methods as to their applicability regarding the nature of the core material (solid or liquid) and suitable particle size range. In general, coacervation-phase separation and multiorifice-centrifugal methods have the widest applicability. These two processes can be used to microencapsulate solids and liquids, and the size of the resulting microcapsules can range from 1 to 5000 µm.

Acetaminophen

Acetaminophen (N-acetyl-para-aminophenol, paracetamol) is a widely used antipyretic and analgesic agent which was first used in medical therapy in 1893 (Woodbury and Fingl, 1975). Although its antipyretic and analgesic actions are similar to those of aspirin (Beaver, 1966), acetaminophen has only weak anti-inflammatory action. It has been reported that acetaminophen reduces fever by inhibiting the actions of endogenous pyrogen on the hypothalamic heat regulating centers (Clark and Moyer, 1972). The analgesic action may be central.

Acetaminophen is a moderately water soluble (1 g/70 ml), bitter-tasting, odorless white crystalline powder. It has a pK_a of 9.5 which means that it is largely unionized over the physiological range of pH. Acetaminophen is extrememly stable in aqueous solution,

but degradation to p-aminophenol and acetic acid can be catalyzed by acids and bases (Koshy and Lack, 1961).

Acetaminophen pharmacokinetics following intravenous and oral administration are best described by a two compartment open model with a fairly rapid distribution phase and an elimination half-life of 2.5 to 3 hours (Albert et al., 1974; Rawlins et al., 1977; Clements et al., 1978; Ameer et al., 1983). Although acetaminophen is rapidly absorbed from the GI tract, it is incompletely available to the systemic circulation after oral administration with a variable proportion being lost presumably through first-pass metabolism (Chiou, 1975; Rawlins et al., 1977; Perucca and Richens, 1979; Ameer et al., 1983). Acetaminophen absorption is dependent on the rate of gastric emptying (Heading et al., 1973; Clements et al., 1978) and occurs primarily from the small intestine by passive transport (Bagnall et al., 1979). Several factors, such as other drugs, disease, or other conditions which alter the rate of gastric emptying will influence the rate of acetaminophen absorption (Nimmo, 1976). In particular, it has been demonstrated that food will delay the rate of drug absorption, but have no effect on the total amount of drug absorbed (Jaffe et al., 1971; McGilveray and Mattok, 1972).

Acetaminophen is relatively uniformly distributed

throughout most body fluids and tissues, except fat and cerebrospinal fluid (Brodie and Axelrod, 1949; Gwilt et al., 1963). Acetaminophen exhibits negligible plasma protein binding at therapeutic plasma concentrations of 10 to 20 µg/ml (Wagner, 1975) but is 15 to 21% bound at a plasma concentration of 280 µg/ml (Gazzard et al., 1973) which would be associated with overdosage.

The drug is eliminated in the urine primarily as glucuronide and sulfate conjugates with only 2 to 5% of a therapeutic dose being excreted unchanged (Cummings et al., 1967). A small fraction is converted by cytochrome P-450 dependent mixed function oxidase to a highly reactive alkylating metabolite, which is probably N-acetyl-p-benzo-quinoneimine (Miner and Kissenger, 1979). This metabolite is normally rapidly inactivated by conjugation with reduced glutathione, eventually being excreted in the urine as cysteine and mercapturic acid conjugates. Hepatic necrosis occurs when overdoses of acetaminophen are ingested, and this has been attributed to depletion of glutathione resulting in covalent binding of the excess reactive metabolite to vital cell constituents (Mitchell et al., 1973, 1974). Acetaminophen half-life exceeds 4 hours when hepatic necrosis is present (Prescott et al., 1971). This prolongation in half-life is associated with a marked increase in the ratio of unchanged to conjugated drug plasma concentrations (Prescott and Wright, 1973).

MATERIALS AND METHODS

Preparation of Microcapsules

A phase-separation coacervation method was used to prepare acetaminophen microcapsules (Anderson et al., 1967; Powell et al., 1968; Bakan and Anderson, 1976). Acetaminophen (Malinckrodt, Inc., St. Louis, MO, Lot No. 1A030 and Ruger Chemical Co., Inc., Irvington, NJ, Lot No. 7032-LPR-94) was ground through a 200-mesh standard sieve prior to microencapsulation. A g ethylcellulose, 100 cps (Aldrich Chemical Co., Inc., Milwaukie, WI), B g high density polyethylene (Aldrich Chemical Co., Inc., Milwaukee, WI), and C g acetaminophen were added to a 2-liter 3-neck roundbottom flask fitted with a condenser, thermometer and motor-driven high speed stirrer (Table I.1). 600 ml cyclohexane were added to the flask and contents were stirred at 1100 rpm. A heating mantle was used to increase the temperature of the mixture to 80^{o}C (reflux temperature) over a 15 minute period. Reflux temperature was maintained for an additional 15 minutes, after which time the temperature was decreased to room temperature over a one hour period with continued stirring. The mixture was poured into a beaker through a 10-mesh standard sieve to remove polyethylene particles. Microcapsules were allowed to settle, the

Table I.1 Composition of Mixture Used to Prepare Microcapsules

Microcapsules	g Ethylcellulose (A)	g Polyethylene (B)	g Acetaminophen (C)
97.5% acetaminophen/ 2.5% ethylcellulose	1	3	39
90.0% acetaminophen/ 10.0% ethylcellulose	4	12	36
80.0% acetaminophen/ 20.0% ethylcellulose	8	24	32

cyclohexane was decanted, and the microcapsules were washed three times with 250 ml cyclohexane. After the final wash, the microcapsules were collected by gravity filtration through Whatman No. 1 filter paper and air-dried for 90 minutes. The damp microcapsules were dried at room temperature for five minutes in a fluid bed dryer (Lab-Line/PRL, Melrose Park, IL). Large chunks were manually broken up and drying was continued for an additional five minutes at which time more clumps were broken. Microcapsules were then dried for thirty minutes at 60^{o}C, removed, and placed in a 100-mesh standard sieve. Particles of size $\leq$150 µm (100 mesh) were recovered by gently rubbing microcapsules through the sieve with a small Erlenmeyer flask using a circular motion.

Dosage Form Preparation

The ingredients listed in Table I.2 were combined by geometric dilution with magnesium stearate being added last. This tablet formulation was placed in a capped, glass container and tumbled with a rotating motion to ensure uniform lubricant coating.

Small tablets ($\leq$400 mg each) were prepared using a single punch tabletting machine (Model TPK-12, Chemical and Pharmaceutical Industry Co.). Tablet hardness was measured using a tablet hardness tester (Strong, Cobb, and Co.) and ranged from 3.5 to 5.0 kg/sq in. Tablet

Table I.2 Composition of Tablet Formulation

Ingredient	Weight %
Acetaminophen Microcapsules	80.0
Di-Pac[a]	17.5
Magnesium Stearate[b]	1.0
Sodium Saccharin[c]	0.5
Flavoring Agent[d]	0.5
Coloring Agent[e]	0.5
	100.0%

[a] Amstar Corp., New York, NY.

[b] Fischer Scientific Company, Fair Lawn, NJ.

[c] Merck and Co., Inc., Rahway, NJ.

[d] Aromalok artificial wild cherry flavor, 182344, Fritzsche Dodge and Olcott, Inc., New York, NY.

[e] Di-Pac with added F.D.&C. aluminum lake (<0.5% Red No. 3), Amstar Corp., New York, NY.

formulation was also hand-packed into size 0 hard gelatin capsules (Eli Lilly Co.) to give capsules containing ≤430 mg tablet formulation each. Intact tablets were also crushed by pressing between two spoons prior to dissolution testing to evaluate possible "dose dumping" and the feasibility of administering crushed tablets to patients.

Granules containing 97.5% acetaminophen/ 2.5% ethylcellulose microcapsules were prepared by wet granulation using the following binder solutions: 1) 10% w/w starch in distilled water, 2) 10% w/w gelatin (175 bloom, Dyna Gel, Inc., Calumet City, IL) in distilled water, and 3) 10% w/w ethylcellulose in 95% ethyl alcohol (Table I.3). Microcapsules were also sprayed with 95% ethanol until a wet mass formed (Table I.3). The wet granulation masses were screened through a 6-mesh standard sieve and tray-dried in a 50^{o}C oven for three to five hours. Granules of size ≤10 mesh were used for *in vitro* dissolution testing.

In Vitro Dissolution Procedures

Acetaminophen-containing preparations were subjected to the United States Pharmacopeia XX rotating basket and paddle dissolution tests, as well as a modified dissolution test consisting of a stationary basket situated to the side and just above the paddle. The bottom of the paddle was 2 cm from the bottom of the

Table I.3 Composition of Microcapsule Granulations

Binder	Amount Binder, g/10g microcapsules	Wt % Acetaminophen
Starch	1.07	88.1
Gelatin	1.00	91.2
Ethylcellulose	3.00	94.6
Ethanol-sprayed	----	97.5

flask, and the bottom of the basket was 1 cm from the top of the paddle. The basket was situated midway between the paddle shaft and the side of the flask. Formulations containing 1.0 g acetaminophen were placed in standard dissolution baskets containing a disk of filter paper at the bottom of the basket to prevent powders from falling through the basket, or directly in flasks for paddle tests, and rotated at 50 rpm in 900 ml of dissolution medium at 37 $\pm$ 0.5^{o}C. The dissolution medium consisted of simulated enzyme-free intestinal fluid prepared by dissolving 6.8 g potassium phosphate monobasic (Mallinckrodt, Inc., St. Louis, MO, Lot XDX) in 250 ml deaerated, deionized water and adding 190 ml of 0.2 N NaOH and an additional 400 ml water. pH was adjusted to 7.4 $\pm$ 0.1 with 2 N NaOH, and water was added to give one liter of solution. Three ml samples were collected with a continuous flow (5-10 ml/min) eight channel peristaltic pump (Gilson minipuls 2, Gilson Medical Electronics, Middleton, WI) fitted with stainless steel 20-30 µm in-line filters. Sampling times were 15, 30, 45, 60, 90 minutes and 2, 3, 4, 5, 6, 8, 12 and 24 hours. An equivalent volume of temperature-equilibrated dissolution fluid was replaced after each collection.

Dissolution samples were diluted with enzyme-free simulated intestinal fluid, and absorbances were

measured at 244 nm using a double-beam spectrophotometer equipped with a sipper system (Beckman Instruments, Inc., Model 34). A standard curve ranging from 0.5 to 20 µg/ml acetaminophen was prepared, fitted to a line *via* linear regression ($r \geq 0.9996$), and used to determine drug concentration in the dissolution samples. Percentage drug released was based on the theoretical amount of acetaminophen present as calculated from percent drug loading of microcapsules and percent microcapsules in the formulation.

Wall Thickness of Microcapsules

The thickness of the ethylcellulose coat was calculated using an equation reported by Madan et al. (1974):

$$\text{wall thickness} = \frac{\text{volume of wall material recovered}}{\text{surface area of particles encapsulated}} \qquad \text{(Eq. 1)}$$

In applying this relationship the assumption is made that the drug particles are uniform, smooth and spherical and that all the ethylcellulose has been deposited as wall material. The latter assumption was verified by *in vitro* dissolution studies in which the total amount of drug dissolved was consistent with the theoretical amount of drug present. The derivation of Equation 1 and the physical/chemical constants necessary to perform the calculations are described in Appendix A.

In Vivo Administration of Acetaminophen Microcapsules

Four different oral dosage forms of microcapsules and a 1.0 g dose of Tylenol (two 500 mg tablets of Tylenol Extra Strength Acetaminophen, McNeil Laboratories, Fort Washington, PA, Lot No. PS2300) were administered to a healthy, male volunteer who gave informed written consent. Treatments were taken on five separate occasions with a wash-out period of at least three days prior to dosing, and no alcohol was allowed on treatment days. Acetaminophen preparations were swallowed with six fluid ounces of water immediately followed by a thorough mouthwash rinse with 20 ml of Scope (Proctor and Gamble, Cincinnati, OH) in an attempt to remove any drug that may have adsorbed to the buccal mucosa. Saliva samples were collected in 12 ml glass centrifuge tubes, each over a one minute period. Saliva production was stimulated by chewing a one-inch by one-inch square of Parafilm (American Can Co., Greenwich, CT). Samples were collected at 0, 10, 20, 30, 45, 60, 90, 120, 150 minutes and 3, 4, 6, 8, 12, 16, 20, 24, 30 and 36 hours. The saliva was centrifuged at 3000 rpm for 25 minutes to remove mucous and particulate matter. The salivary supernatant was transferred to a polypropylene container with a lock cap and frozen at $-20^{o}C$ until analyzed.

Acetaminophen HPLC Assay

Stock solutions containing 20, 50, 100, 200, 300, 400, 500, 600, 1000 and 1500 µg/ml of acetaminophen (USP reference standard, USP, Inc., Rockville, MD) were prepared in distilled, deionized water. An 80 µg/ml solution of 2-acetamidophenol (Aldrich Chemical Co., Inc., Milwaukee, WI) in water was used as the internal standard. Standards were prepared by spiking 500 µl of blank saliva with 25 µl of the above stock solutions. 50 µl of standard or unknown was combined with 50 µl of internal standard solution in a 250-µl polyethylene centrifuge tube and vortexed thoroughly. All samples were analyzed in duplicate on two different days. Acetaminophen concentration was determined by HPLC analysis using a delivery pump (M-6000A, Waters Associates, Milford, MA), automatic sample injector (WISP 710 B, Waters Associates, Milford, MA), 30-cm reverse phase C18 column (µBondapak, Waters Associates, Milford, MA), 10-cm guard column packed with reverse phase C18, uV detector (Model 440, Waters Associates, Milford, MA) set at 254 nm and dual pen recorder (Soltec Co., Encino, CA). The mobile phase (Gwilt, 1984) consisted of methanol in distilled water (25:75) and was pumped at a flow rate of 1.5 ml/min with a chart speed of four inches per hour. Ten microliter injections were made at 0.02 AUFS sensitivity for concentrations under

20 µg/ml. For higher concentrations the sensitivity was adjusted to 0.05 AUFS. Retention times for acetaminophen and 2-acetamidophenol were four and six minutes, respectively.

Peak height ratios versus standard concentrations were fit to a line via linear regression. Standard curves were prepared daily and had correlation coefficients (r) $\geq$0.996. The coefficient of variation varied from 2.0 to 10.4% over the range 0.95 to 50 µg/ml of acetaminophen. The sensitivity of the assay was approximately 1 µg/ml.

RESULTS AND DISCUSSION

Batch-to-Batch Comparisons

Comparison of *in vitro* dissolution in the modified apparatus for two different batches of 97.5% acetaminophen/2.5% ethylcellulose microcapsules revealed no marked differences between the microcapsules (Table I.4 and Figure I.1). Release of acetaminophen from both batches of microcapsules was very slow with only 10 to 15% of the drug released after 24 hours. However, some of the dosage forms containing these two batches of microcapsules varied with respect to dissolution behavior (Table I.4 and Figures I.2a-I.2d). The time for 50% of the drug to be released *in vitro* ($d_{50\%}$) was estimated from percent released versus time profiles using linear extrapolation. There was a significant difference in $d_{50\%}$ between batches for the tablet formulation and crushed tablets ($p<0.05$). The cause of the differences in dissolution rate of acetaminophen from the tablet formulations is unknown. The difference in dissolution rate of the crushed tablets may be due to variability in the particle sizes produced when the tablets were crushed since this factor was not controlled.

Dissolution rate of acetaminophen from ethylcellulose microcapsules appears to be reproducible

Table I.4 Time to 50% Dissolution of 97.5% Acetaminophen/2.5% Ethylcellulose Microcapsules in Modified Apparatus

Dosage Form	Amt Acetaminophen, g		$d_{50\%}$[a]	
	Batch 1	Batch 2	Batch 1	Batch 2
Microcapsules	1.00	1.00	>24	>24
Tablets[b]	0.90±0.03	0.87±0.01	5.1±0.88	4.3±0.47
Capsules[c]	0.90±0.04	1.00	6.5±0.70	6.4±0.43
Tablet Formulation[d]	0.98	1.00	8.1±1.8	13.1±0.80
Crushed Tablets[d,e]	0.98	1.00	2.6±0.42	1.2±0.55

[a]Time for 50% of the drug to dissolve. Values are expressed in hours as mean ± standard deviation for three replications.

[b]Three intact tablets.

[c]Three size 0 hard gelatin capsules containing tablet formulation.

[d]Significant difference in $d_{50\%}$ between batches ($p<0.05$).

[e]Three crushed tablets.

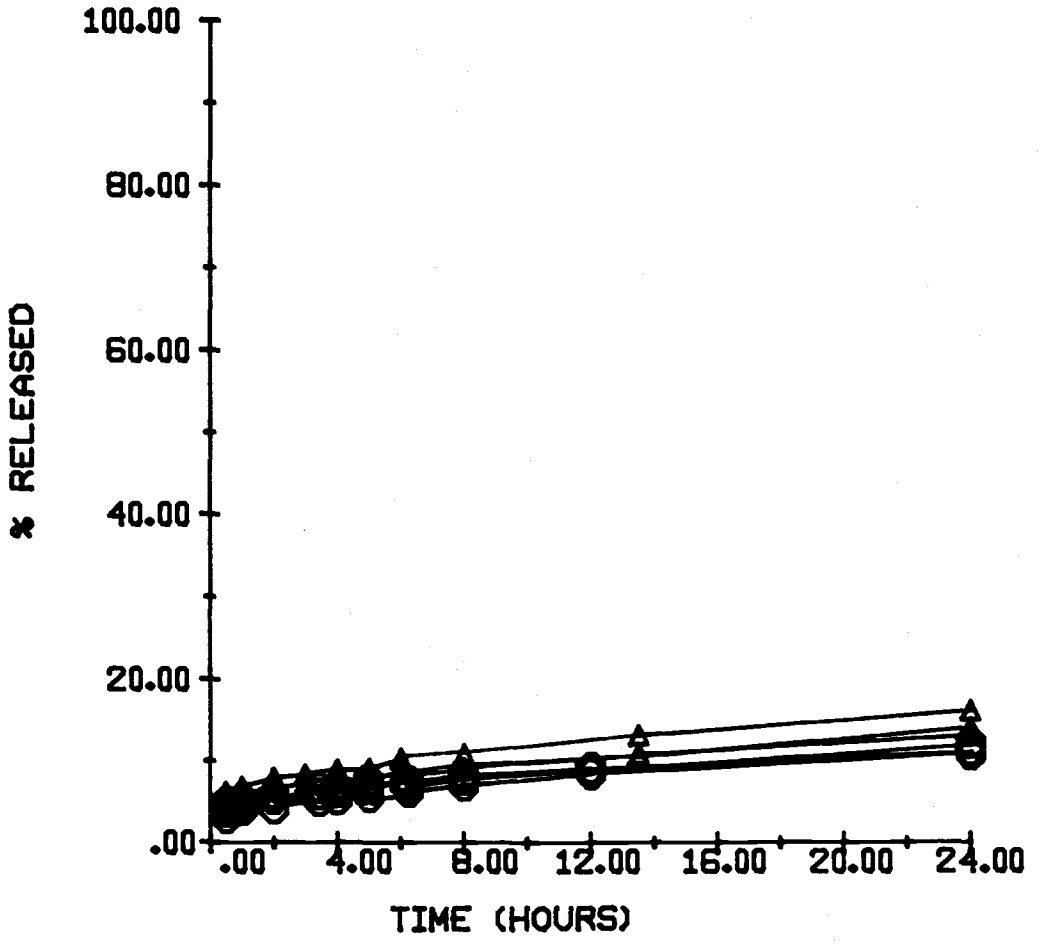

Figure I.1 *In vitro* dissolution of 97.5% acetaminophen/ 2.5% ethylcellulose microcapsules in modified apparatus. Key: (△) Batch 1; (⬡) Batch 2.

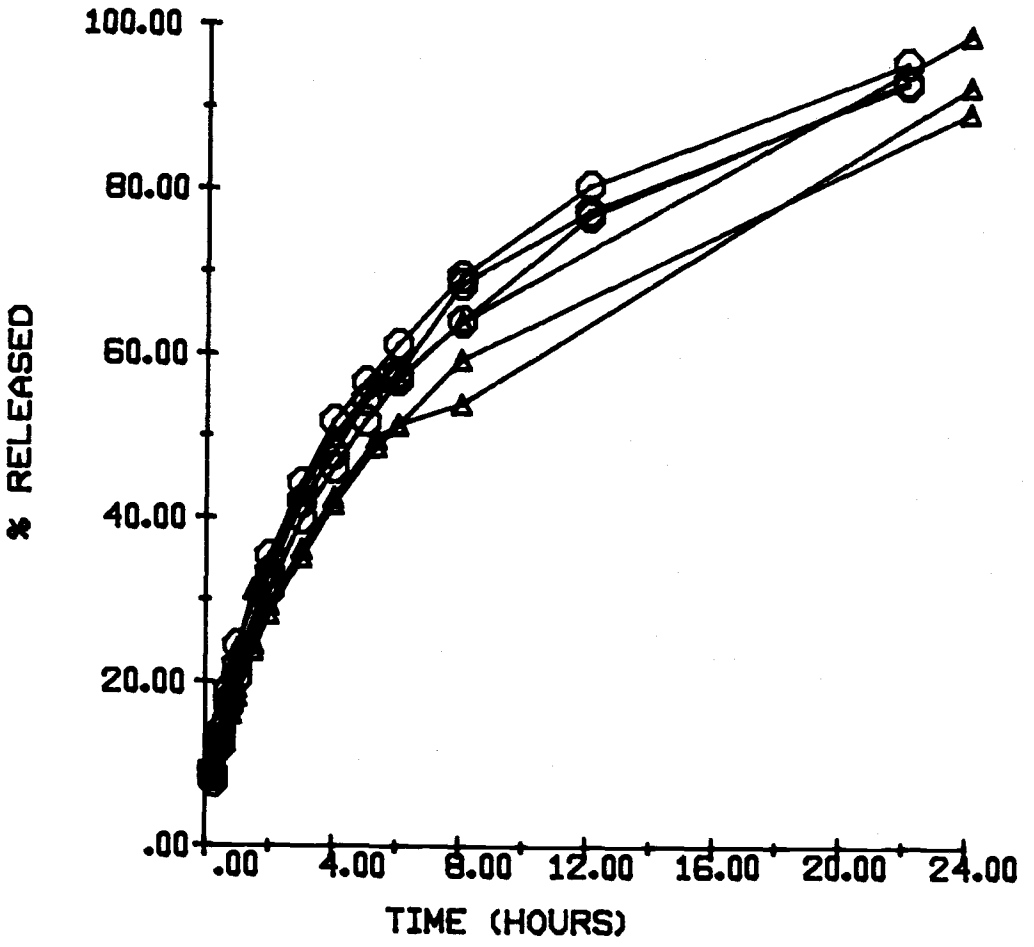

Figure I.2a In vitro dissolution of intact tablets containing 97.5% acetaminophen/2.5% ethylcellulose microcapsules in modified apparatus. Key: (△) Batch 1; (◯) Batch 2.

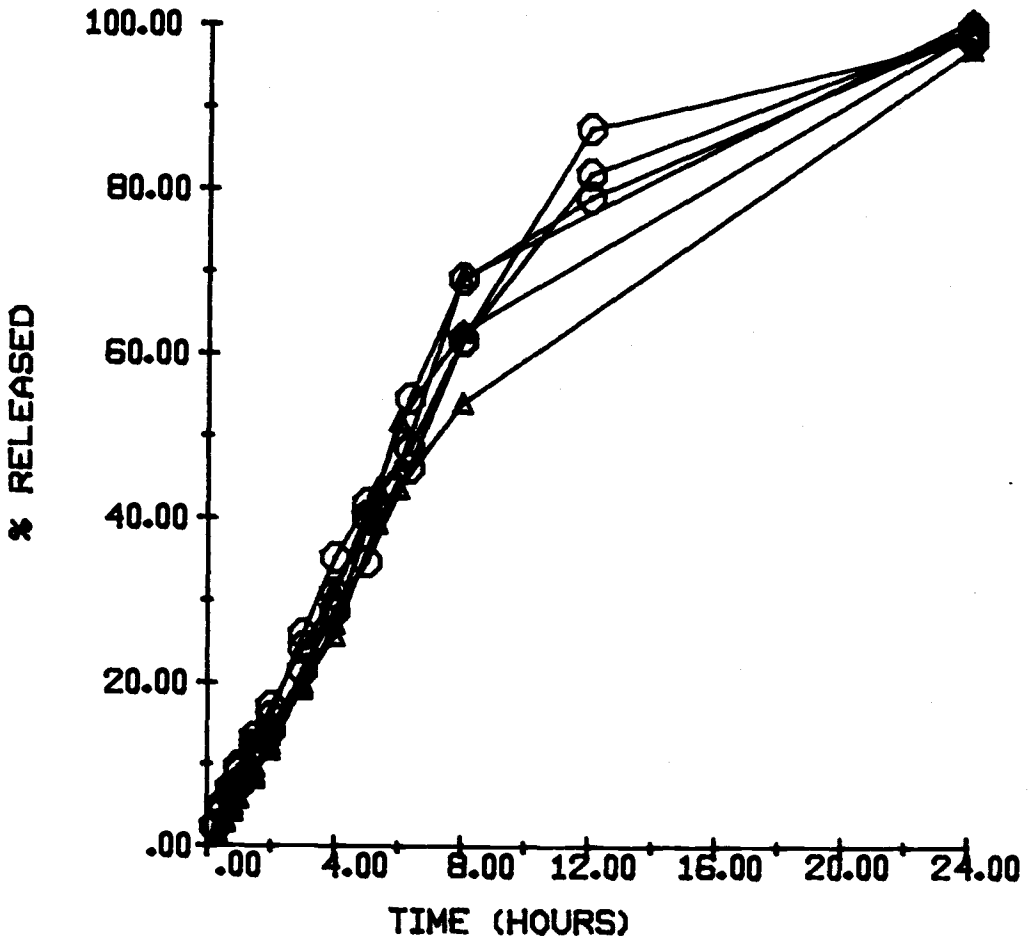

Figure I.2b *In vitro* dissolution of capsules containing tablet formulation (97.5% acetaminophen/2.5% ethylcellulose microcapsules) in modified apparatus. Key: (△) Batch 1; (◯) Batch 2.

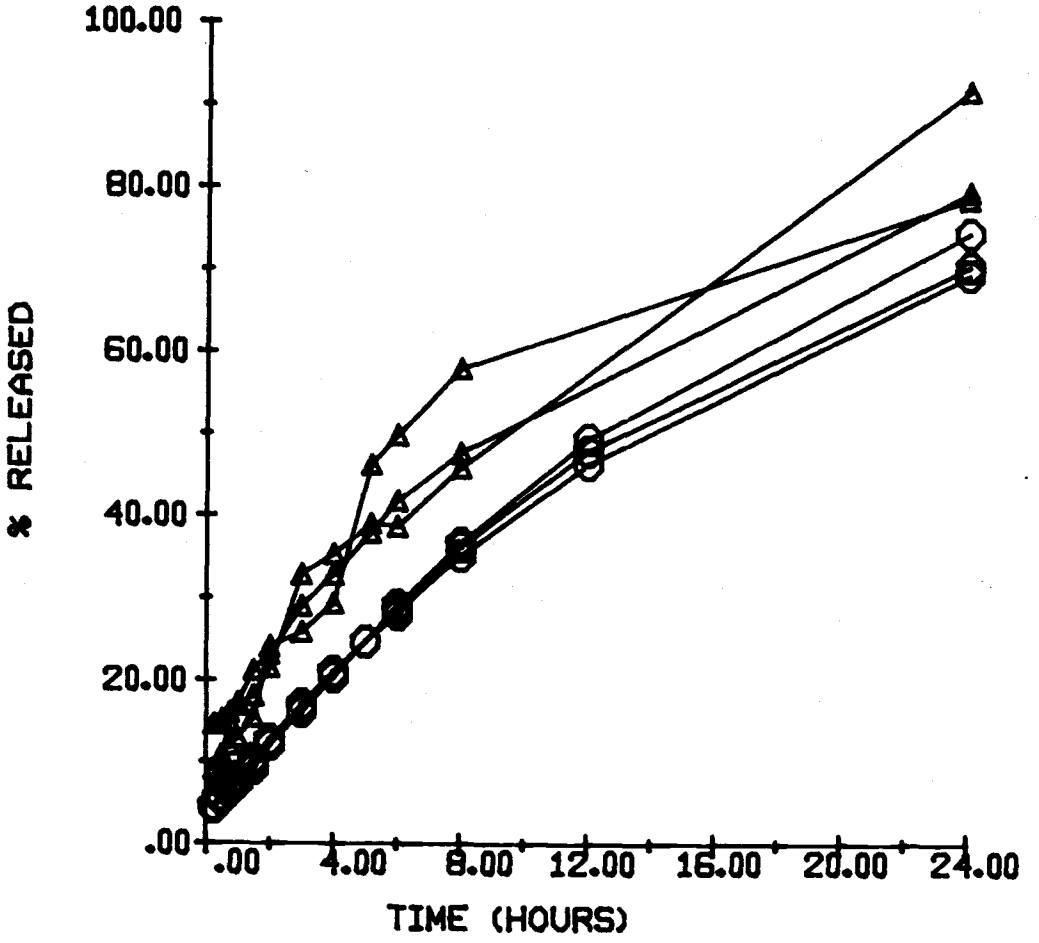

Figure I.2c *In vitro* dissolution of uncompressed tablet formulation (97.5% acetaminophen/2.5% ethylcellulose microcapsules) in modified apparatus. Key: (△) Batch 1; (◯) Batch 2.

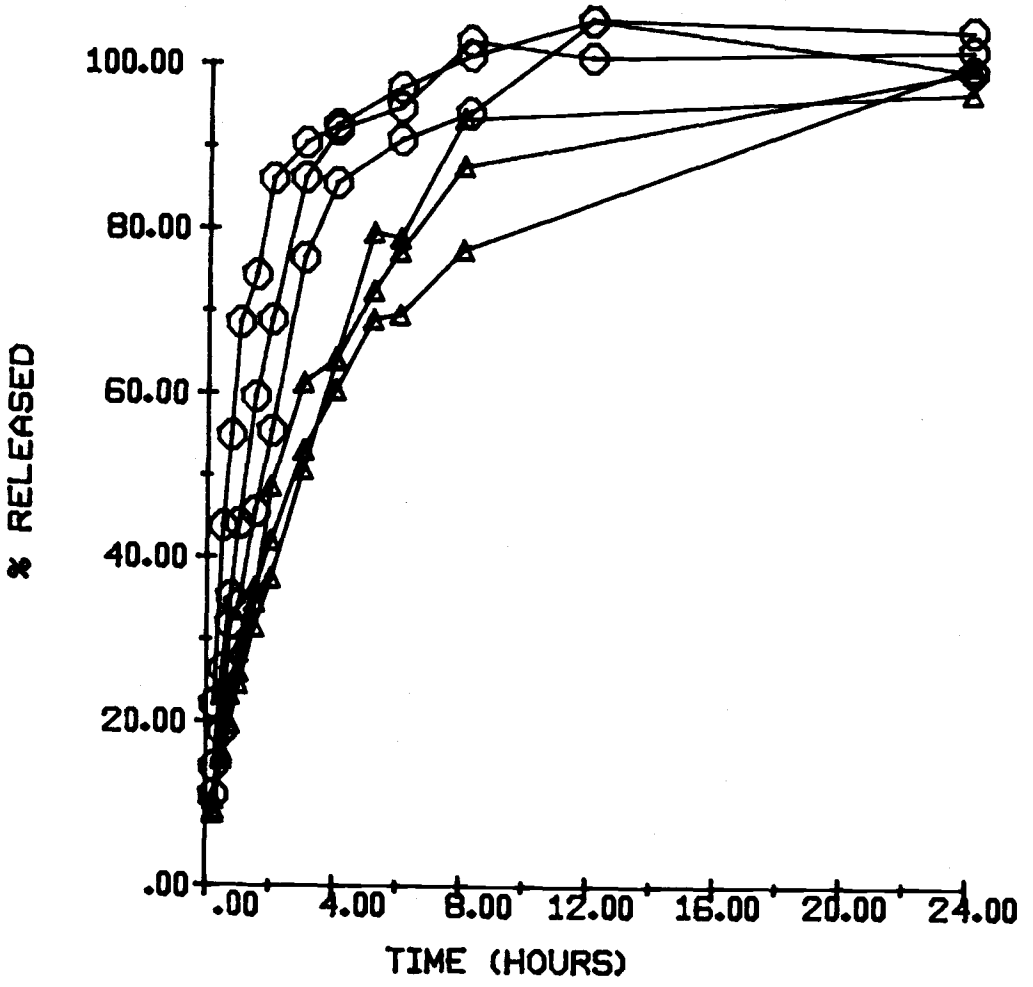

Figure I.2d *In vitro* dissolution of crushed tablets containing 97.5% acetaminophen/2.5% ethylcellulose microcapsules in modified apparatus. Key: (△) Batch 1; (◯) Batch 2.

from batch to batch. However, the observed differences in dissolution profiles for some of the dosage forms containing the microcapsules may be due to unknown differences in dosage form preparation.

Comparison of Dissolution Methods

When tested with the USP rotating basket apparatus, 97.5% acetaminophen/ 2.5% ethylcellulose microcapsules (Batch 2) and microcapsule dosage forms exhibited dissolution behavior similar to that observed with the modified apparatus, as evidenced by $d_{50\%}$ values (Tables I.4-I.6 and Figures I.3a, I.3b). However, the intact tablets dissolved more slowly ($d_{50\%}$ of 5.6 ± 0.36 hrs in basket and 4.3 ± 0.43 hrs in modified apparatus). Although statistically significant ($p<0.025$), this difference may reflect variability in dissolution testing rather than a difference between apparatuses. Based on these results, the rotating basket apparatus was used for all subsequent dissolution tests due to ease of set-up and its acceptability as a standard dissolution method.

Batch 2 microcapsules were also tested with the USP paddle apparatus (Table I.6 and Figure I.4). The mean $d_{50\%}$ (9.1 hours) was lower than for the other two apparatuses but was also extremely variable, as seen by the high standard deviation (6.9 hours) associated with the mean value. This method is unsuitable for testing microcapsules because the microcapsules float on top of

Table I.5 Time to 50% Dissolution[a] of Acetaminophen Microcapsule Dosage Forms in Rotating Basket Apparatus

Dosage Form[b]	Acetaminophen Content in Microcapsules 80%	90%	97.5%
Tablets	0.71±0.28	7.8±0.62	5.6±0.36
Crushed Tablets	2.2±0.67	0.89±0.13	0.91±0.16
Capsules	1.9±0.10	4.1±0.29	6.0±0.36
Tablet Formulation	3.4±1.4	3.2±0.87	12.2±1.2[c]

[a] Values are expressed in hours as mean ± standard deviation for three replications.

[b] The number of tablets and capsules or the amount of tablet formulation was adjusted to give about 1.0 g acetaminophen per basket. Dosage forms prepared with Batch 2 microcapsules.

[c] n = 2.

Table I.6 Time to 50% Dissolution of 97.5% Acetaminophen/2.5% Ethylcellulose Microcapsules[a] (Batch 2)

Apparatus	$d_{50\%}$[b]
Rotating Basket	>24
Paddle	9.1±6.9
Modified	>24

[a] 1.0 g acetaminophen with 3 replications per apparatus.

[b] Time for 50% of the drug to dissolve. Values are expressed in hours as mean ± standard deviation.

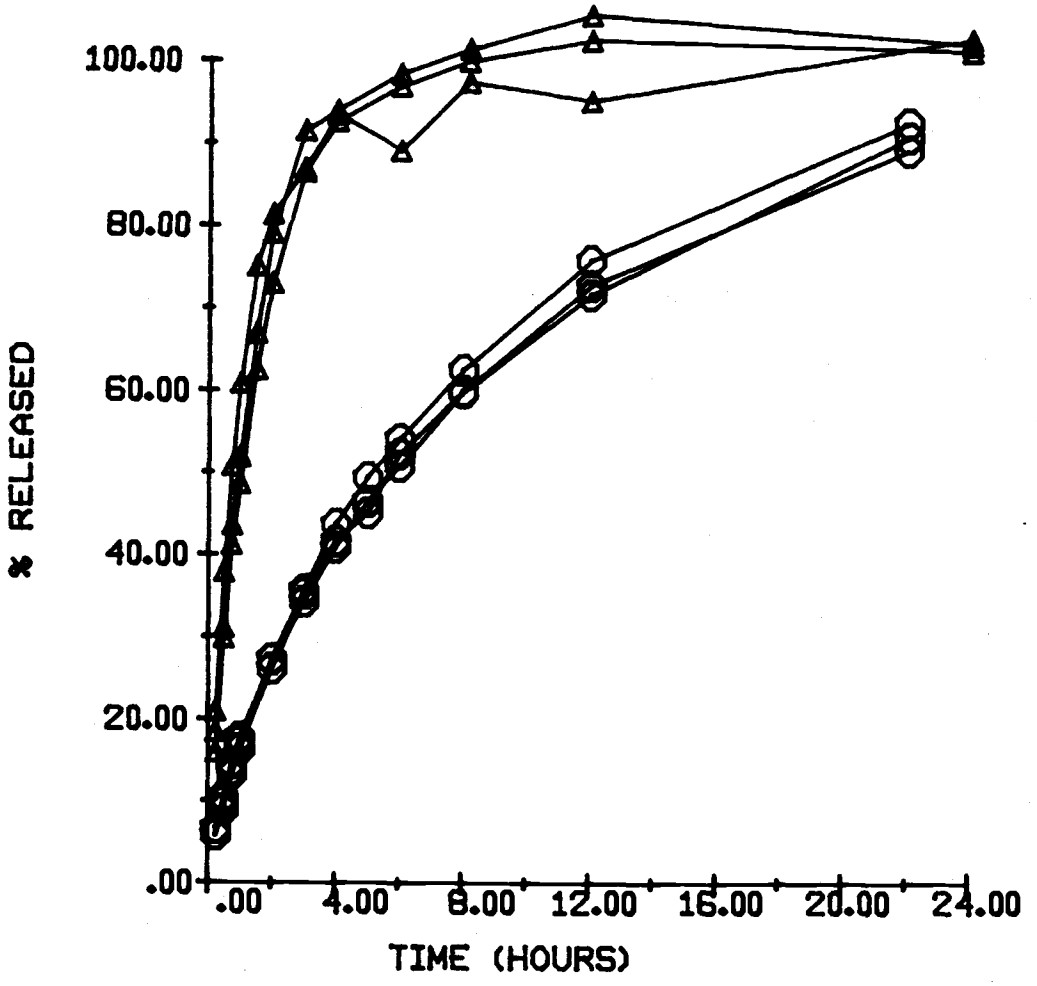

Figure I.3a *In vitro* dissolution of intact tablets (○) and crushed tablets (△) containing 97.5% acetaminophen/2.5% ethylcellulose microcapsules in rotating basket apparatus.

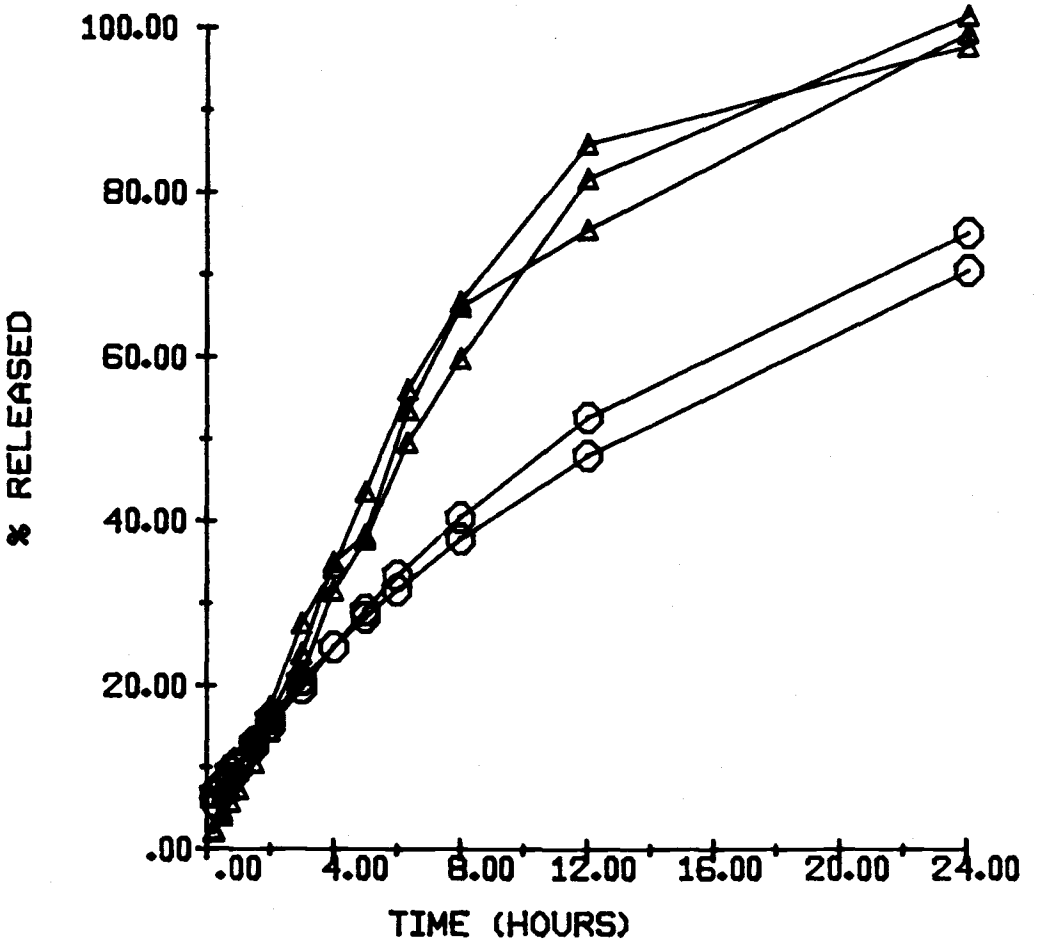

Figure I.3b In vitro dissolution of capsules containing tablet formulation (△) and uncompressed tablet formulation (⬡) (97.5% acetaminophen/ 2.5% ethylcellulose microcapsules) in rotating basket apparatus.

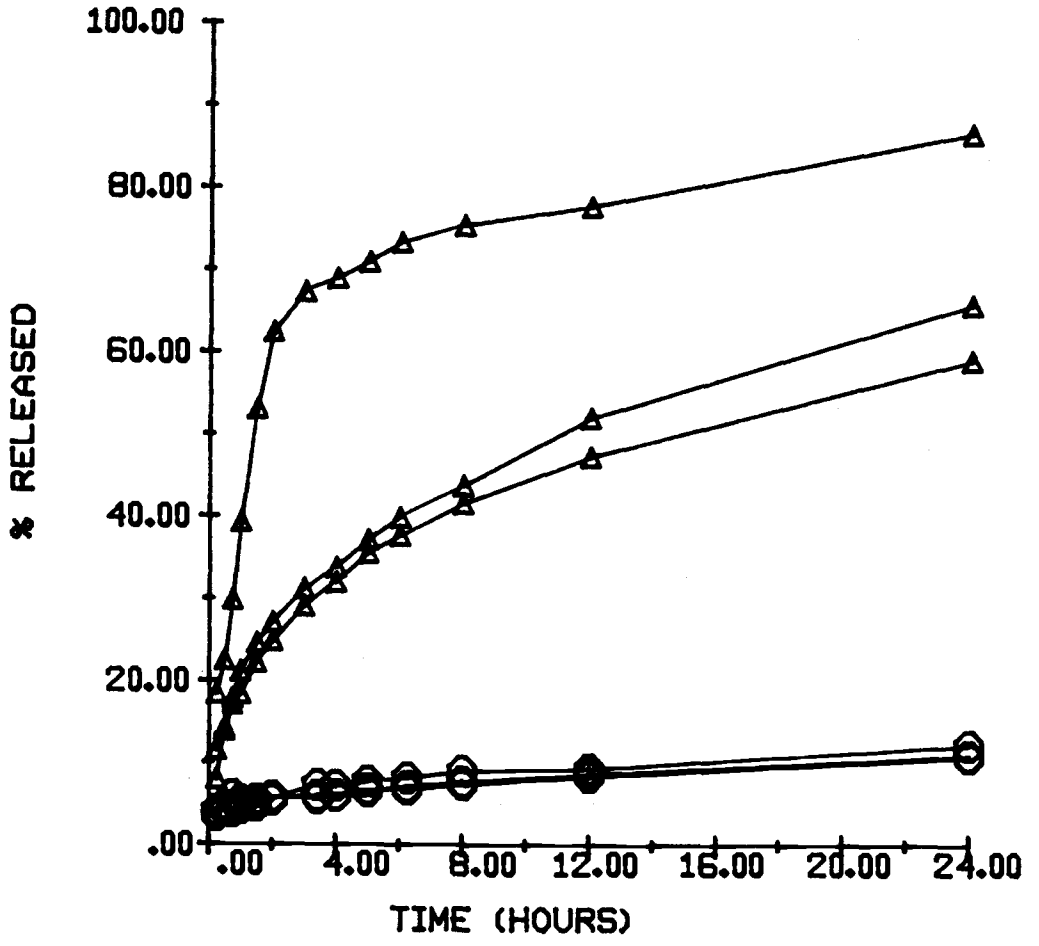

Figure I.4 In vitro dissolution of 97.5% acetaminophen/ 2.5% ethylcellulose microcapsules (Batch 2). Key: (◯) rotating basket apparatus; (△) paddle apparatus.

the dissolution fluid which does not allow for uniform wetting (Hanson, 1982a).

It appears that dissolution of these microcapsule dosage forms in the modified apparatus is the same as in the rotating basket. It has been shown that dissolution of dosage forms in the paddle apparatus is faster than in the rotating basket at the same rotation speed (Hanson, 1982b) due to the more vigorous agitation afforded by the paddle. However, in the modified apparatus this effect seemed to be offset by the confinement of the dosage form in the basket. As expected, dissolution testing of microcapsules with the paddle led to highly variable results which were caused by nonuniform distribution of microcapsules in the dissolution vessel.

Dissolution of 97.5% Acetaminophen/2.5% Ethylcellulose Microcapsules

As noted above, dissolution of microcapsules in the USP XX rotating basket and modified apparatus was very slow, with <15% of the drug released after 24 hours. Drug release from microcapsules under these conditions appears to be a zero order process up to 24 hours. The slow dissolution can be attributed to the lack of wetting since a tightly packed clump of dry microcapsules remains in the basket after 24 hours in simulated intestinal fluid. By mixing the microcapsules

with Di-Pac, wetting is facilitated due to the presence of this water soluble excipient, and release is more rapid as reflected by the mean $d_{50\%}$ of 12.2 $\pm$ 1.2 hours for the tablet formulation. Addition of a surfactant to the dissolution medium has been shown to increase the dissolution rate of dyphylline and theophylline ethylcellulose microcapsules under similar dissolution conditions by improving the accessibility of solvent to the drug (Sommers, 1983).

Wet granulation of these microcapsules resulted in granules from which drug release was very rapid (Table I.7). These results are similar to those reported by Deshpande and Njikam (1977) in which acetaminophen microcapsules were granulated using 10% maize starch. During wet granulation, the microcapsules may be wetted which results in rapid drug release. Partial dissolution of the ethylcellulose coat may also occur when microcapsules are mixed with an ethanol binder solution. Once the mixture is granulated and the granules have been dried, dissolution is rapid due to the presence of free drug on the surface and inside of the granules.

Thus, dissolution of 97.5% acetaminophen/ 2.5% ethylcellulose microcapsules in the basket apparatus is extremely slow due to lack of wetting. Granulating the microcapsules results in rapid drug dissolution because free drug may be present within and on the outside of

Table I.7 Time to 50% Dissolution of 97.5% Acetaminophen/2.5% Ethylcellulose Microcapsule Granulations

Binder	$d_{50\%}$[a]
Starch	<15
Gelatin	<40
Ethanol-Sprayed	<15
Ethylcellulose	<60

[a]Time in minutes for 50% of the drug to dissolve for two replications. Values were the same for basket, paddle, and modified apparatuses.

the granules.

Amount of Ethylcellulose Coat

Microcapsules with a 2.5% ethylcellulose coat were relatively homogeneous with respect to particle size and there was no visual evidence of clumping. The particle size was ≤150 µm. However, microcapsules having 10% or 20% ethylcellulose coats agglomerated and clumped during drying. This phenomenon was also observed in the preparation of dyphylline and theophylline ethylcellulose microcapsules using a similar procedure (Chang, 1984 and Sommers, 1983) and can be attributed to the ethylcellulose coming out of solution solvated with cyclohexane when it is precipitated by cooling or coacervation (Morse et al., 1978). It has been shown that clumping can be avoided by displacing the cyclohexane with pentane, hexane, heptane or octane prior to filtration and subsequent drying of microcapsules (Morse et al., 1978). Formation of aggregates in production of ethylcellulose microcapsules has been reported for other drugs, as well (Fanger et al., 1970, Jalsenjak et al., 1976; Agyilirah and Nixon, 1980). 80 to 90% of microcapsule particles with a 10% ethylcellulose coat were ≤150 µm in size with the remaining portion being larger. The product having a 20% ethylcellulose coat consisted of particles ranging in size from 3.5 mm down to ≤150 µm. In preparation of

dosage forms containing microcapsules with 80% or 90% acetaminophen, only particles of size $\leq$850 µm were used.

The effect of varying the amount of ethylcellulose coating on release of drug from microcapsules was examined by comparing *in vitro* dissolution (rotating basket apparatus) profiles of dosage forms containing microcapsules with 2.5%, 10% and 20% ethylcellulose coats. Dissolution profiles for a representative batch of each of the microcapsules are given in Figures I.5a-I.5d, and $d_{50\%}$ values are given in Table I.5. Analysis of variance (Snedecor and Cochran, 1980) revealed that there was a significant difference in $d_{50\%}$ for different ethylcellulose coating levels for all of the dosage forms ($p<0.01$). However, the rate of dissolution from microcapsules was influenced by the dosage form since no one dissolution pattern was observed as the amount of ethylcellulose coating was increased.

It would be expected that increasing the amount of coating applied to drug particles and thus increasing the thickness of the coat should slow the observed dissolution rate of drug from microcapsules provided that drug release occurs according to a diffusional process which can be described by Fick's Law (Baker and Lonsdale, 1974). However, Chang (1984) unexpectedly found that release of drug from dyphylline

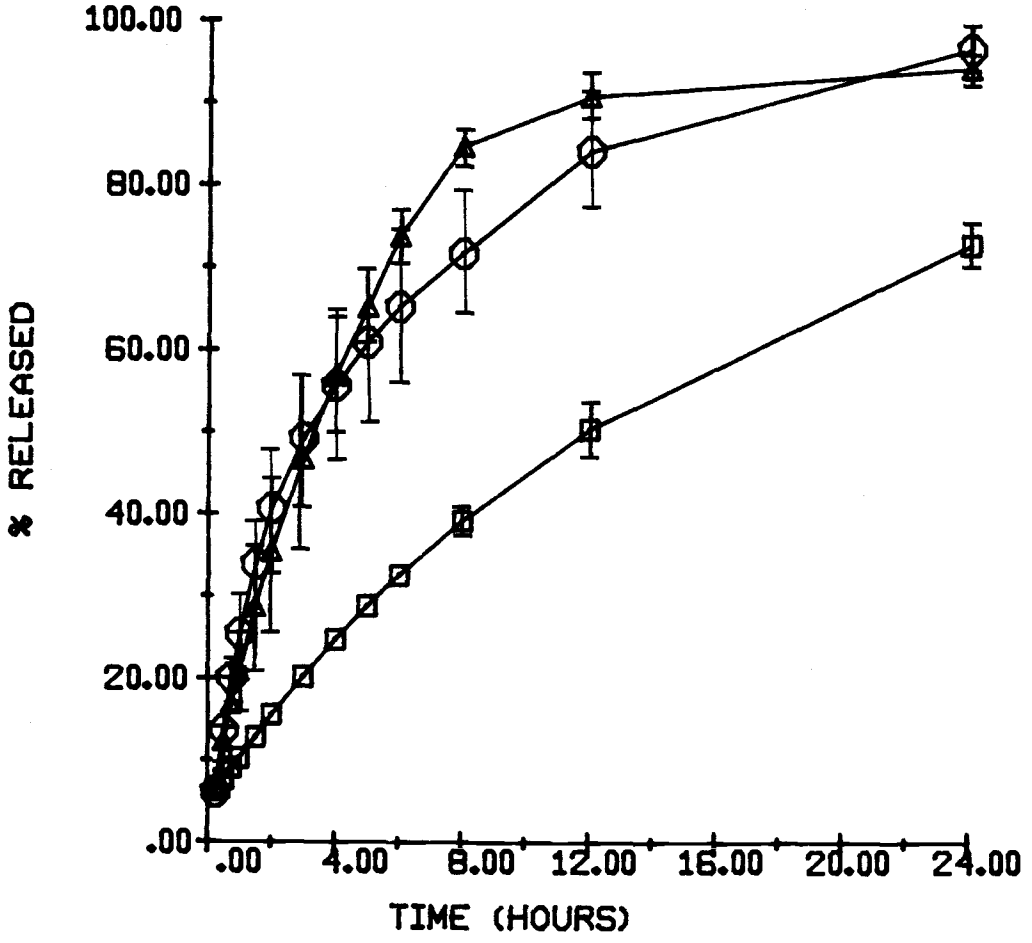

Figure I.5a In vitro dissolution of uncompressed tablet formulations containing microencapsulated acetaminophen. Key: (□) 97.5% acetaminophen/2.5% ethylcellulose; (△) 90% acetaminophen/ 10% ethylcelulose; (○) 80% acetaminophen/20% ethylcellulose microcapsules. Each point is the mean ± standard deviation of three replications.

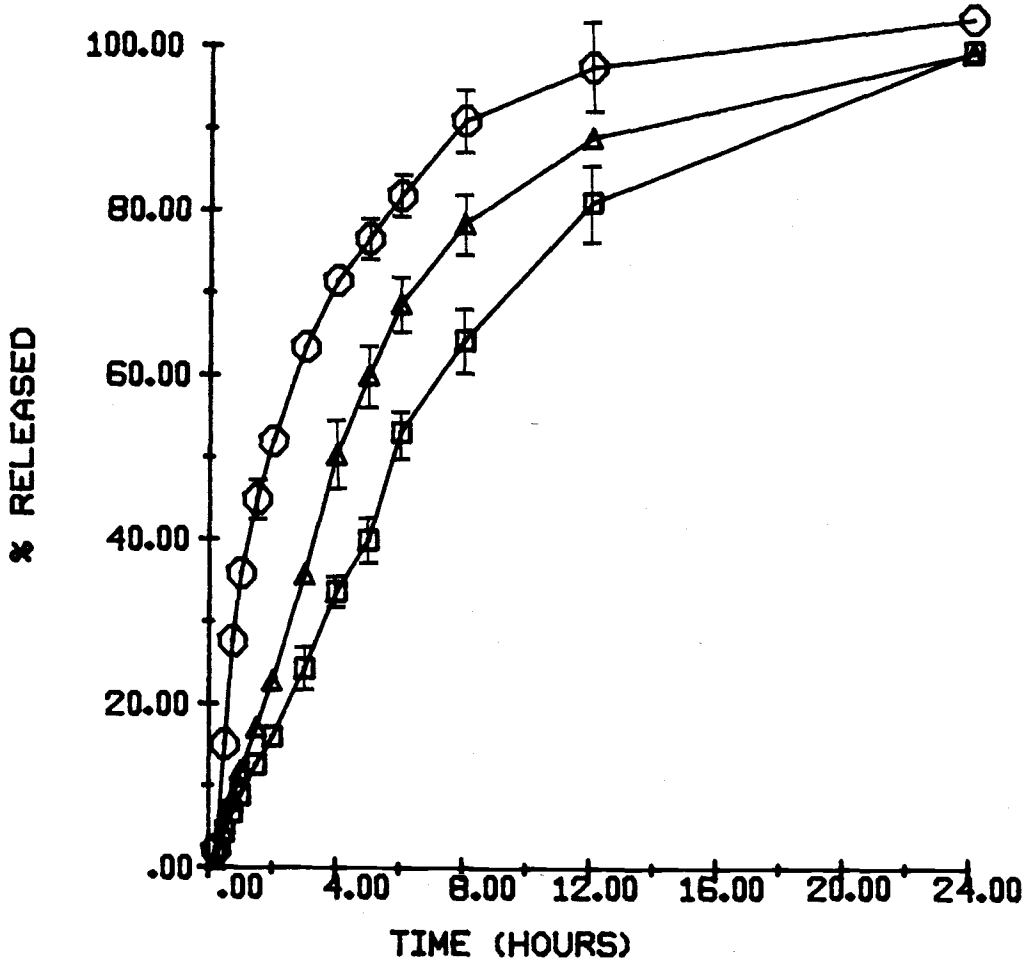

Figure I.5b In vitro dissolution of capsules containing microencapsulated acetaminophen tablet formulations. Key: (□) 97.5% acetaminophen/2.5% ethylcellulose; (△) 90% acetaminophen/10% ethylcelulose; (◯) 80% acetaminophen/20% ethylcellulose microcapsules. Each point is the mean ± standard deviation of three replications.

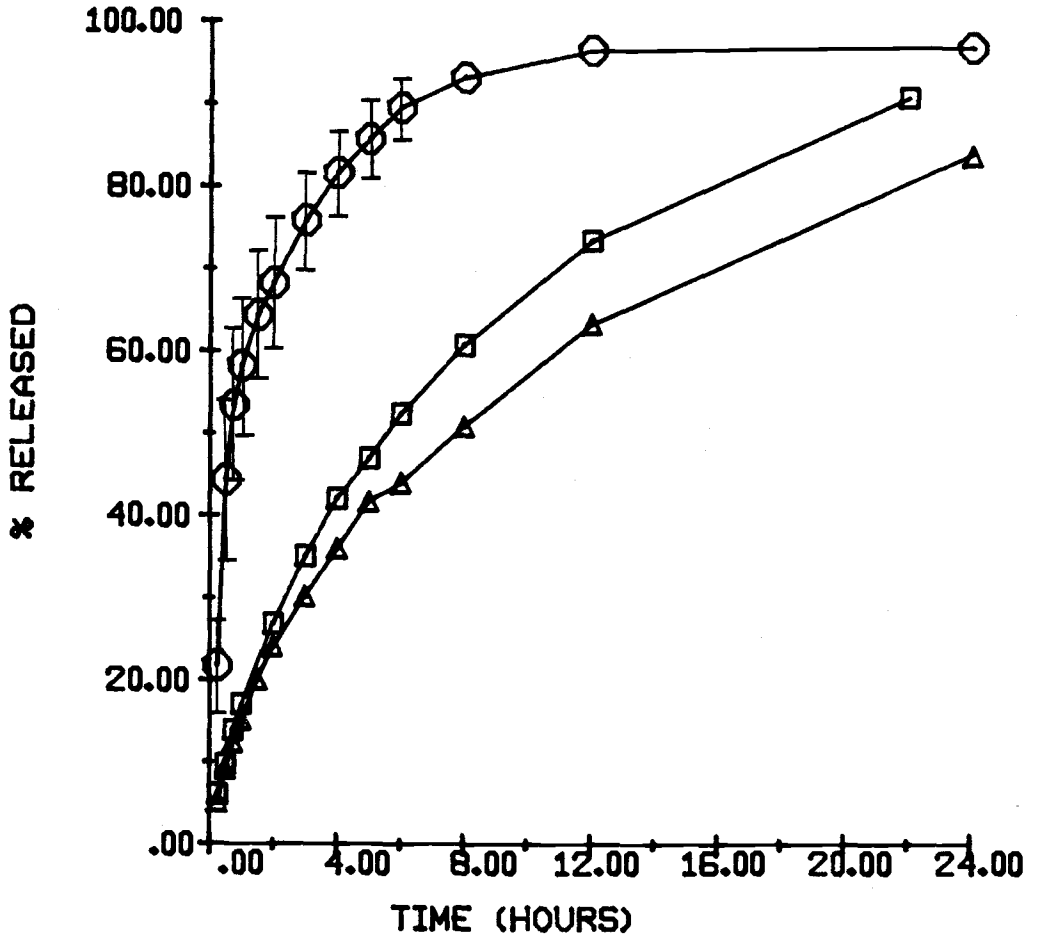

Figure I.5c *In vitro* dissolution of intact tablets containing microencapsulated acetaminophen. Key: (□) 97.5% acetaminophen/2.5% ethylcellulose; (△) 90% acetaminophen/10% ethylcellulose; (○) 80% acetaminophen/20% ethylcellulose microcapsules. Each point is the mean ± standard deviation of three replications.

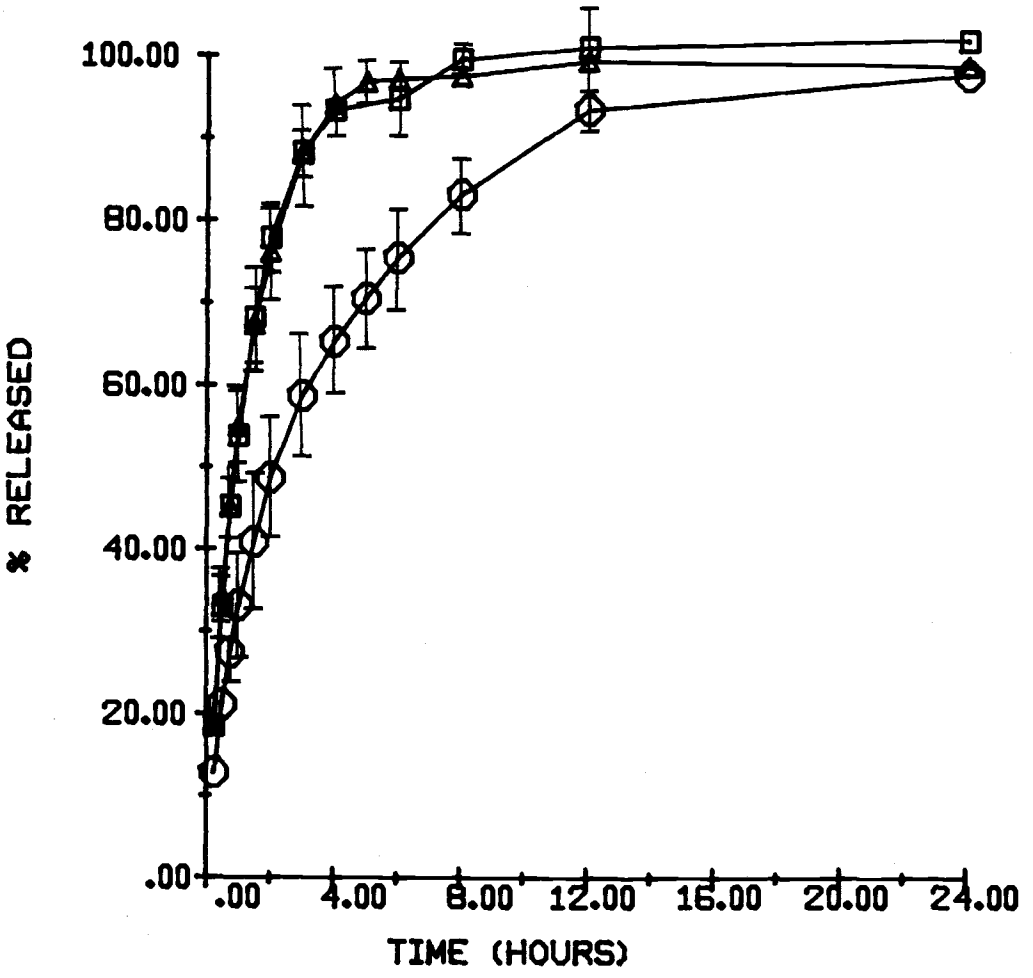

Figure I.5d *In vitro* dissolution of crushed tablets containing microencapsulated acetaminophen. Key: (□) 97.5% acetaminophen/2.5% ethylcellulose; (△) 90% acetaminophen/10% ethylcelulose; (○) 80% acetaminophen/ 20% ethylcellulose microcapsules. Each point is the mean ± standard deviation of three replications.

ethylcellulose microcapsules increased as the amount of ethylcellulose applied was increased. This phenomenon was left unexplained but is now hypothesized to be due to differences in particle sizes between microcapsules with different amounts of ethylcellulose coat. Smaller particles, such as microcapsules with a 2.5% ethylcellulose coat, resist wetting when confined to a basket, presumably by forming a unified hydrophobic surface which repels water. As the amount of ethylcellulose is increased, the particle size increases due to clumping of microcapsules during drying, as described previously. These larger particles wet more readily and thus exhibit more rapid in vitro dissolution under the specified conditions.

For acetaminophen it was also found that in vitro dissolution of drug was slower from acetaminophen microcapsules having only a 2.5% ethylcellulose coat (Figure I.5a). The $d_{50\%}$ for the uncompressed tablet formulation containing 97.5% acetaminophen/ 2.5% ethylcellulose (12.2$\pm$1.2 hours) was significantly longer than that of microcapsules with 20% or 10% coats (3.4$\pm$1.4 and 3.2$\pm$0.87 hours, respectively; $p<0.01$). This was also true for the tablet formulation packed into hard gelatin capsules (Table I.5 and Figure I.5b).

For tablets containing acetaminophen microcapsules, the observed in vitro dissolution profiles (Figure I.5c)

reflect a combination of possible release mechanisms, and the dissolution results are not as easily explained as the "loose" tablet formulation which contains uncompressed microcapsules. When a polymer is combined with drug and compressed into tablets, it may form an insoluble plastic matrix or shell which slows drug release (Dittgen et al., 1977; Lee and Robinson, 1978; Kala et al., 1980; Georgakopoulos et al., 1981). When a water soluble drug and water soluble excipients, such as Di-Pac, are combined with ethylcellulose and then compressed to form a tablet, drug release may occur by a combination of diffusion and leaching via channels which are formed as the excipients and drug dissolve within the matrix. When all the drug has been released, an empty, plastic skeleton remains which is then excreted from the body. Drug release rate will be largely independent of pH, motility and enzymes. For tabletted microcapsules the microcapsule wall still has to be penetrated to release the core. However, compacting the microcapsules results in a greatly reduced surface area being available for release. Even after the drug has been released from microcapsules composing the tablet, the dissolved drug still has to permeate narrow channels in the tablet prior to release. The combined effects of reduced surface area and channel permeation result in slowing of drug release from

tabletted microcapsules relative to untabletted microcapsules (Nixon and Agyilirah, 1984). This effect was observed for the 90% acetaminophen/ 10% ethylcellulose microcapsules when one compares the $d_{50\%}$ for tablets with that of tablet formulation (Table I.5) but not for the 97.5% acetaminophen/ 2.5% ethylcellulose microcapsules. The probable reason for this is that release from the latter microcapsules is retarded by lack of wetting, as has been discussed previously.

The mean $d_{50\%}$ for tablets made with 2.5% ethylcellulose microcapsules was significantly shorter than the $d_{50\%}$ for tablets made with 10% ethylcellulose microcapsules ($p<0.01$). This observation cannot be explained by differences in drug release from the microcapsules since release from 90% acetaminophen/ 10% ethylcellulose microcapsules was much more rapid than from 97.5% acetaminophen/2.5% ethylcellulose microcapsules. Thus, it must be due to the higher ethylcellulose content which resulted in formation of a more extensive matrix upon compression which further slows drug release. The results obtained for tablets prepared with 80% acetaminophen/20% ethylcellulose microcapsules are not in agreement with this finding since release from these tablets was much more rapid with a mean $d_{50\%}$ of <1 hour (Table I.5 and Figure I.5c). This can be explained by the observation that these

tablets disintegrated and did not form a plastic matrix upon compression like tablets containing 2.5% and 10% ethylcellulose microcapsules. The tablets were fairly soft (hardness $\leq$ 5 kg/sq in) and thus the compression force may not have been high enough to form the plastic matrix at this ethylcellulose content. Nixon and Agyilirah (1984) found that for sodium phenobarbital/ ethylcellulose microcapsules, release was faster from tablets made from larger aggregates of microcapsules. This result was explained by an increase in tablet strength as particle size increased, which was due to a breakdown of aggregates and perhaps even individual microcapsule walls, thus exposing free drug for dissolution. The breakdown would be greater for larger microcapsule particle sizes.

Crushing the tablets had a significant effect on *in vitro* dissolution. Release of drug from crushed tablets containing 90% acetaminophen/10% ethylcellulose and 97.5% acetaminophen/2.5% ethylcellulose microcapsules was much more rapid than from intact tablets (Table I.5 and Figure I.5d). This is as expected since the plastic matrix has been destroyed. Such prompt release of drug *in vivo* has been reported when tablets containing drug in an insoluble polymer matrix are chewed (Ritschel, 1971). In addition, some of the microcapsules may have cracked as a result of crushing between two spoons. It

has been shown that upon compression of aspirin microcapsules, some of the particles are fractured, but the degree of fracture and immediate release are small (Green, 1966). Release of acetaminophen from crushed tablets containing microcapsules with a 20% ethylcellulose coat was slower than from intact tablets (Table I.5 and Figures I.5c, I.5d). This was not expected and even though the difference in mean $d_{50\%}$ was statistically significant ($p \leq 0.05$), the sample size was small and the standard deviation was high. It is unlikely that there actually is a difference in release rate since the intact tablets disintegrate and thus should release drug slightly slower or at the same rate as tablets which have been crushed.

Release of drug from crushed tablets (Figure I.5d) was also faster than from uncompressed tablet formulation (Figure I.5a), and this can be explained by increased wetting of crushed tablet particles when compared to microcapsules which clump together in the basket and resist wetting. This is consistent with the finding that the largest difference in dissolution rate between crushed and intact tablets was observed for 97.5% acetaminophen/2.5% ethylcellulose microcapsules which have the smallest particle size.

Dissolution of uncompressed tablet formulation packed into three hard gelatin capsules was

significantly faster than that of uncompressed tablet formulation for 97.5% acetaminophen/2.5% ethylcellulose microcapsules when placed "loose" in the dissolution basket (Table I.5, Figures I.5a, I.5b; $p<0.01$). Again, this may be explained by increased wetting of microcapsules since they have been divided into three portions. Differences in $d_{50\%}$ between capsules and "loose" tablet formulation containing microcapsules with 20% and 10% ethylcellulose coats, respectively, were not significant ($p>0.05$). This finding is consistent with the observation that products with higher levels of ethylcellulose coating are composed of larger particles which wet more readily and thus dissolution is not affected by dividing the tablet formulation into separate portions.

The effect of compression forces on the ethylcellulose coat can not be elucidated from the dissolution data because compression of ethylcellulose results in formation of a plastic matrix, as described previously. Thus, the microcapsules in the tablet are no longer discrete particles since some of them have been molded together. Differences in dissolution profiles between capsules containing tablet formulation and tablets were observed for microcapsules with 10% and 20% ethylcellulose coats. Because the tablets with a 20% ethylcellulose coat disintegrated, it was not

possible to determine whether the release rate of microencapsulated drug from nondisintegrating tablets would be slower than from capsules, or whether the amount of ethylcellulose would have an effect on the magnitude of this difference.

In conclusion, tablets with 2.5% and 10% ethylcellulose-coated acetaminophen microcapsules provided prolonged drug release *in vitro*. However, when these tablets were crushed, release was very rapid and based on this observation, one would expect "dose dumping" to occur *in vivo* if such a dosage form was crushed or chewed. Observed differences in *in vitro* dissolution between the various dosage forms can primarily be attributed to differences in particle sizes of microcapsule aggregates as the amount of ethylcellulose coat was varied. Because discrete microcapsules were not obtained at the higher coating levels, the effect of increasing the amount of ethylcellulose coat on dissolution of drug from microcapsules can not be determined.

Ethylcellulose Wall Thickness

Table I.8 gives the estimated thickness of the ethylcellulose coat for the three levels of ethylcellulose applied onto acetaminophen particles. These values were calculated using Equation 1 with an acetaminophen particle size of 75 μm, which is the size

Table I.8 Calculated Ethylcellulose Wall Thickness of Acetaminophen Microcapsules

Weight % Ethylcellulose	Wall Thickness, μm
2.5	$\leq$ 0.37
10.0	$\leq$ 1.59
20.0	$\leq$ 3.58

of the standard mesh sieve through which acetaminophen powder was sieved prior to microencapsulation. It is likely that many of the particles were smaller than 75 µm, and thus these values are given as upper limits. However, the size of some of the particles obtained after microencapsulation was larger than 75 µm which means that either the microcapsules have agglomerated during drying or the ethylcellulose has been deposited around several drug particles rather than discrete particles. The latter hypothesis is unlikely since the agitation rate during the entire microencapsulation process was maintained at a high speed (1100 rpm) which should break up any aggregates.

For such thin coatings, one would not expect much of a sustained release effect since Lehmann and Dreher (1979) have found that a 10 µm thick uniform layer of acryclic resins around small particles (0.1-1.0 mm) affords both complete coverage and taste proofing, but to achieve a more pronounced delayed-release effect, thicker coats are needed which correspond to applications of 2-3 mg/sq cm of surface. Thus, the ethylcellulose coating is not expected to be responsible for the observed sustained release of acetaminophen *in vitro*.

Release Patterns

Microcapsules with a water insoluble membrane can

be considered as a type of reservoir controlled release device from which the release of drug occurs by diffusion. Assuming the microcapsules are spherical, the release rate can be described by Equation 2 (Baker and Lonsdale, 1974):

$$dM_t/dt = (4\pi r_o r_i / r_o - r_i) Dk\Delta C \qquad \text{(Eq. 2)}$$

where M_t is the amount of drug released, dM_t/dt is the steady state release rate at time t, r_o and r_i are the outer and inner radius of the sphere, respectively, D is the diffusion coefficient of the permeant in the membrane, k is the distribution coefficient, Dk is the membrane permeability, and ΔC is the difference between the internal and external drug concentration. The term $4\pi r_o r_i / r_o - r_i$ represents the surface area per membrane thickness. Zero order release occurs when all the terms on the right side of the equation are constant, and a plot of amount (or percent) released versus time would give a straight line. It has been demonstrated that an approximate constant release of drug can be achieved when small drug particles (about 10 μm in diameter) are coated with thin coats (Robinson et al., 1968). Although it is often desirable to achieve and maintain zero order drug release from a sustained release dosage form, sustained release can still be obtained if first order absorption of drug occurs (Gibaldi and Perrier, 1982a; Boxenbaum, 1984). Several different sustained

release forms of microencapsulated drug, such as rapidly disintegrating tablets containing coated drug particles, microencapsulated powder and a blend of coated pellets, have illustrated apparent first order release kinetics *in vitro*, although diverse mechanisms are involved (Bakan and Anderson, 1976; Bakan and Powell, 1983).

In vitro dissolution data for acetaminophen microcapsules and dosage forms containing microcapsules in the rotating basket apparatus were plotted as log of percent unreleased versus time to determine whether release of drug could be described by a first order process since drug release was not zero order for most of the dosage forms, as seen previously from the plots in Figures I.5a-I.5d. In addition, percent released versus square root of time plots were made since such a dependency has been described for monolithic devices which consist of drug homogeneously dispersed in a release-rate-controlling membrane (Baker and Lonsdale, 1974). Release from microcapsules should not follow such a pattern. However, such a relationship may hold for tablets containing compressed microcapsules since the polymer compresses to form a plastic matrix.

Because release from the 97.5% acetaminophen/ 2.5% ethylcellulose microcapsules was so slow, it appears to be linear for zero order, first order, and square root of time relationships (Figures I.4, I.6). The plots

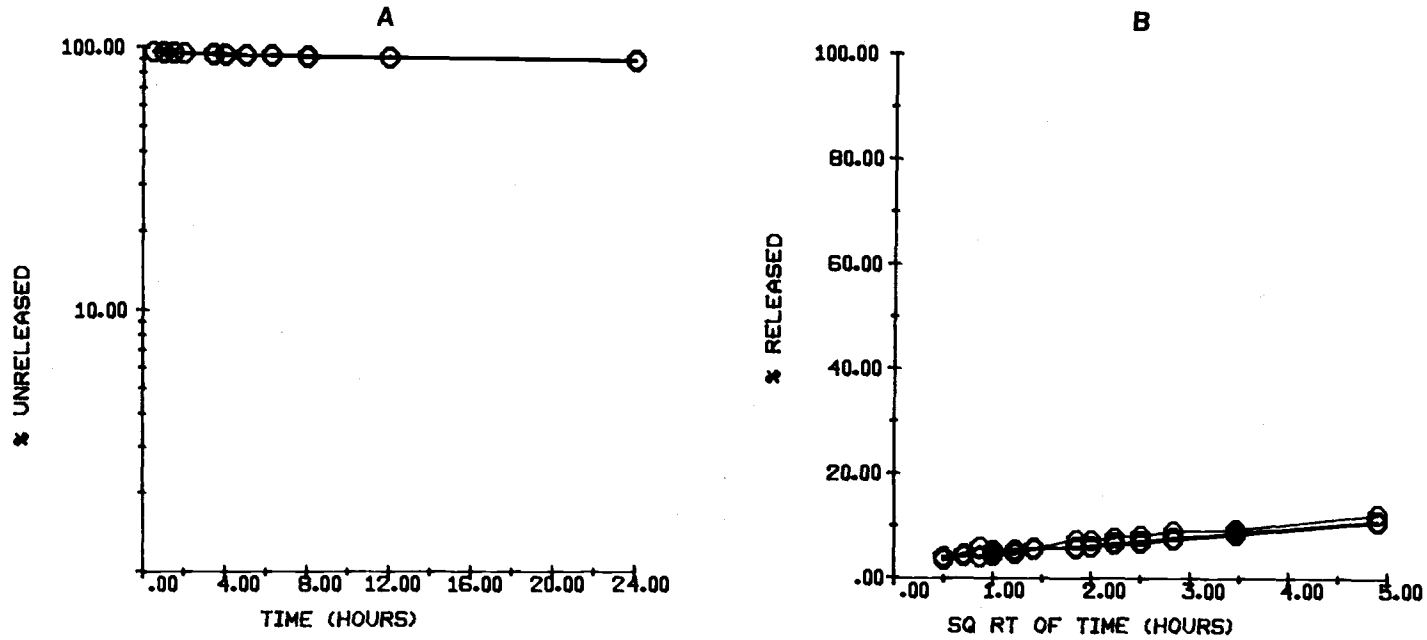

Figure I.6 In vitro dissolution of 97.5% acetaminophen/2.5% ethylcellulose microcapsules: (A) percent acetaminophen unreleased versus time; (B) percent acetaminophen released versus square root of time.

shown in Figures I.7-I.12 reveal that total release patterns for microcapsule dosage forms are complex and cannot be described by any one mathematical model. For tablets containing microcapsules with 2.5% and 10% ethylcellulose coats, respectively, release appears to be first order as evidenced by the linear curves on percent unreleased versus time plots in Figure I.7, but tablets made with 80% acetaminophen/20% ethylcellulose microcapsules do not follow such a trend. Crushed tablets (Figure I.8) also appear to exhibit first order release kinetics for the first 90% of drug released, although some curvature is present. Deviations from linearity were observed for capsules (Figure I.9) and the tablet formulation (Figure I.10), as well, with the exception of the tablet formulation containing 97.5% acetaminophen/2.5% ethylcellulose microcapsules.

Possible linear relationships between percent released and square root of time were observed only for tablets containing 97.5% acetaminophen/ 2.5% ethylcellulose and 90% acetaminophen/10% ethylcellulose microcapsules (Figure I.11). The other dosage forms gave release profiles which were curved, such as those shown for the uncompressed tablet formulation in Figure I.12. These results were as expected since release of drug from microcapsules and dosage forms containing microcapsules should not follow patterns for monolithic

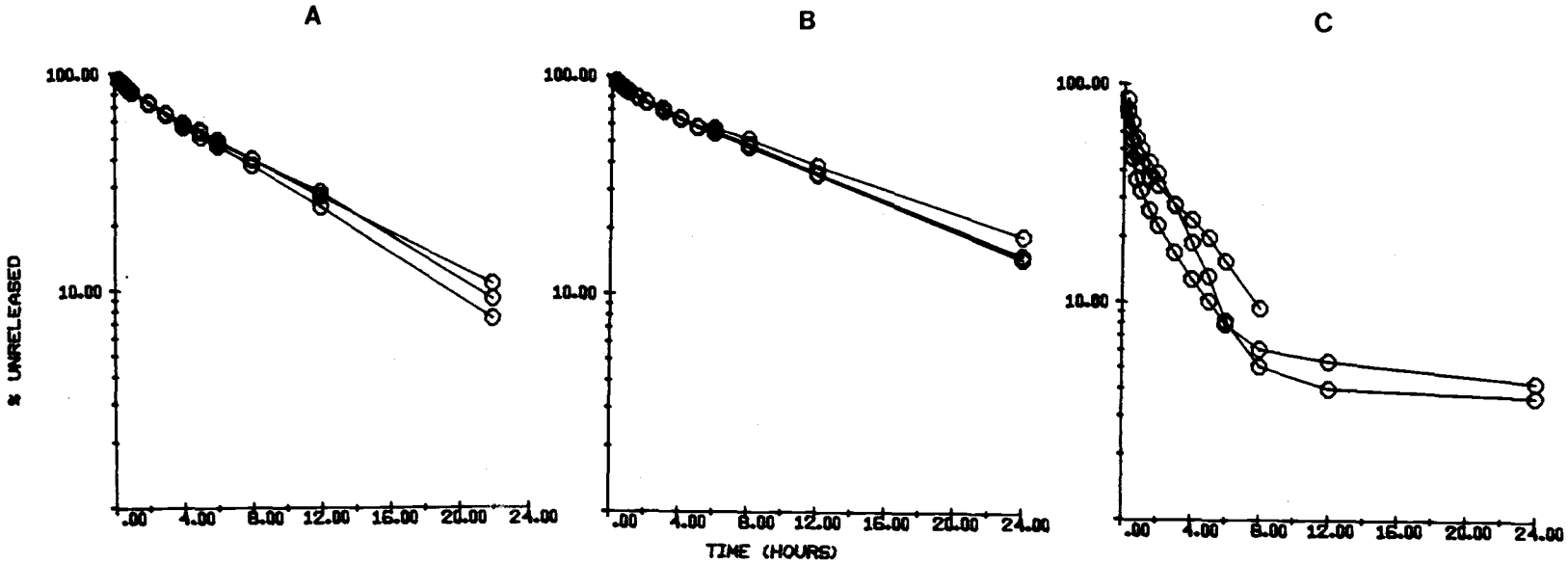

Figure I.7 In vitro dissolution of intact tablets containing microencapsulated acetaminophen: percent acetaminophen unreleased versus time. Key: (A) 97.5% acetaminophen/2.5% ethylcellulose; (B) 90% acetaminophen/ 10% ethylcellulose; (C) 80% acetaminophen/20% ethylcellulose microcapsules.

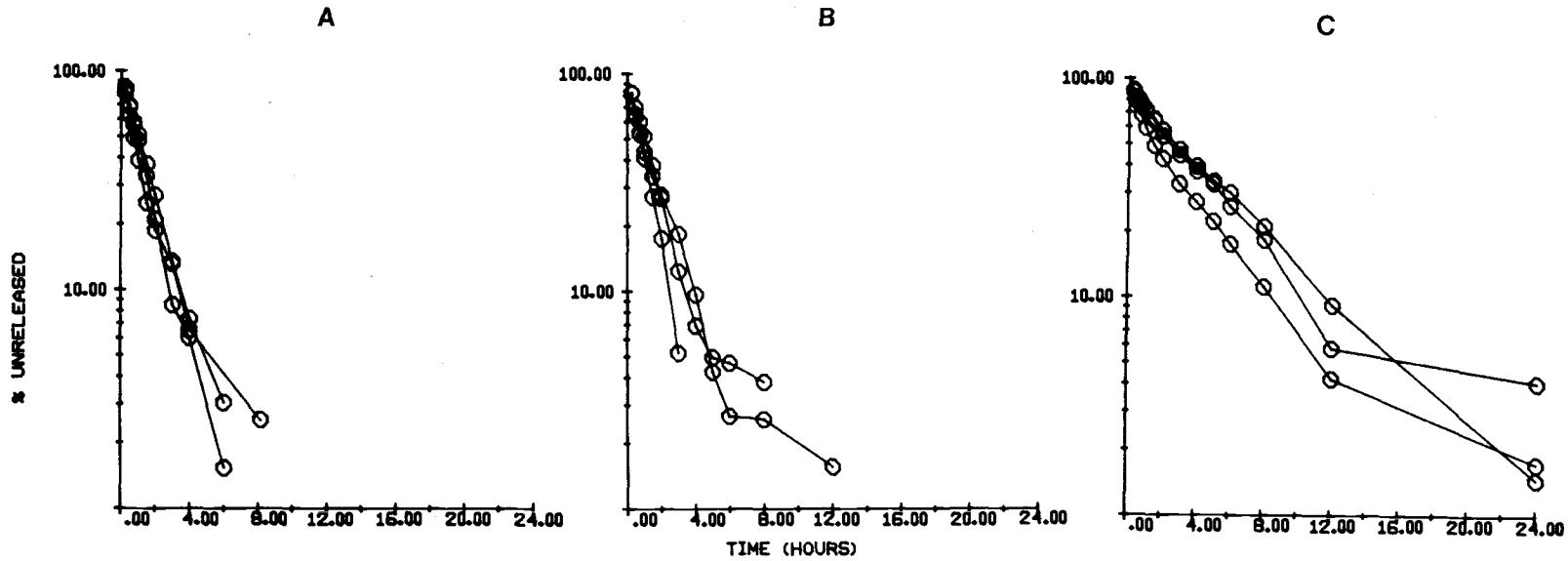

Figure I.8 In vitro dissolution of crushed tablets containing microencapsulated acetaminophen: percent acetaminophen unreleased versus time. Key: (A) 97.5% acetaminophen/2.5% ethylcellulose; (B) 90% acetaminophen/ 10% ethylcellulose; (C) 80% acetaminophen/20% ethylcellulose microcapsules.

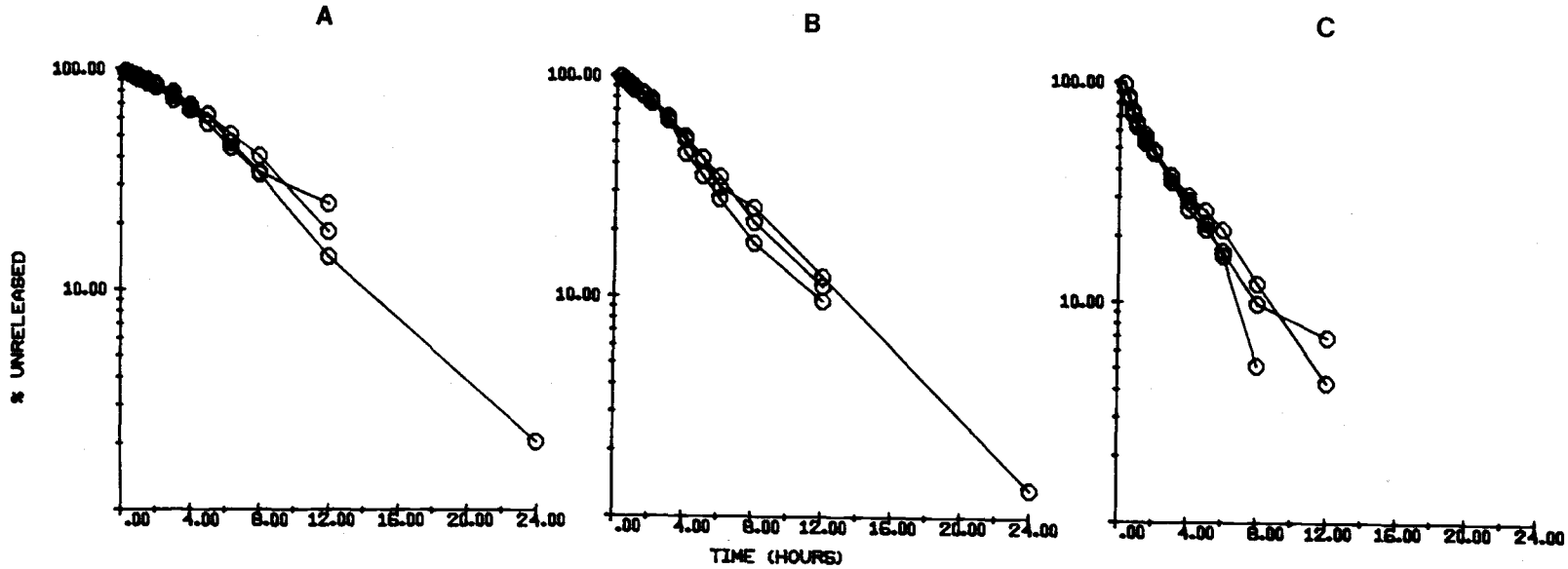

Figure I.9 In vitro dissolution of capsules containing microencapsulated acetaminophen tablet formulations: percent acetaminophen unreleased versus time. Key: (A) 97.5% acetaminophen/2.5% ethylcellulose; (B) 90% acetaminophen/10% ethylcellulose; (C) 80% acetaminophen/20% ethylcellulose microcapsules.

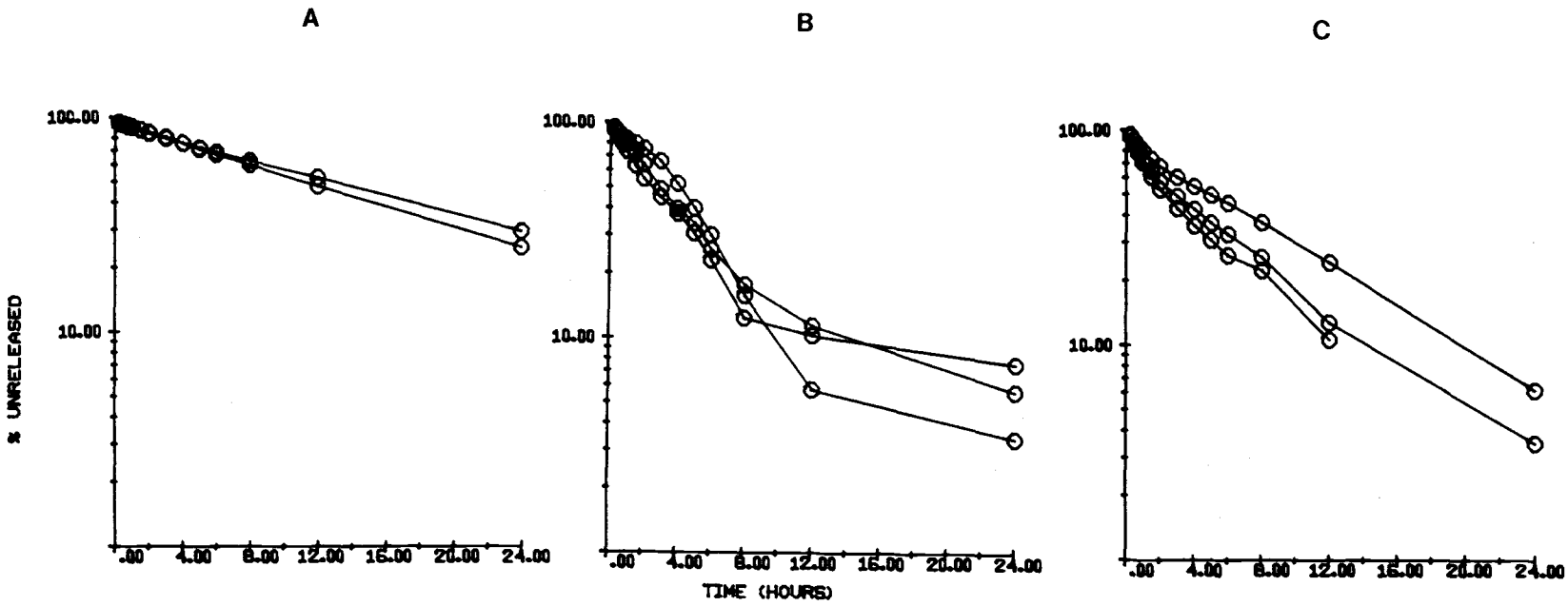

Figure I.10 In vitro dissolution of uncompressed tablet formulations containing microencapsulated acetaminophen: percent acetaminophen unreleased versus time. Key: (A) 97.5% acetaminophen/2.5% ethylcellulose; (B) 90% acetaminophen/10% ethylcellulose; (C) 80% acetaminophen/20% ethylcellulose microcapsules.

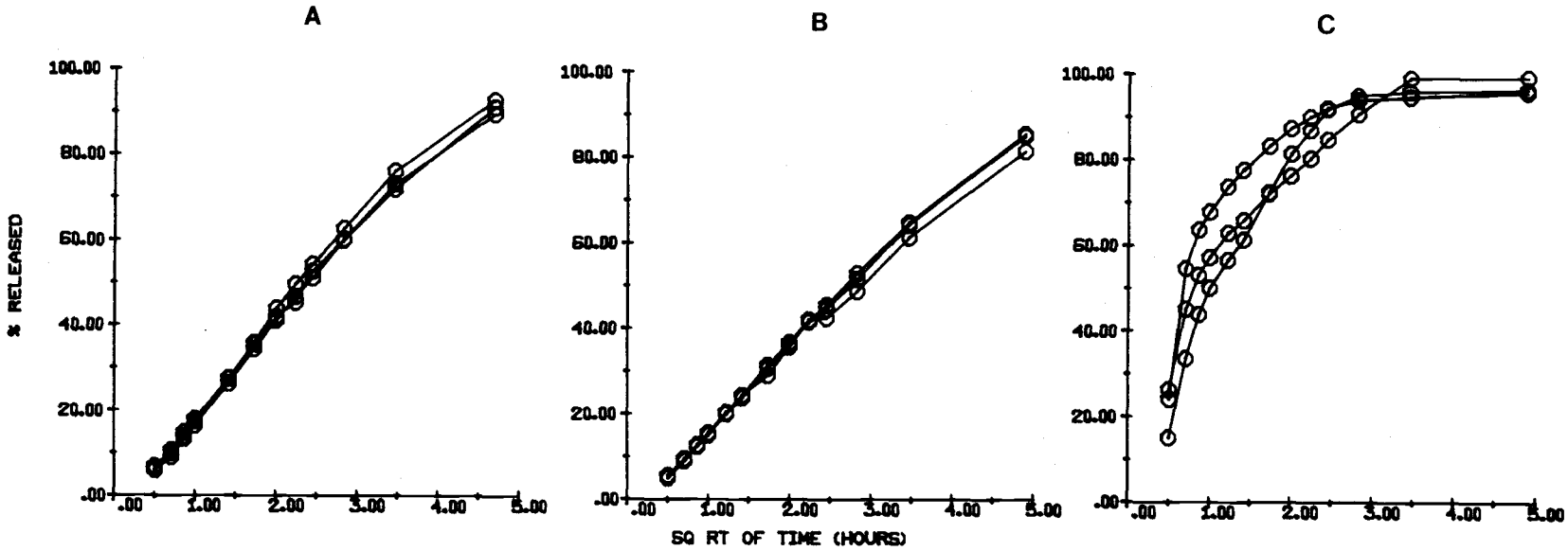

Figure I.11 In vitro dissolution of intact tablets containing microencapsulated acetaminophen: percent acetaminophen released versus square root of time. Key: (A) 97.5% acetaminophen/2.5% ethylcellulose; (B) 90% acetaminophen/10% ethylcellulose; (C) 80% acetaminophen/20% ethylcellulose microcapsules.

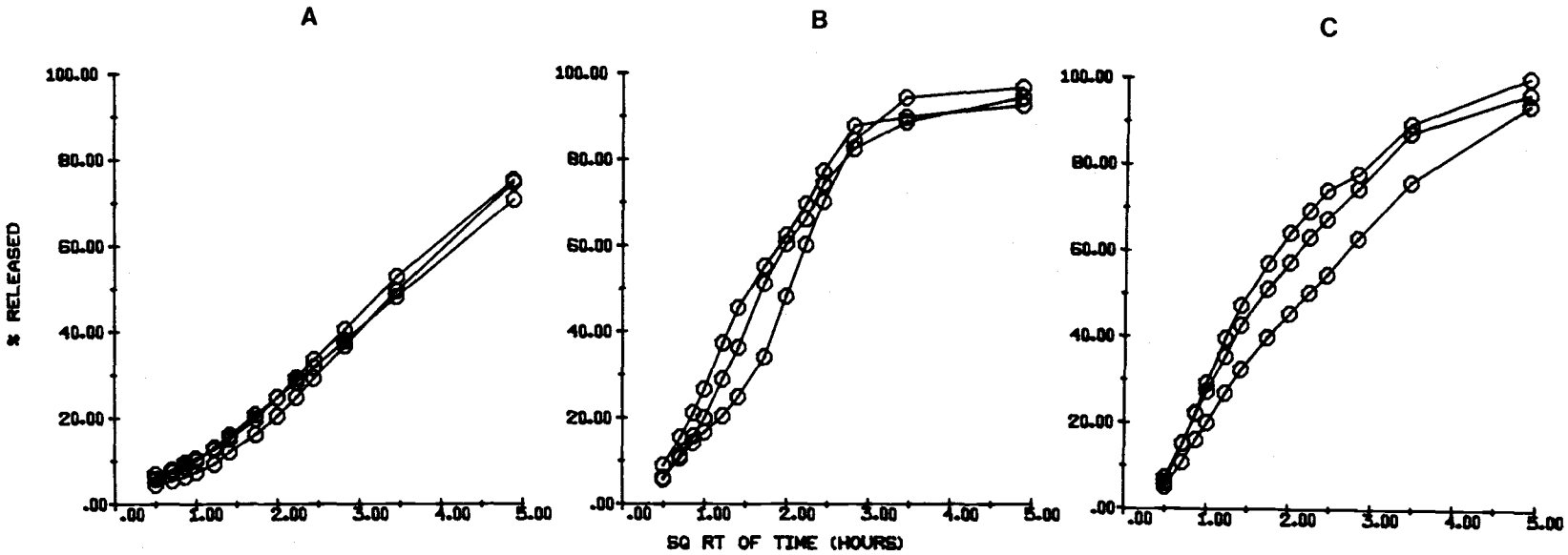

Figure I.12 In vitro dissolution of uncompressed tablet formulations containing microencapsulated acetaminophen: percent acetaminophen released versus square root of time. Key: (A) 97.5% acetaminophen/2.5% ethylcellulose; (B) 90% acetaminophen/10% ethylcellulose; (C) 80% acetaminophen/ 20% ethylcellulose microcapsules.

devices. However, it has been reported that if cracks or pores are present in microcapsule walls, release of drug may follow square root of time kinetics (Kydonieus, 1980).

Thus, release of drug from acetaminophen microcapsules and dosage forms containing the microcapsules occurs by a combination of processes and cannot be described by any one equation.

Bioavailability and Pharmacokinetics of Microencapsulated Acetaminophen

Saliva acetaminophen concentrations in one subject following oral administration of several dosage forms containing microcapsules are shown in Figure I.13. The dose administered was about 1.0 g. Only products made with 97.5% acetaminophen/2.5% ethylcellulose microcapsules were tested *in vivo* since these microcapsules exhibited the slowest release *in vitro*, were homogenous with respect to particle size, and had the highest drug loading.

Drug levels from microcapsules in one large capsule were barely above 1 µg/ml for the first four hours postdose and were maintained at about 3 µg/ml for 6 to 16 hours postdose. In contrast, the tablet formulation in three capsules provided higher drug concentrations over the first four hours postdose, but the saliva drug concentration began to decline 8 hours postdose from a

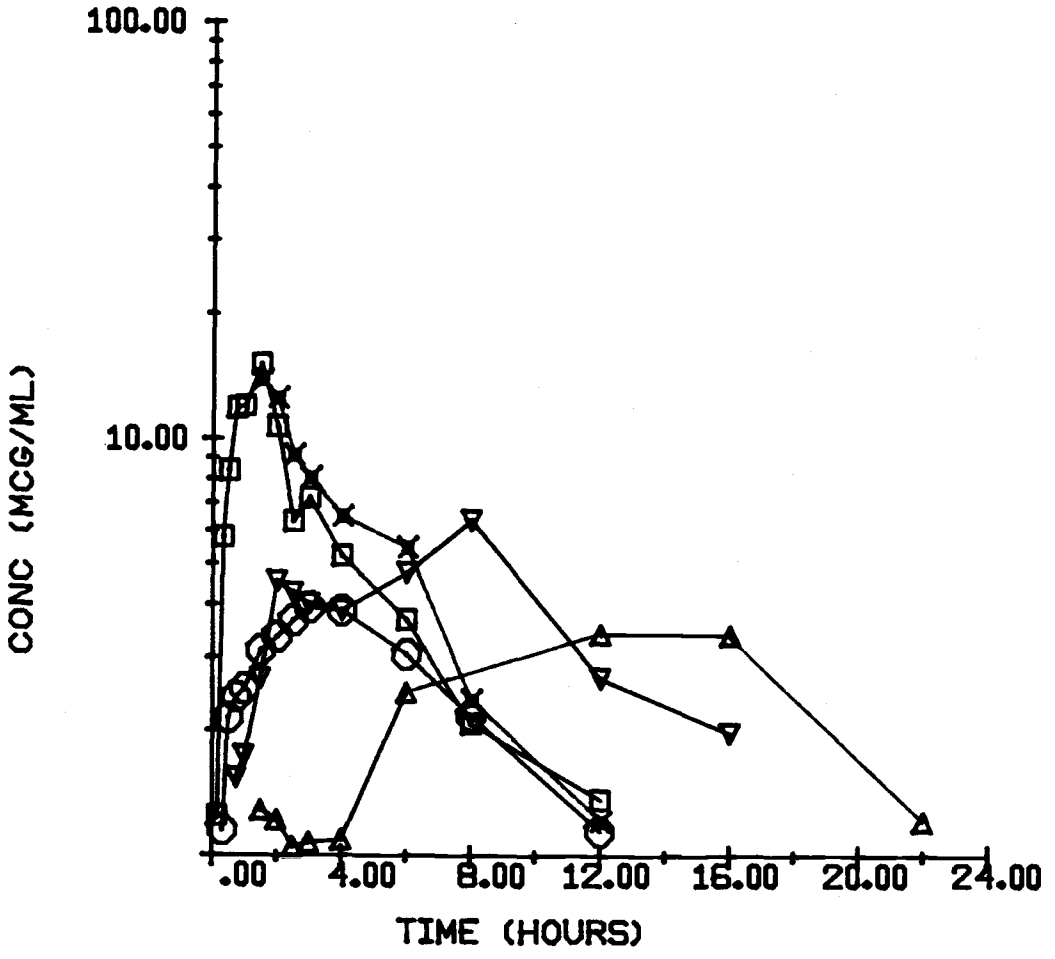

Figure I.13 Saliva acetaminophen concentrations in one subject following administration of 97.5% acetaminophen/ 2.5% ethylcellulose microcapsule dosage forms and a commercial acetaminophen product. Key: (□) two 500 mg tablets Tylenol (1000 mg dose); (△) microcapsules in one size 000 capsule (1000 mg dose); (▽) microcapsule tablet formulation in three size 0 capsules (1000 mg dose; (◯) four intact tablets (1050 mg dose); (✕) four chewed tablets (1120 mg dose).

peak of 6.4 µg/ml. This difference can be attributed to the presence of Di-Pac in the tablet formulation which facilitates wetting of microcapsules. Intact tablets did not provide sustained release of acetaminophen which is unexpected since *in vitro* drug dissolution results indicated otherwise. Drug concentrations rose to a peak of 4 µg/ml at three hours and declined according to first order kinetics over the next 9 hours. Drug concentrations from the chewed tablets were similar to those of the commercial tablet throughout the elimination phase, and this is reflected in the similar elimination rate constants (Table I.9). Apparently, chewing of the microcapsule tablet spreads apart the microcapsules which allows for wetting and subsequent rapid *in vivo* dissolution. In addition, chewing may crack some of the microcapsules, resulting in release of uncoated drug in the mouth. The subject did indeed comment on the bitterness of the chewable tablets which is probably due to free drug present in the mouth. No data points for the first 90 minutes were plotted for chewed tablets because it was discovered that when the tablet is chewed, residual drug in the mouth due to adsorption results in extrememly high saliva drug concentrations at early sampling times. This was determined by administering tablets which were chewed but not swallowed. This finding is in agreement with

Table I.9 Pharmacokinetic Parameters Following Administration of 97.5% Acetaminophen/2.5% Ethylcellulose Microcapsule Dosage Forms and a Commercial Product

Treatment	Dose g	k_{el}[a], hr^{-1}	$t_{1/2}$[b], hr	t_p[c], hr	C_p[d], µg/ml	$AUC_{o\rightarrow\infty}$/1.0 g drug[e], µg-hr/ml	F[f]
Tylenol[g]	1.00	0.185	3.75	1.5	15.2	62.87	--
Microcapsules in one size 000 capsule	1.00	0.172	4.03	12.0	3.4	59.16	0.94
Tablet Formulation in three size 0 capsules	1.00	0.146	4.75	8.0	6.4	69.99	1.11
Intact Tablets (4)	1.05	0.162	4.28	3.0	3.9	35.47	0.56
Chewed Tablets (4)	1.12	0.223	3.11	1.5	13.6	59.17	0.94

[a] [b] Apparent elimination rate constant.
[c] Apparent half-life.
[d] Time to peak.
[e] Peak saliva concentration.
$AUC_{o\rightarrow\infty}$ was multiplied by 1.0/dose to adjust for differences in dose between treatments.
[f] F is the ratio of the normalized AUC for each treatment to the AUC for the commercial product, Tylenol.
[g] Two 500 mg tablets Acetaminophen Extra-Strength Tylenol, Lot No. PS2300.

Gwilt et al. (1979) who monitored saliva acetaminophen levels following administration of an oral solution of acetaminophen.

Relative bioavailability of the sustained release dosage forms was determined by comparison of the total area under the saliva acetaminophen concentration curves ($AUC_{0 \rightarrow \infty}$). The AUC from time zero to the last time point was calculated using the linear trapezoidal method (Gibaldi and Perrier, 1982b). Assuming absorption to be complete by the last time point, the residual area extrapolated to infinity was calculated as the final plasma concentration divided by the elimination rate constant for the commercial product. The sum of these two areas gives $AUC_{0 \rightarrow \infty}$. These values are presented in Table I.9. The capsule dosage forms and the chewed tablets were bioequivalent to the commercial product with respect to systemic availability. However, only 56% of the drug in the intact tablets was absorbed relative to the commercial product. The intact tablets may have passed through the GI tract and been eliminated before all the drug could be released. This is in agreement with the observation that the tablets do not disintegrate in vitro. Apparent elimination rate constants, apparent half-life, the time to peak, and the bioavailability for all these treatments are given in Table I.9. The apparent elimination rate constants were

determined by calculating the slope of the elimination phase based on first order kinetics. The apparent half-lives for the capsules and intact tablet were somewhat prolonged relative to that for the commercial tablets, which indicated prolonged absorption in this subject, as described by a "flip-flop" model (Gibaldi and Perrier, 1982c). The apparent half-life for the chewed tablets was faster, meaning that absorption was rapid. These *in vivo* results are consistent with the trends observed in $d_{50\%}$ from the *in vitro* dissolution studies in which dissolution of drug from microcapsules was very slow, dissolution of drug from intact tablets and tablet formulation in capsules was more rapid but still slower than from the crushed tablets. *In vitro* release of acetaminophen from crushed tablets was about the same as that from commercial products tested under the same conditions (Borin, 1984) which would account for the similar *in vivo* profiles.

Based on these preliminary findings, it appears that sustained release of acetaminophen can be achieved using microencapsulation. However, the saliva acetaminophen concentrations obtained (assuming that they are approximately equivalent to plasma concentrations (Ahmed and Enever, 1981)) were lower than the reported therapeutic levels of 10 to 20 µg/ml (Wagner, 1975). Thus, it appears necessary to

administer higher doses of microencapsulated acetaminophen in order to achieve therapeutic drug concentrations. The calculated dose required to obtain a steady state acetaminophen concentration of 15 µg/ml with a 12 hour dosing interval, assuming that the volume of distribution is unchanged relative to an immediate release product, is about 3.5 g. The equation and pharmacokinetic parameters used to obtain this value are given in Appendix B. Ahmed and Enever (1981) administered a 1.4 g dose of acetaminophen as two 700 mg tablets and reported sustained saliva acetaminophen concentrations of about 15 µg/ml from 20 min to 5 hr post dosing. Each of the tablets contained 200 mg immediate release acetaminophen and a 500 mg sustained release core. To sustain saliva acetaminophen concentrations at 15 µg/ml for 12 hours, a dose of at least 3.36 g (i.e., 12 hr/5 hr = 2.4 increase in time; 2.4 X 1.4 g = 3.36 g) is suggested by their data.

In conclusion, capsule dosage forms containing 97.5% acetaminophen/2.5% ethylcellulose microcapsules provided sustained release of drug in vivo in one subject. However, tabletted microcapsules had low bioavailability (F = 0.56) and rapid drug release. Chewed tablets gave a drug concentration-time profile parallel to that of intact commercial tablets. With the exception of the intact tablets, these in vivo results

were consistent with the trends observed for *in vitro* dissolution testing.

CONCLUSION

Microencapsulation of acetmainophen with only 2.5% ethylcellulose resulted in extremely slow drug release *in vitro* which was unexpected due to the very thin powder coat, but could be explained by the lack of wetting of such microcapsules when confined inside the rotating basket. Microencapsulation with higher amounts of ethylcellulose resulted in agglomeration and led to faster drug release. Tabletted 97.5% acetaminophen/2.5% ethylcellulose microcapsules had slower drug release than the uncompressed tablet formulation due to formation of a plastic matrix which traps the acetaminophen inside the tablet and allows for drug release only by diffusion and leaching. However, *in vitro* drug release was very rapid when tablets were crushed. With the exception of the tablet dosage form, preliminary *in vivo* data for 97.5% acetaminophen/2.5% ethylcellulose microcapsule dosage forms was in agreement with *in vitro* results. Sustained drug release was obtained for capsule dosage forms, but not for tablets and chewed tablets.

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CHAPTER II

SPRAY-COATED ACETAMINOPHEN POWDER AND PELLETS: FORMULATION OF SUSTAINED RELEASE DOSAGE FORMS

ABSTRACT

Spray-coated acetaminophen powder and pellets were formulated into oral dosage forms. Spray-coated powders with 20% inner enteric coats and ethylcellulose overcoats of 2.5 to 10% as well as triple-coated powders having a 10% inner ethylcellulose coat, 10 or 20% center enteric coat, and a 10% outer ethylcellulose coat had the slowest *in vitro* drug release (time to 50% dissolution, $d_{50\%}$, of 3.75 to 6.31 hours). Tablets containing spray-coated acetaminophen powders provided slow *in vitro* drug release when tested intact ($d_{50\%}$ ranged from 5.4 hours up to 22.6 hours) and rapid release when crushed ($d_{50\%}$ <2 hours). Acetaminophen release from ethylcellulose-coated pellets was extremely slow at coatings >4% with <25% of the drug released after 48 hours. In comparison, triple-coated acetaminophen pellets with a 5% inner ethylcellulose coat, 5,10 or 20% center enteric coat, and 5% outer ethylcellulose coat provided more rapid release ($d_{50\%}$ $\leq$ 48hours). Compression of spray-coated pellets (triple or single coats) into tablets resulted in faster drug release and release was the same with or without a disintegrant ($d_{50\%}$ of 7.8 to 25 hours). The effects of crushing such tablets was dependent on the type of pellet coating. For pellets having a 5% inner and outer

ethylcellulose coat and a 15% center enteric coat, crushed tablets gave a dissolution profile similar to that of intact tablets ($d_{50\%}$ of 20 hours versus 25 hours). Tablets containing pellets with "combination" polymer coats had rapid drug release both as intact and crushed tablets ($d_{50\%}$ <5 hours) due to deformation and rupturing of this coating upon compression. Preliminary *in vivo* data was supportive of *in vitro* results in that sustained release was achieved in one subject following administration of tablets and capsules containing spray-coated acetaminophen powders that had slow *in vitro* drug release. However, when tablets containing triple-coated acetaminophen pellets were vigorously chewed, only a slight sustained release effect was achieved.

INTRODUCTION

Statement of the Problem

The primary objective of this research was to develop a sustained release crushable and chewable acetaminophen tablet by spray coating acetaminophen powder or pellets with water-based film-forming dispersions, and then incorporating the coated drug particles into tablets. During the course of this work it was necessary, for comparison purposes, to develop other sustained release oral dosage forms containing film-coated acetaminophen such as hard gelatin capsules and intact tablets. Reasons for developing a crushable or chewable sustained release oral dosage form of acetaminophen, along with *in vitro* and *in vivo* methods used to investigate release of drug from sustained release formulations, have been discussed in Chapter I.

Environmental and economic pressures have caused an ambitious shift from organic solvent to aqueous film coating in the pharmaceutical industry. This work investigated the feasibility of using aqueous film-forming dispersions for sustaining release of acetaminophen instead of the polymer/organic solvent coating system described in Chapter I. In addition, a novel coating of drug particles and pellets was developed in order to increase flexibility of the

coating and/or maximize control of drug release. Both factors are important in developing a product from which drug release is not greatly affected by chewing. Two different types of coating materials were applied over the drug particle (resulting in particles with multilayered coats), or mixtures of coating materials were applied resulting in formation of a film having different permeability, flexibility, and strength.

Aqueous Film Coating

The film coating process involves evaporation of solvent from a liquid preparation of coating material, leaving a film of coating material on the surface of the solid material. Films sprayed from organic solvents may offer processing advantages due to the solvent's low heat of vaporization, but environmental and economic concerns have made water a more attractive solvent. Introduction of latex and pseudolatex materials used with correctly selected equipment and processing conditions have resulted in process times comparable to organic solvent coating. In addition, with this technique it is possible, using the same polymer, to obtain films with diverse properties such as permeability and mechanical strength. Aqueous film coating methods have been applied to coating of tablets, pellets, granules, crystals, particles, and even finely divided powders (Jones, 1984). Coating functions such

as enteric, sustained release, and taste masking are achievable in addition to improved appearance and protection. Polymers used in film coating can be classified as water soluble, gastro-soluble, entero-soluble, and water insoluble. Water insoluble films are most often used for applications in controlled release delivery systems since release can be controlled by diffusion through a membrane. Release rates are a function of coating thickness, plasticizer concentration, drug polymer solubility, and film coalescence (which is affected by the temperature and duration of drying).

The most commonly used aqueous-based coating materials are the commercially available latexes and pseudolatexes which are low viscosity aqueous dispersions of polymeric spheres (20 to 30% solids). An advantage of these systems is that they are less likely to result in agglomeration than are dissolved film-forming agents. Most of these latex materials are produced by polymerization of a monomer (Champetier and Monnerie, 1969) which was previously emulsified or dissolved in the aqueous phase. Examples of such latexes are the polymethacrylate dispersions (Eudragit E30D and L30D; Rohm Pharma, Weiterstadt, West Germany). Another method involves dissolving the polymer in an organic solvent and then preparing an O/W emulsion. The

solvent is then evaporated, obtaining a stable suspension comprised of submicron spherical particles (El-Aasser et al., 1977a; El-Aasser et al., 1977b). This procedure can be applied to derivatives which cannot be manufactured by polymerization in situ, and it also eliminates the presence of residual toxic monomer. Aquacoat (FMC Corp., Philadelphia, PA) is manufactured using this technique and contains ethylcellulose particles having a mean dimension of 0.3 µm. Aquacoat is not a true latex in that it contains sodium lauryl sulfate and cetyl alcohol at 2.7% and 5%, respectively, of the amount of ethylcellulose in the formulation (Vanderhoff et al., 1979).

Film formation in organic solvent systems occurs by entangling and packing together of the molecules which form an increasingly dense network as the solvent is removed (Banker and Peck, 1981). The mechanisms involved in evaporation of a latex are quite different (Brown, 1956; Sheetz, 1965; Bindschaedler et al., 1983). In liquid state, the latex emulsion consists of discrete polymer spheres which are independently suspended in water. To form a clear, continuous film, these individual particles must coalesce, become deformed, and then fuse together during evaporation of water. In general, plasticizers increase polymer pliability but in latexes, they also serve to promote film coalescence. A

plasticizer reduces the interchain forces of a polymer film, thus resulting in increased mobility of the film structure. This is accomplished by a lowering of the polymer's glass transition temperature which is a measure of plasticizer efficiency (Bolker, 1974). The second step, deformation, requires a driving force to overcome the inherent hardness of these polymer spheres and electrostatic charges that these spheres bear. Forces determining this process have been reported in the literature (Vanderhoff et al., 1966; Vanderhoff, 1970). Softening and swelling of latex spheres by plasticization aids in overcoming resistance to deformation. In latexes where large surface areas exist, the driving force to overcome repulsive forces is known as capillarity. Capillarity is caused by the high interfacial surface tension of water. When polymer spheres are wetted and as the water of the wetting droplet evaporates, the spheres are brought closer together as the surrounding aqueous film constricts. As water continues to evaporate, a critical point is reached at which the resistance of the stabilizing layers on two spheres is overcome and polymer-polymer contact occurs. Continued interfacial tension between water and polymer spheres causes fusing of deformable spheres into a clear, continuous film. Mutual interdiffusion of free polymer chains in deformed latex

spheres causes overall knitting of film into one continuous polymeric sheet. This is a physical process which can be accelerated with elevated temperatures.

There are several types of equipment which have been adapted or developed for aqueous film coating processes (Jones, 1984). The perforated pan, a modified round pan, was developed to improve drying efficiency by drawing air through the bed as opposed to supplying it to the bed surface only, as is done with round pans. Its primary use is for coating of tablets. Air suspension for application of aqueous film coats has also been used. The Wurster system, which was described in Chapter I, can be used to coat both tablets and smaller particles such as pellets, granules, and materials as fine as 50 µm. Another type of air suspension technique is the conventional top spray fluidized bed granulator which can be used for small particles but not for tablets. However, films formed in this process are not as uniform as those obtained with the Wurster system. A more recently developed system is the rotary fluidized bed which is an air suspension system using a rotating disc to add centrifugal force to fluidization and gravity forces, thus affording rapid mixing.

There are several kinds of pumps used in coating applications. The peristaltic pump is the simplest and easiest to clean but has several disadvantages such as

pulsation, low liquid pressure, inability to pump viscous liquids and fluctuations in liquid delivery rate (Jones, 1984). The gear pump provides smooth and precise liquid delivery but is more difficult to clean, and close tolerances between gears present a wear problem when using liquids which contain undissolved solids. The piston pump has the ability to clear minor clogs in nozzles due to its pressure reserve. However, it is also difficult to clean, and there is pulsation in flow as the piston changes direction. Production coating equipment uses one to seven nozzles which are usually pneumatic for aqueous film coating systems since droplet size is smaller than with hydraulic nozzles and can be controlled independently of flow rate (Jones, 1984).

Many factors affect selection of the appropriate process. Physical characteristics of the product, such as surface area, shape, and friability all affect final release properties. Surface area and shape are reproducible for tablets but may vary considerably within and between batches for smaller particles. Variations in surface porosity and friability are also more common for smaller particles. Scanning electron microscopy has revealed that the most uniform films are those applied wet to the surface, but under conditions where the solvent or water is evaporated before core

penetration occurs (Jones, 1984). For this reason, sustained release coating of small particles should be limited to the Wurster or rotary systems in which the nozzle is immersed in the suspended particles and is spraying concurrently with particle flow.

MATERIALS AND METHODS

Preparation of Spray-Coated Acetaminophen Powder and Pellets

Acetaminophen powder and pellets were spray coated with several sustained release coating materials by the pharmaceutics group at Warner-Lambert Company in Morris Plains, New Jersey. One set of coated particles was prepared by applying Eudragit L30D (Rohm Pharma, Weiterstadt, West Germany), an enteric coating material of polymethacrylic acid and acrylic acid esters, to acetaminophen powder followed by application of an outer ethylcellulose coat, Aquacoat (FMC Corp., Philadelphia, PA), which was plasticized with triethyl citrate. A second set of coated particles was made by first coating acetaminophen with ethylcellulose and then applying the enteric coating material as the outer coat. Each of the coating materials was varied from 0 to 20% by weight, with a total coating of $\leq$30%. Acetaminophen particles with various amounts of coating were made from the same batch of acetaminophen powder on the same day by starting with a fixed amount of acetaminophen, removing a portion after it had been coated with the first (lowest) amount of coating, applying additional coating and removing another portion, etc., until the highest desired amount of coating material had been sprayed onto

the particles. A schematic of this procedure is shown in Figure II.1.

Acetaminophen particles with three separate layers of coating materials were also prepared using the same procedure and coating materials described above. The innermost and outermost coats were 5 or 10% Aquacoat, and the center coat was 10 or 20% Eudragit L30D. A schematic of the coating procedure and the final products obtained are given in Figure II.2.

Acetaminophen pellets were also triple-coated with inner and outer coats consisting of 5% Aquacoat and a center coat of 5, 10, or 15% Eudragit L30D. Acetaminophen pellets were prepared by coating non-pareil sugar seeds with acetaminophen. The resulting pellets were approximately 1.3 mm in diameter and contained 73% acetaminophen by weight. These pellets were also coated with a single layer of Aquacoat in the following amounts: 0.5, 1, 2, 3, 4, 5, and 10% by weight. A schematic of the coating procedure and the final products obtained are shown in Figure II.3.

Another sustained release coating was made by mixing Eudragit E30D (Rohm Pharma, Weiterstadt, West Germany), an insoluble, permeable film-coating material based on polymethacrylic acid esters, and Aquacoat together prior to spray coating the pellets. This mixture was then applied in amounts of 2, 3, and 4% by

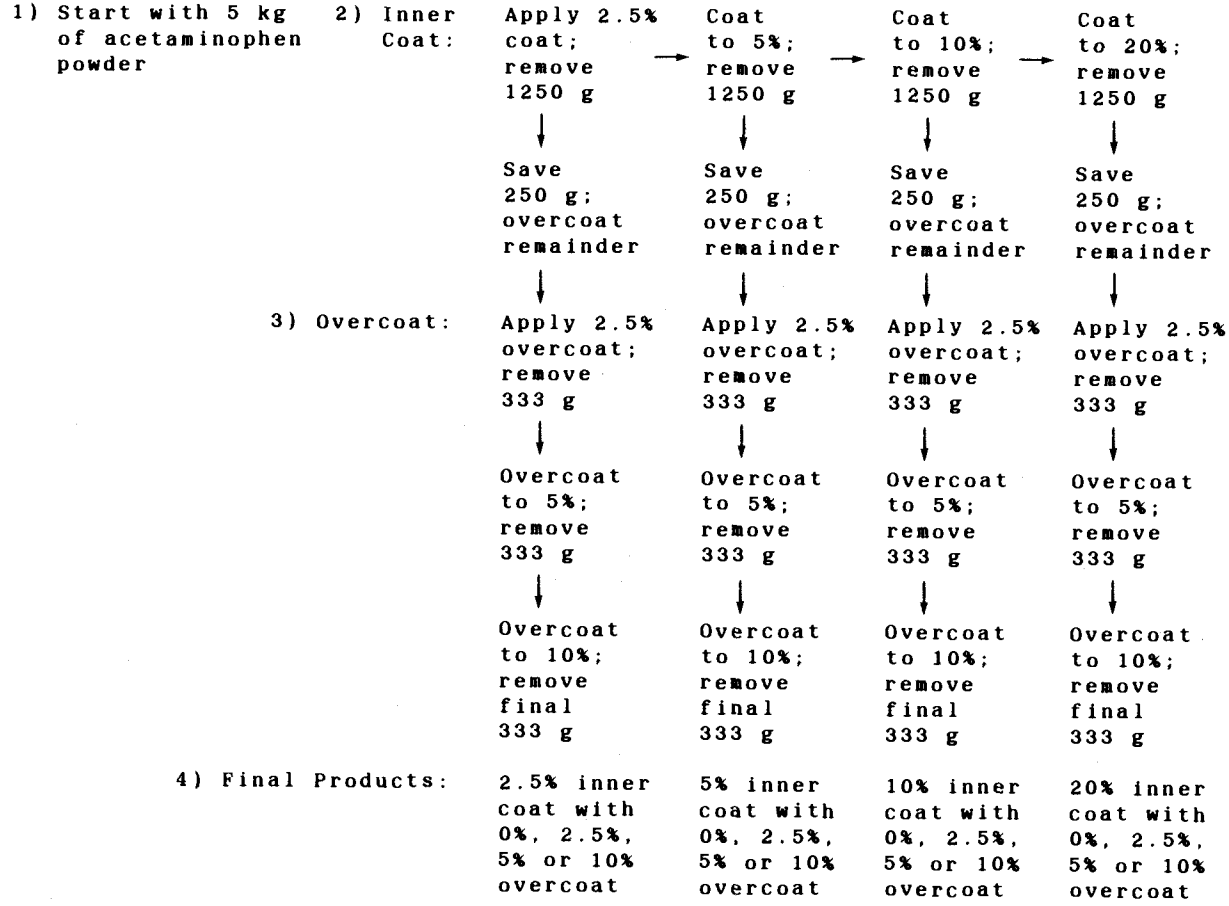

Figure II.1 Flow Chart for Spray Coating of Acetaminophen Powder. Key: Inner coat is Eudragit L30D (an enteric coating material, RohmPharma, Weiterstadt, West Germany) and Aquacoat (an aqueous ethylcellulose dispersion, FMC Corp., Philadelphia, PA) is overcoat for first batch. For the second batch the inner coat is Aquacoat and overcoat is Eudragit L30D.

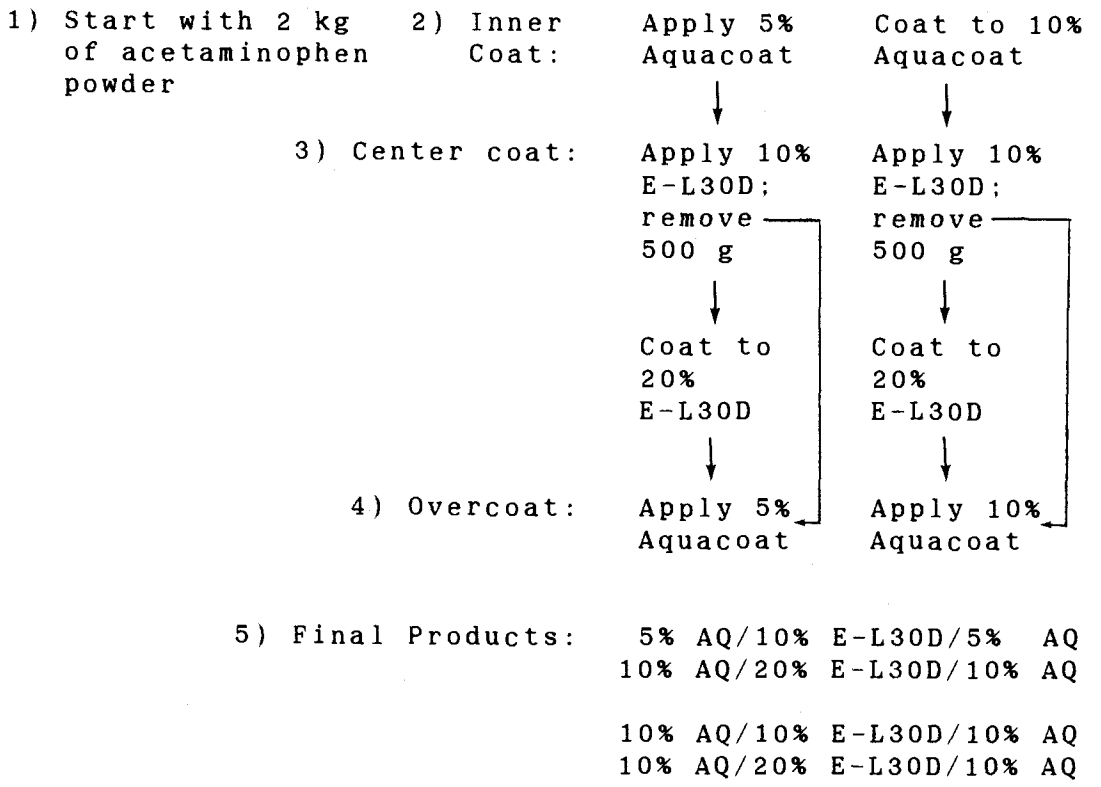

Figure II.2 Flow Chart for Triple Coating of Acetaminophen Powder. Key: AQ is Aquacoat and E-L30D is Eudragit L30D.

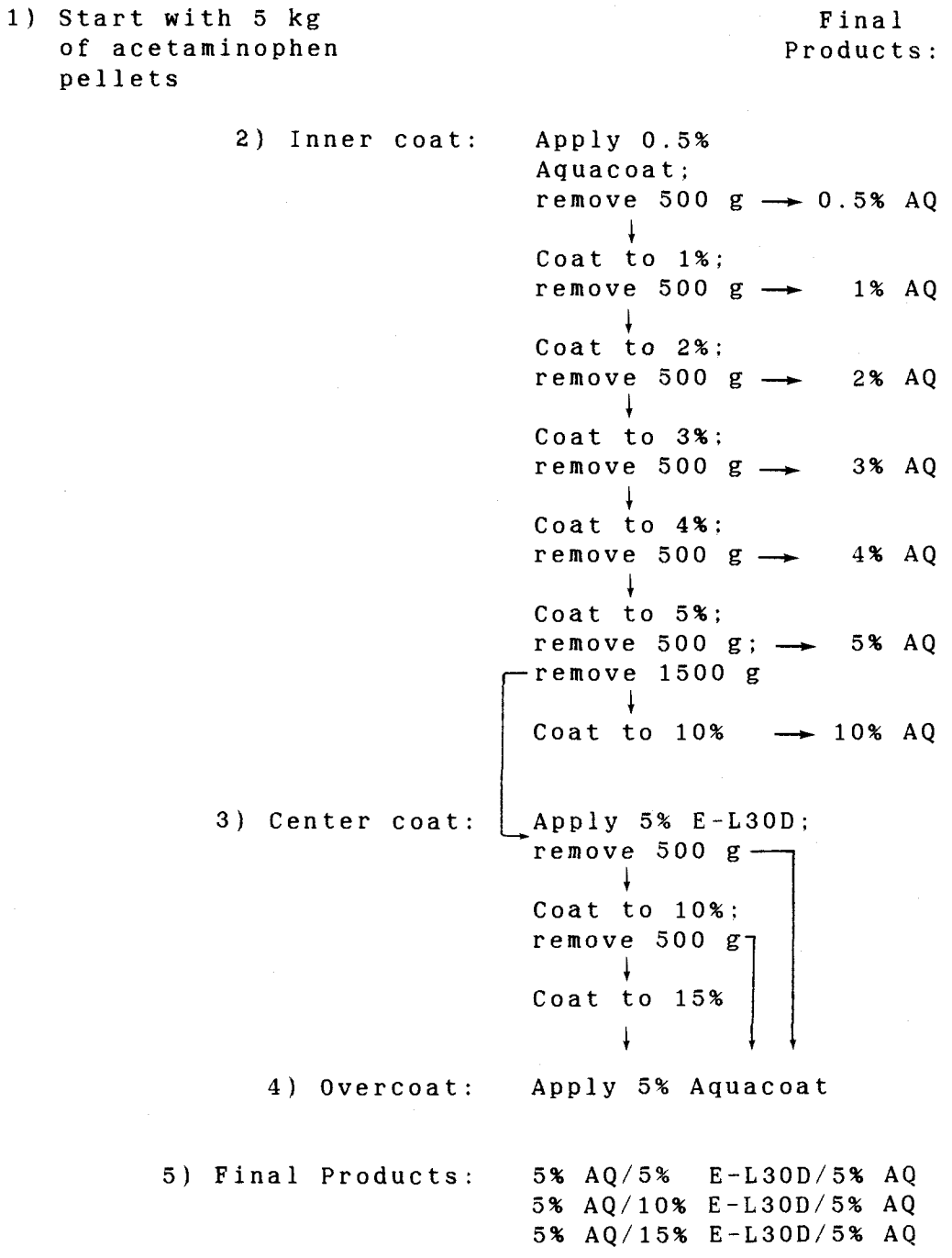

Figure II.3 Flow Chart for Spray Coating of Acetaminophen Pellets. Key: E-L30D is Eudragit L30D and AQ is Aquacoat.

weight.

Dosage Form Preparation

The ingredients listed in Tables II.1a and II.1b were combined by geometric dilution with magnesium stearate being added last. These tablet formulations were placed in a capped, rectangular, glass container and tumbled with a rotating motion to provide uniform mixing.

Acetaminophen granules used in the tablet formulation along with spray-coated acetaminophen powder (Table II.1a) were prepared by wetting acetaminophen powder with a 5% w/w starch solution, screening the wet mass through a 6-mesh standard sieve, tray drying the granules in a 50^{o}C oven for three hours, and sieving again to obtain the desired granule size.

Capsule-shaped tablets ("caplets") having a total weight of 1.1 to 1.5 g were prepared with a manual hydraulic tablet press (Carver Laboratory Press, Model B, Summit, N.J.). The compression pressure was adjusted to give tablets of hardness 14$\pm$1 kg/sq in for spray-coated acetaminophen powder in tablets. These tablets were 2 cm long, 10 cm wide, and 0.8 cm high. Compression pressures necessary to obtain this hardness for several of the spray-coated acetaminophen powders are listed in Table II.2. The amount of drug in each tablet was 750 or 1000 mg, depending on the amount of

Table II.1a Composition of Tablet Formulation for Spray-Coated Acetaminophen Powders

Ingredient	Weight %
Spray-Coated Acetaminophen Powder	84.0
Granulated Chewable Tablet Excipient Blend[a] or Acetaminophen Granules[b] (40 mesh)	15.0
Magnesium Stearate	1.0
	100.0

[a]Warner-Lambert Company, Morris Plains, NJ.

[b]98.2% acetaminophen and 1.8% corn starch.

Table II.1b Composition of Tablet Formulation for Spray-Coated Acetaminophen Pellets

Ingredient	Weight %
Spray-Coated Acetaminophen Pellets	69.0
Granulated Chewable Tablet Excipient Blend[a] (10-mesh)	27.5-30.0
Disintegrant[b]	0-2.5
Magnesium Stearate	1.0
	100.0

[a]Warner-Lambert Company, Morris Plains, NJ.

[b]Ac-Di-Sol (FMC Corp., Philadelphia, PA).

Table II.2 Tabletting Compression Force of Spray-Coated Acetaminophen Powder Tablet Formulations[a]

Coating[b]	Compression Force, lbs/sq in
2.5% E-L30D/2.5% AQ	5056
5% E-L30D/5% AQ	2889
20% E-L30D/2.5% AQ	1878
20% E-L30D/5% AQ	939
20% E-L30D/10% AQ	939
5% AQ	5345
10% AQ	2456
20% AQ	1445
20% AQ + acetaminophen granules	1734
5% AQ/5% E-L30D	2600
20% AQ/10% E-L30D	506

[a] Composition of tablet formulation is given in Table II.1a.

[b] AQ is Aquacoat and E-L30D is Eudragit L30D. If more than one coating was applied, application was in the order listed from left to right, i.e. for 2.5% E-L30D/ 2.5% AQ the inner coat is Eudragit L30D and the outer coat is Aquacoat.

coating present.

Tablet formulation containing spray-coated acetaminophen pellets was compressed at 4334 lbs/sq in, giving tablets of hardness 10 kg/sq in. Hardness values were determined for tablets ("caplets") aligned horizontally and laying "on edge" in the hardness testing apparatus (Strong, Cobb, and Co.). Because of lower drug loading in acetaminophen pellets, the amount of drug per tablet was only 500 or 650 mg.

As indicated in Table II.1a, some tablets were made by combining spray-coated acetaminophen powder with uncoated acetaminophen granules instead of the chewable tablet excipient mixture. These tablets could either be swallowed intact or crushed if appropriate excipients were added. If crushed, the uncoated granules would provide some immediate release of drug. Tablets containing a disintegrant (Table II.1b) were meant to be crushable, but incorporation of a disintegrant would be useful in the event that a patient preferred to swallow the tablet intact.

A capsule dosage form was made by hand-packing tablet formulations into size 00 hard gelatin capsules. In comparison to tablets, the capsule dosage form allowed evaluation of the effects of compression on coated powders and pellets. Tablets were evaluated intact and also were crushed by pressing between two

spoons to evaluate the effects of crushing on dissolution. Such crushing may be desirable in elderly or pediatric patients who have difficulty chewing. It was also anticipated that *in vitro* dissolution of such crushed tablets would help predict the effects of chewing.

In Vitro Dissolution Procedures

In vitro dissolution tests were performed using the USP XX rotating basket apparatus at a rotation speed of 50 rpm. Test conditions were as described in Chapter I, with the exception that the dissolution medium for the first two hours of the test was simulated gastric fluid, which was prepared by dissolving 2 g sodium chloride in 7 ml hydrochloric acid and adding enough deaerated, deionized water to give one liter of fluid. The pH was adjusted to 1.4 ± 0.1 with hydrochloric acid. Several spray-coated acetaminophen pellet formulations were also tested with the paddle apparatus under the same conditions.

Transfer of dosage forms from gastric to intestinal fluid was carried out by carefully removing the basket from the shaft, filtering the gastric medium to recover any particles that may have come out of the basket, and then placing 900 ml of temperature-equilibrated simulated intestinal fluid into the vessel, along with any recovered particles on the filter paper. The basket

was then replaced onto the end of the shaft and rotation was resumed for the duration of the test. This "switching" procedure took 8 to 12 minutes. For dissolution tests conducted with the paddle apparatus, pellets were recovered from gastric fluid by filtration and then placed (with the filter paper) into the vessel containing temperature-equilibrated simulated intestinal fluid.

Dissolution tests of all spray-coated acetaminophen powders were performed on hand-packed powders in two size 00 hard gelatin capsules because dissolution of free powder in the basket was found to be quite variable. Each formulation was tested at least in duplicate, with up to as many as six replications.

Samples were collected at 15, 30, 45, 60, 90, 120 minutes (gastric fluid pretreatment period) and 2.25, 3, 3.5, 4, 5, 6, 8, 12, and 24 hours. For some tablets and coated acetaminophen pellets, additional samples were collected at 30, 36, 48, 54, 60, 72, and 84 hours. Dissolution fluid volume was maintained at 900 ml by adding fluid as needed prior to sample collection to offset any significant fluid evaporation.

Wall Thickness of Spray-Coated Acetaminophen Formulations

Wall thickness of coated acetaminophen powders and pellets was determined using the equation described in

Chapter I (Equation 1). Representative calculations are given in Appendix A.

In Vivo Administration of Spray-Coated Acetaminophen Formulations

Several capsules and tablets containing spray-coated acetaminophen powders and pellets were administered to a healthy, male volunteer who gave informed written consent. Treatments were taken on separate occasions with a wash-out period of at least three days between doses. The dose of acetaminophen administered varied between 1.25 and 2.0 g. Study protocol, collection of saliva samples, and acetaminophen assay procedures were the same as described in Chapter I. In addition, one of the dosage forms was administered immediately after a meal rather than under fasting conditions to investigate the effect of food on absorption of acetaminophen from a spray-coated formulation.

RESULTS AND DISCUSSION

Dissolution of Spray-Coated Acetaminophen Powders

In vitro dissolution profiles of spray-coated acetaminophen powders in hard gelatin capsules (600 mg acetaminophen per capsule, 2 capsules per basket) are given in Figures II.4a-d and II.5a-d. The dissolution profile for uncoated acetaminophen is included in each figure for comparison. Each point represents the mean $\pm$ standard deviation of two to six replications. A split plot repeated measures analysis of variance (ANOVA) (Bolton, 1984) was performed to test for differences with respect to dissolution between the different coatings (treatments). The subplot factor is time and the time X treatment factor is a measure of interaction; in particular, the time X treatment factor compares whether the pattern of the dissolution curves (percent acetaminophen released versus time) is the same. The treatment factor measures only the difference between overall averages of percent drug released (for the time period tested) from the different coated particles. In comparing these formulations, the time X treatment factor is of most importance and interest since it is a test of dissolution pattern over time.

Four separate ANOVAs were performed for dissolution

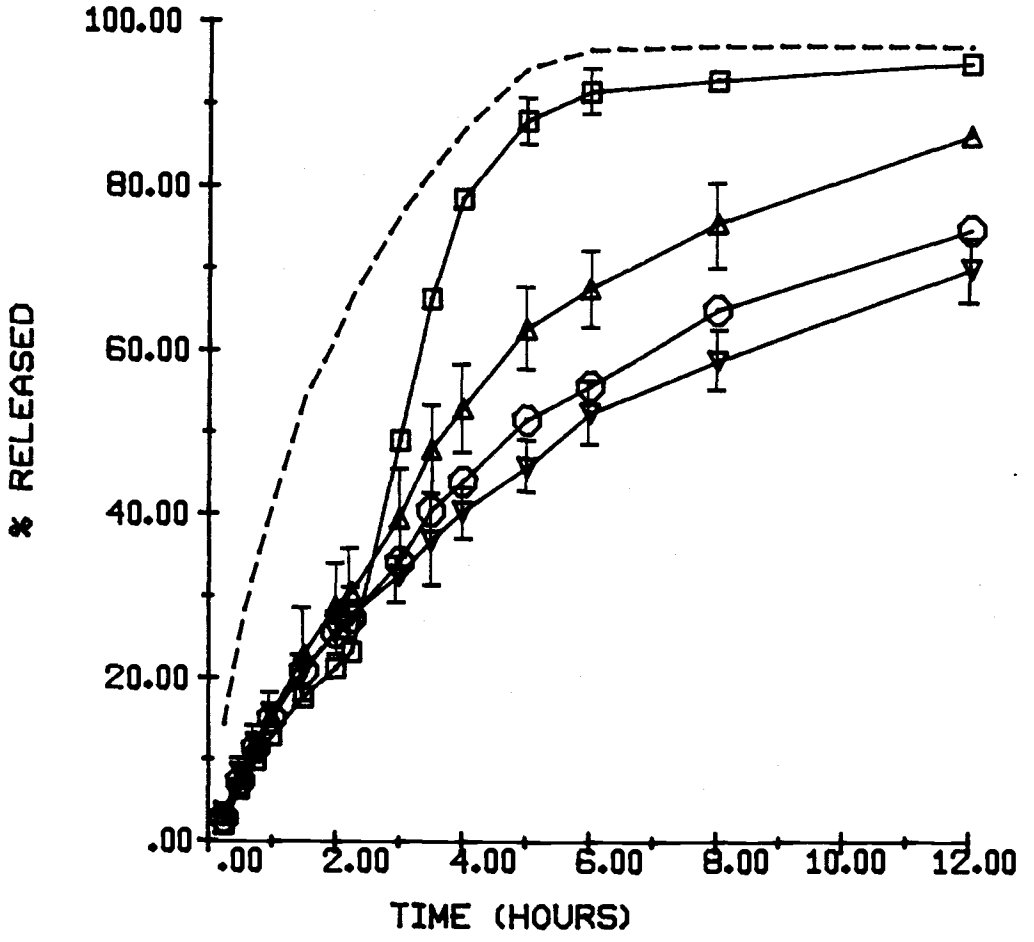

Figure II.4a In vitro dissolution of spray-coated acetaminophen powder with 20% Eudragit L30D inner coat. Key: (□) 0%; (△) 2.5%; (⬡) 5%; (▽) 10% Aquacoat overcoat; (———) uncoated acetaminophen powder. Each point is the mean ± standard deviation of two to six replications.

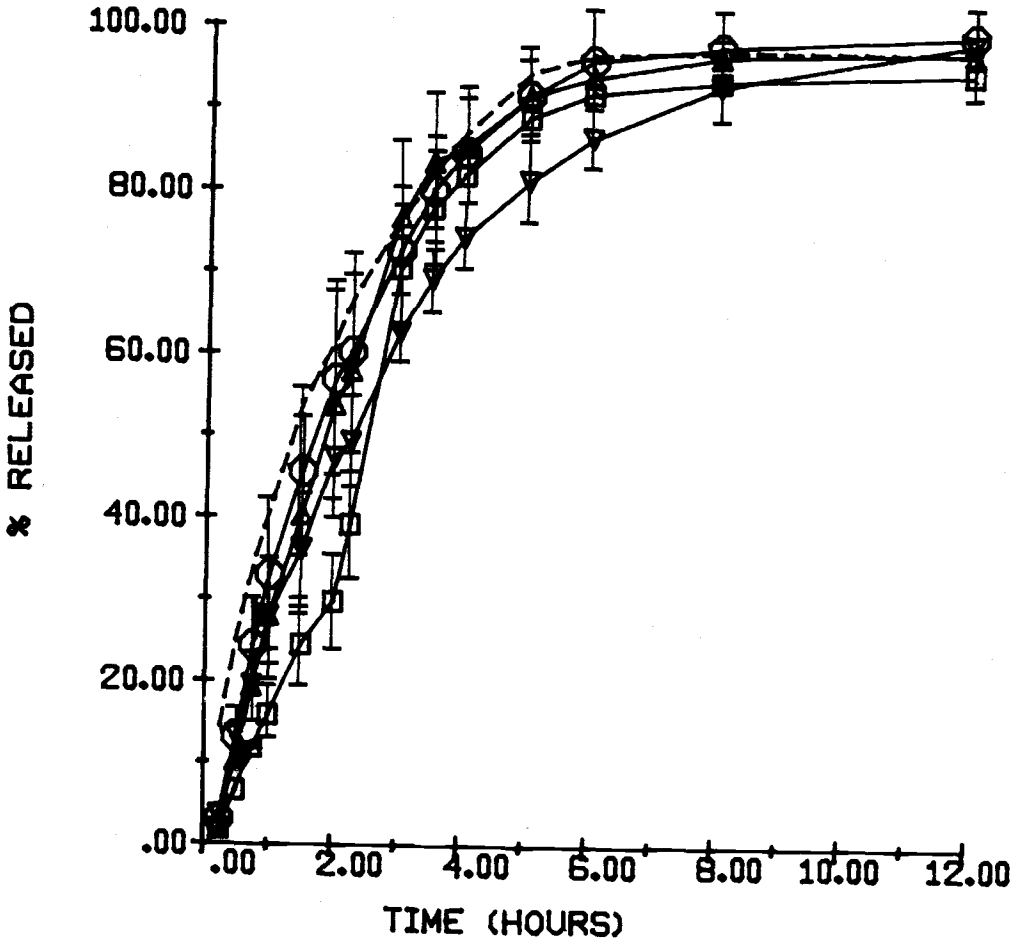

Figure II.4b *In vitro* dissolution of spray-coated acetaminophen powder with 10% Eudragit L30D inner coat. Key: (□) 0%; (△) 2.5%; (⬡) 5%; (▽) 10% Aquacoat overcoat; (———) uncoated acetaminophen powder. Each point is the mean ± standard deviation of two to six replications.

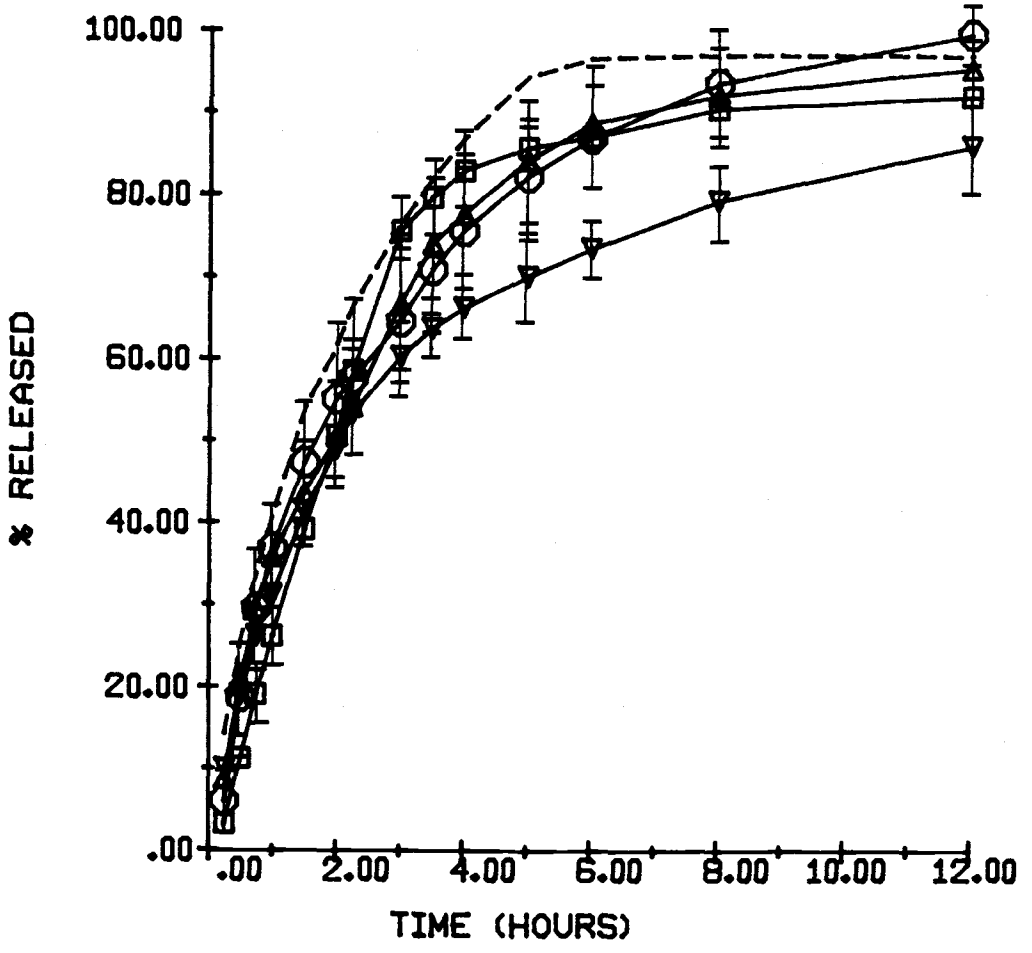

Figure II.4c In vitro dissolution of spray-coated acetaminophen powder with 5% Eudragit L30D inner coat. Key: (□) 0%; (△) 2.5%; (○) 5%; (▽) 10% Aquacoat overcoat; (———) uncoated acetaminophen powder. Each point is the mean ± standard deviation of two to six replications.

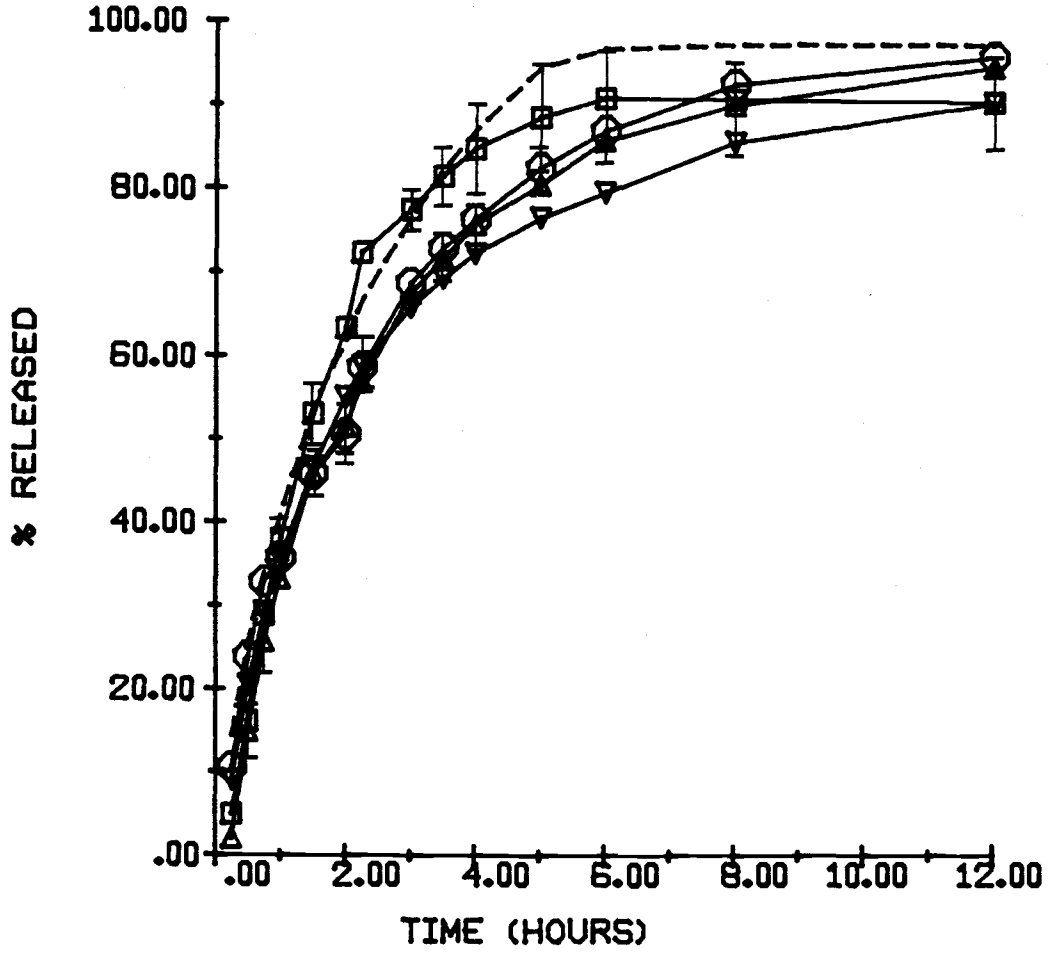

Figure II.4d *In vitro* dissolution of spray-coated acetaminophen powder with 2.5% Eudragit L30D inner coat. Key: (□) 0%; (△) 2.5%; (○) 5%; (▽) 10% Aquacoat overcoat; (———) uncoated acetaminophen powder. Each point is the mean ± standard deviation of two to six replications.

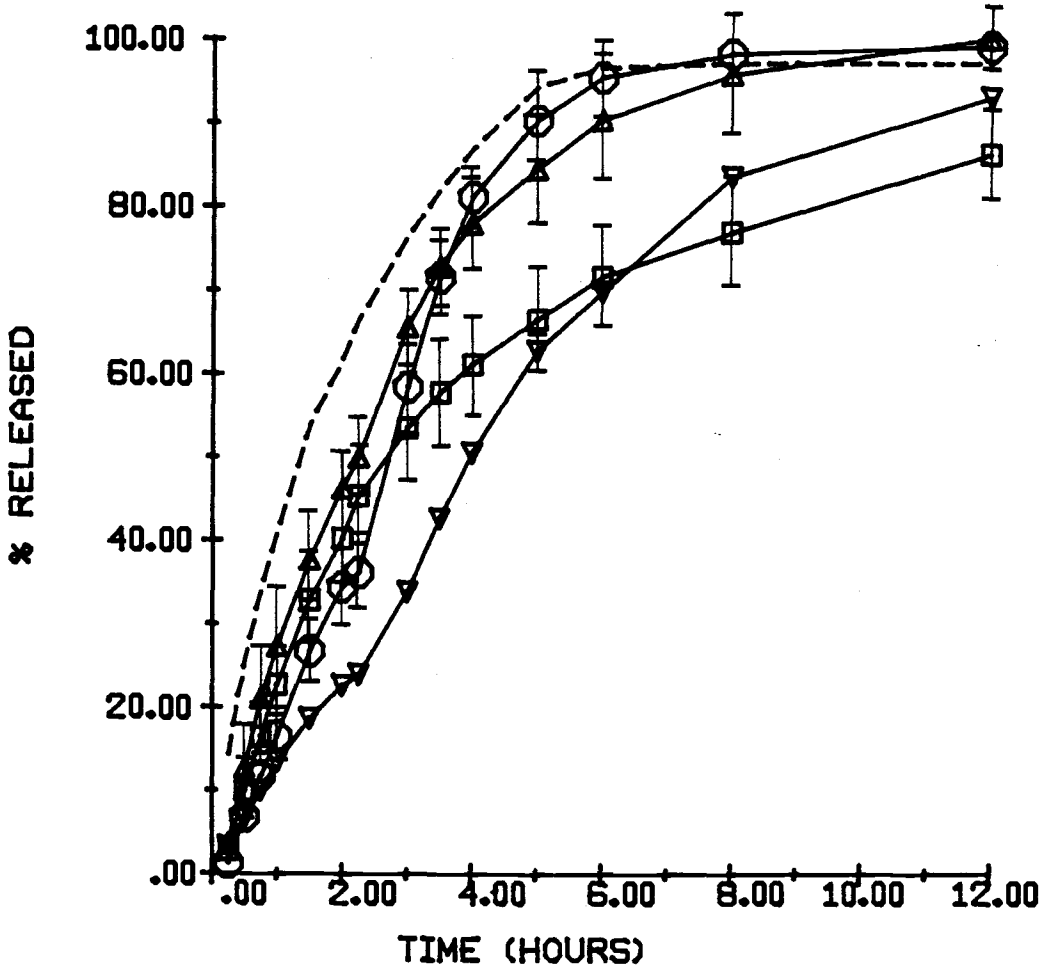

Figure II.5a In vitro dissolution of spray-coated acetaminophen powder with 20% Aquacoat inner coat. Key: (□) 0%; (△) 2.5%; (○) 5%; (▽) 10% Eudragit L30D overcoat; (———) uncoated acetaminophen powder. Each point is the mean ± standard deviation of two to six replications.

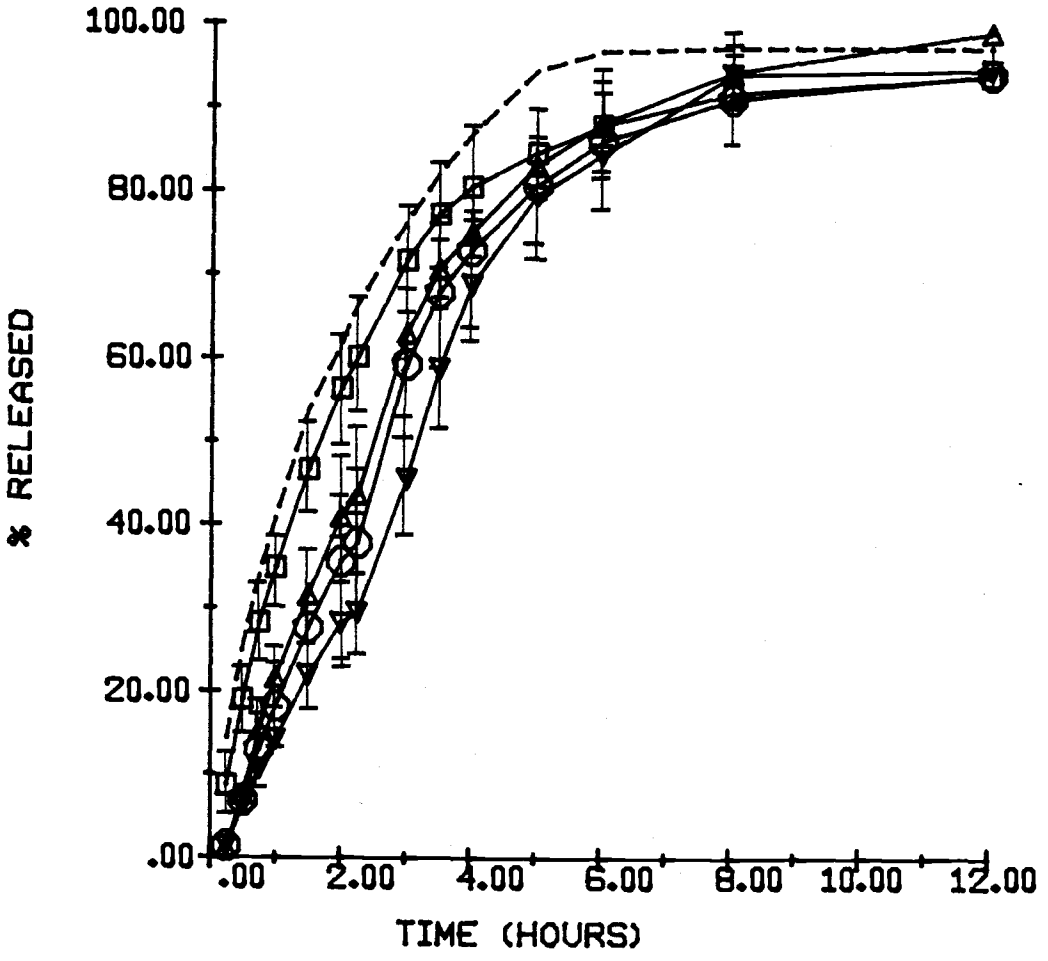

Figure II.5b In vitro dissolution of spray-coated acetaminophen powder with 10% Aquacoat inner coat. Key: (□) 0%; (△) 2.5%; (⬡) 5%; (▽) 10% Eudragit L30D overcoat; (———) uncoated acetaminophen powder. Each point is the mean ± standard deviation of two to six replications.

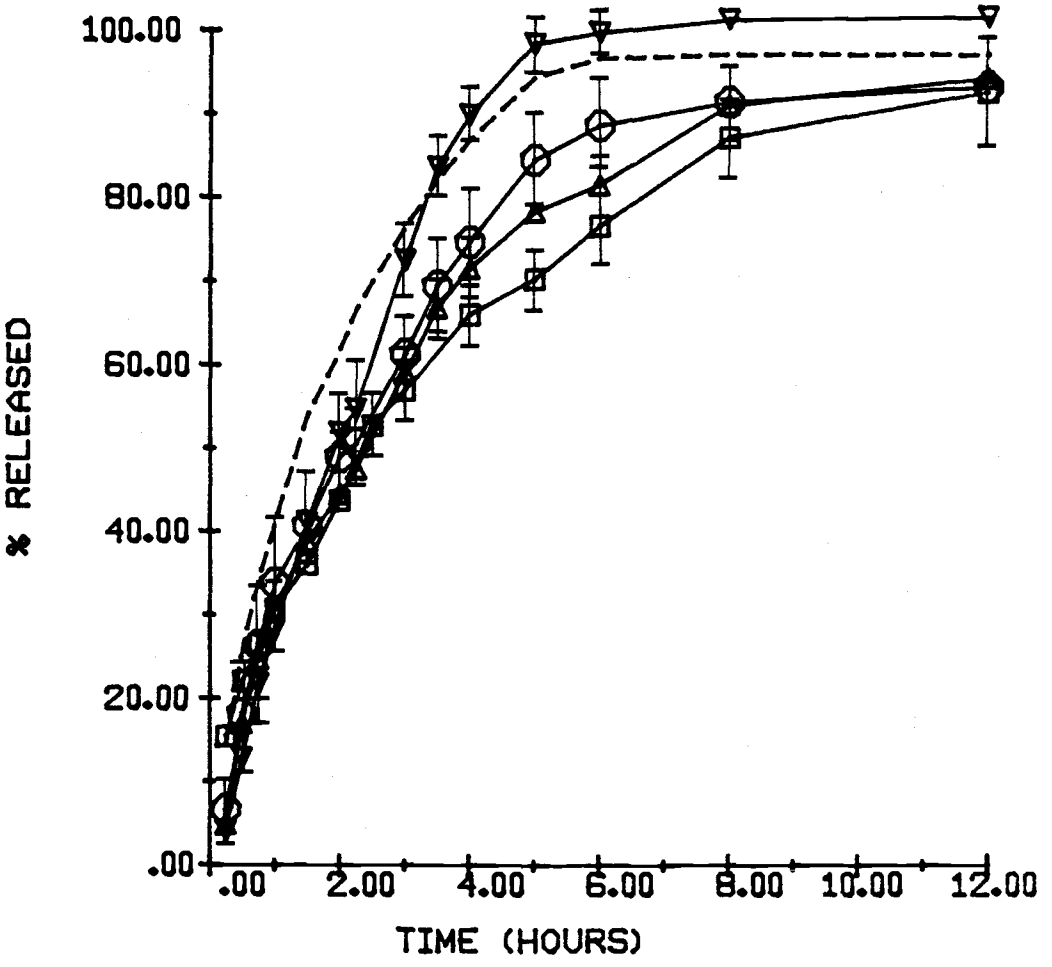

Figure II.5c In vitro dissolution of spray-coated acetaminophen powder with 5% Aquacoat inner coat. Key: (□) 0%; (△) 2.5%; (⬡) 5%; (▽) 10% Eudragit L30D overcoat; (———) uncoated acetaminophen powder. Each point is the mean ± standard deviation of two to six replications.

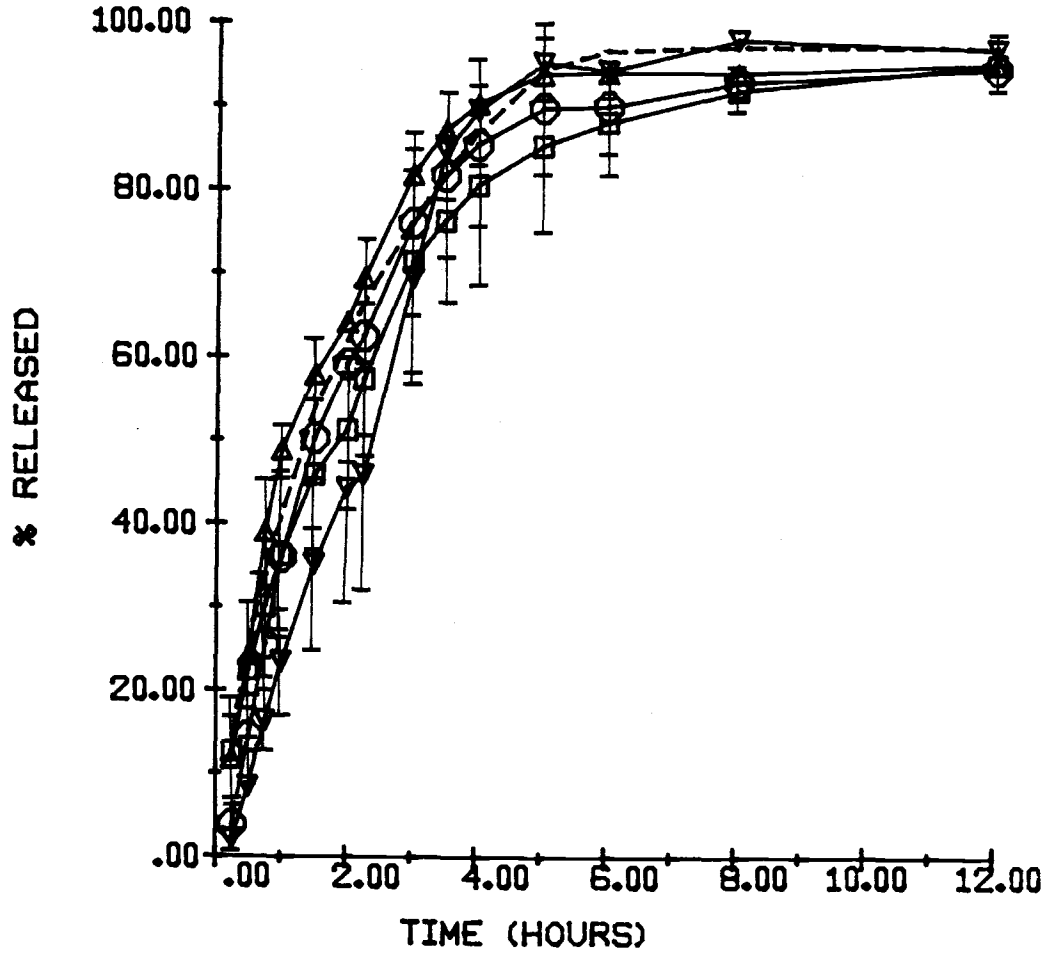

Figure II.5d *In vitro* dissolution of spray-coated acetaminophen powder with 2.5% Aquacoat inner coat. Key: (□) 0%; (△) 2.5%; (◯) 5%; (▽) 10% Eudragit L30D overcoat; (———) uncoated acetaminophen powder. Each point is the mean ± standard deviation of two to six replications.

of drug particles with 1) Eudragit L30D inner coat and Aquacoat outer coat in simulated gastric fluid, 2) Aquacoat inner coat and Eudragit L30D outer coat in simulated gastric fluid, 3) Eudragit L30D inner coat and Aquacoat outer coat in simulated intestinal fluid, and 4) Aquacoat inner coat and Eudragit L30D outer coat in simulated intestinal fluid. Data were divided in this manner to determine the effect of type and quantity of coating on dissolution in these two different fluids. As noted in Figures II.4a-d and II.5a-d, there is a sharp break in the dissolution profile at 2 hours for several coated powders when the dissolution medium is changed from simulated gastric to simulated intestinal fluid. It is instructive to determine whether this effect is time and pH dependent. ANOVAs for each of these groups of data are given in Tables II.3a-d. The treatment (coating) and time X treatment effects were broken down into separate tests of each treatment versus the control to provide comparisons between coated and uncoated acetaminophen (control).

For all four groups of data, treatment and time X treatment interactions were highly significant ($p<0.01$), as judged by the F values for treatment and time X treatment interaction in Tables II.3a-d. This means that there were significant differences between some formulations and control with respect to mean

Table II.3a ANOVA for Dissolution Profiles of Spray-Coated Acetaminophen Powders (Eudragit L30D (E-L30D) inner coat and Aquacoat (AQ) outer coat) in Simulated Gastric Fluid

Source			df	SSE	MSE	F
Treatment			16	18337.98	1146.12	7.97**
20% E-L30D	vs.	Control[a]	1	4298.19	4298.19	29.90**
20% E-L30D/2.5% AQ	vs.	Control	1	3298.95	3298.95	22.95**
20% E-L30D/5% AQ	vs.	Control	1	3641.05	3641.05	25.33**
20% E-L30D/10% AQ	vs.	Control	1	5214.93	5214.93	36.28**
10% E-L30D	vs.	Control	1	4377.05	4377.05	30.45**
10% E-L30D/2.5% AQ	vs.	Control	1	1299.23	1299.23	9.04**
10% E-L30D/5% AQ	vs.	Control	1	714.89	714.89	4.97*
10% E-L30D/10% AQ	vs.	Control	1	1554.59	1554.59	10.82**
5% E-L30D	vs.	Control	1	1096.34	1096.34	7.63**
5% E-L30D/2.5% AQ	vs.	Control	1	322.54	322.54	2.24
5% E-L30D/5% AQ	vs.	Control	1	229.96	229.96	1.60
5% E-L30D/10% AQ	vs.	Control	1	482.77	482.77	3.36
2.5% E-L30D	vs.	Control	1	118.77	118.77	0.83
2.5% E-L30D/2.5% AQ	vs.	Control	1	560.96	560.96	3.90
2.5% E-L30D/5% AQ	vs.	Control	1	167.96	167.96	1.17
2.5% E-L30D/10% AQ	vs.	Control	1	208.51	208.51	1.45
Main Plot Error			31	4456.12	143.75	
Main Plot Total			47	22794.09		
Time			5	46258.72	9251.74	852.81**
Time X Treatment			80	4967.90	62.10	5.72**
Time X 20% E-L30D	vs.	Control	5	553.65	110.73	10.21**
Time X 20% E-L30D/2.5% AQ	vs.	Control	5	336.41	67.28	6.20**
Time X 20% E-L30D/5% AQ	vs.	Control	5	419.89	83.98	7.74**
Time X 20% E-L30D/10% AQ	vs.	Control	5	589.59	117.92	10.87**
Time X 10% E-L30D	vs.	Control	5	322.64	66.53	6.13**
Time X 10% E-L30D/2.5% AQ	vs.	Control	5	48.35	9.67	0.89
Time X 10% E-L30D/5% AQ	vs.	Control	5	48.94	9.79	0.90
Time X 10% E-L30D/10% AQ	vs.	Control	5	36.93	7.39	0.68
Time X 5% E-L30D	vs.	Control	5	17.71	3.54	0.33
Time X 5% E-L30D/2.5% AQ	vs.	Control	5	73.13	14.63	1.35
Time X 5% E-L30D/5% AQ	vs.	Control	5	12.62	2.53	0.23
Time X 5% E-L30D/10% AQ	vs.	Control	5	54.02	10.80	1.00
Time X 2.5% E-L30D	vs.	Control	5	102.95	20.59	1.90
Time X 2.5% E-L30D/2.5% AQ	vs.	Control	5	16.82	3.36	0.31
Time X 2.5% E-L30D/5% AQ	vs.	Control	5	72.57	14.51	1.34
Time X 2.5% E-L30D/10% AQ	vs.	Control	5	4.14	0.83	0.08
Subplot Error			155	1681.52	10.85	
Suplot Total			240	52908.14		

[a]Control is uncoated acetaminophen powder.

* $p<0.05$

** $p<0.01$

Table II.3b ANOVA for Dissolution Profiles of Spray-Coated Acetaminophen Powders (Aquacoat (AQ) inner coat and Eudragit L30D (E-L30D) outer coat) in Simulated Gastric Fluid

Source			df	SSE	MSE	F
Treatment			16	16091.78	1005.74	5.35**
20% AQ	vs.	Control[a]	1	2485.95	2485.95	13.22**
20% AQ/2.5% E-L30D	vs.	Control	1	1684.28	1684.28	8.96**
20% AQ/5% E-L30D	vs.	Control	1	3950.86	3950.86	21.02**
20% AQ/10% E-L30D	vs.	Control	1	4068.75	4068.75	21.64**
10% AQ	vs.	Control	1	229.77	229.77	1.22
10% AQ/2.5% E-L30D	vs.	Control	1	2112.75	2112.75	11.24**
10% AQ/5% E-L30D	vs.	Control	1	2750.12	2750.12	14.63**
10% AQ/10% E-L30D	vs.	Control	1	3671.17	3671.17	19.53**
5% AQ	vs.	Control	1	531.29	531.29	2.83
5% AQ/2.5% E-L30D	vs.	Control	1	819.70	819.70	4.36*
5% AQ/5% E-L30D	vs.	Control	1	708.57	708.57	3.77
5% AQ/10% E-L30D	vs.	Control	1	1134.86	1134.86	6.04*
2.5% AQ	vs.	Control	1	236.89	236.89	1.26
2.5% AQ/2.5% E-L30D	vs.	Control	1	37.78	37.78	0.20
2.5% AQ/5% E-L30D	vs.	Control	1	395.46	395.46	2.10
2.5% AQ/10% E-L30D	vs.	Control	1	2289.73	2289.73	12.18**
Main Plot Error			35	6579.87	188.00	
Main Plot Total			51	22671.65		
Time			5	49000.76	9800.15	960.56**
Time X Treatment			80	2966.04	37.08	3.63**
Time X 20% AQ	vs.	Control	5	91.04	18.21	1.78
Time X 20% AQ/2.5% E-L30D	vs.	Control	5	27.86	5.57	0.55
Time X 20% AQ/5% E-L30D	vs.	Control	5	198.80	39.76	3.90**
Time X 20% AQ/10% E-L30D	vs.	Control	5	532.84	106.57	10.45**
Time X 10% AQ	vs.	Control	5	2.31	0.46	0.05
Time X 10% AQ/2.5% E-L30D	vs.	Control	5	48.81	9.76	0.96
Time X 10% AQ/5% E-L30D	vs.	Control	5	126.43	25.29	2.48*
Time X 10% AQ/10% E-L30D	vs.	Control	5	301.17	60.23	5.90**
Time X 5% AQ	vs.	Control	5	292.65	58.53	5.74**
Time X 5% AQ/2.5% E-L30D	vs.	Control	5	63.79	12.76	1.25
Time X 5% AQ/5% E-L30D	vs.	Control	5	52.03	10.41	1.02
Time X 5% AQ/10% E-L30D	vs.	Control	5	12.69	2.54	0.25
Time X 2.5% AQ	vs.	Control	5	71.84	14.37	1.41
Time X 2.5% AQ/2.5% E-L30D	vs.	Control	5	79.26	15.85	1.55
Time X 2.5% AQ/5% E-L30D	vs.	Control	5	91.26	18.25	1.79
Time X 2.5% AQ/10% E-L30D	vs.	Control	5	35.28	7.06	0.69
Subplot Error			175	1785.45	10.20	
Suplot Total			260	53752.25		

[a]Control is uncoated acetaminophen powder.
* $p<0.05$
** $p<0.01$

Table II.3c ANOVA for Dissolution Profiles of Spray-Coated Acetaminophen Powders (Eudragit L30D (E-L30D) inner coat and Aquacoat (AQ) outer coat) in Simulated Intestinal Fluid

Source			df	SSE	MSE	F
Treatment			16	63976.65	3998.54	23.39**
20% E-L30D	vs.	Control[a]	1	1595.56	1595.56	9.33**
20% E-L30D/2.5% AQ	vs.	Control	1	6895.78	6895.78	40.33**
20% E-L30D/5% AQ	vs.	Control	1	11642.24	11642.24	68.09**
20% E-L30D/10% AQ	vs.	Control	1	20670.62	20670.62	120.89**
10% E-L30D	vs.	Control	1	556.08	556.08	3.25
10% E-L30D/2.5% AQ	vs.	Control	1	22.17	22.17	0.13
10% E-L30D/5% AQ	vs.	Control	1	20.12	20.12	0.12
10% E-L30D/10% AQ	vs.	Control	1	1160.16	1160.16	6.79*
5% E-L30D	vs.	Control	1	255.89	255.89	1.50
5% E-L30D/2.5% AQ	vs.	Control	1	1332.28	1332.28	7.79**
5% E-L30D/5% AQ	vs.	Control	1	547.31	547.31	3.20
5% E-L30D/10% AQ	vs.	Control	1	2623.23	2623.23	15.34**
2.5% E-L30D	vs.	Control	1	58.73	58.73	0.34
2.5% E-L30D/2.5% AQ	vs.	Control	1	716.78	716.78	4.19*
2.5% E-L30D/5% AQ	vs.	Control	1	513.36	513.36	3.00
2.5% E-L30D/10% AQ	vs.	Control	1	1261.26	1261.26	7.38*
Main Plot Error			31	5300.49	170.98	
Main Plot Total			47	69277.15		
Time			7	55211.55	7887.36	601.70**
Time X Treatment			112	7363.87	65.75	5.02**
Time X 20% E-L30D	vs.	Control	7	1454.35	207.76	15.85**
Time X 20% E-L30D/2.5% AQ	vs.	Control	7	555.73	79.39	6.06**
Time X 20% E-L30D/5% AQ	vs.	Control	7	369.89	52.84	4.03**
Time X 20% E-L30D/10% AQ	vs.	Control	7	383.60	54.80	4.18**
Time X 10% E-L30D	vs.	Control	7	650.91	92.99	7.09**
Time X 10% E-L30D/2.5% AQ	vs.	Control	7	102.95	14.71	1.12
Time X 10% E-L30D/5% AQ	vs.	Control	7	78.08	11.15	0.85
Time X 10% E-L30D/10% AQ	vs.	Control	7	341.07	48.72	3.72**
Time X 5% E-L30D	vs.	Control	7	69.26	9.90	0.76
Time X 5% E-L30D/2.5% AQ	vs.	Control	7	115.45	16.49	1.26
Time X 5% E-L30D/5% AQ	vs.	Control	7	188.55	26.94	2.06
Time X 5% E-L30D/10% AQ	vs.	Control	7	149.20	21.31	1.63
Time X 2.5% E-L30D	vs.	Control	7	142.50	20.36	1.55
Time X 2.5% E-L30D/2.5% AQ	vs.	Control	7	79.43	11.35	0.87
Time X 2.5% E-L30D/5% AQ	vs.	Control	7	81.94	11.71	0.89
Time X 2.5% E-L30D/10% AQ	vs.	Control	7	114.09	16.30	1.24
Subplot Error			217	2844.54	13.11	
Suplot Total			336	65419.96		

[a]Control is uncoated acetaminophen powder.
* $p<0.05$
** $p<0.01$

Table II.3d ANOVA for Dissolution Profiles of Spray-Coated Acetaminophen Powders (Aquacoat (AQ) inner coat and Eudragit L30D (E-L30D) outer coat) in Simulated Intestinal Fluid

Source			df	SSE	MSE	F
Treatment			16	25044.31	1565.27	6.23**
20% AQ	vs.	Control[a]	1	5855.63	5855.63	23.29**
20% AQ/2.5% E-L30D	vs.	Control	1	679.73	679.73	2.70
20% AQ/5% E-L30D	vs.	Control	1	748.11	748.11	2.98
20% AQ/10% E-L30D	vs.	Control	1	7064.15	7064.15	28.10**
10% AQ	vs.	Control	1	313.31	313.31	1.25
10% AQ/2.5% E-L30D	vs.	Control	1	817.19	817.19	3.25
10% AQ/5% E-L30D	vs.	Control	1	1469.90	1469.90	5.85*
10% AQ/10% E-L30D	vs.	Control	1	2566.15	2566.15	10.21**
5% AQ	vs.	Control	1	2073.36	2073.36	8.25**
5% AQ/2.5% E-L30D	vs.	Control	1	1442.92	1442.92	5.74*
5% AQ/5% E-L30D	vs.	Control	1	1208.35	1208.35	4.81*
5% AQ/10% E-L30D	vs.	Control	1	3.01	3.01	0.01
2.5% AQ	vs.	Control	1	445.35	445.35	1.77
2.5% AQ/2.5% E-L30D	vs.	Control	1	9.00	9.00	0.04
2.5% AQ/5% E-L30D	vs.	Control	1	102.69	102.69	0.41
2.5% AQ/10% E-L30D	vs.	Control	1	93.08	93.08	0.37
Main Plot Error			35	8800.48	251.44	
Main Plot Total			51	33844.80		
Time			7	77200.28	11028.61	730.84**
Time X Treatment			112	9092.52	81.18	5.38**
Time X 20% AQ	vs.	Control	7	193.52	27.65	1.83
Time X 20% AQ/2.5% E-L30D	vs.	Control	7	377.80	53.97	3.58**
Time X 20% AQ/5% E-L30D	vs.	Control	7	1147.72	163.96	10.87**
Time X 20% AQ/10% E-L30D	vs.	Control	7	1404.97	200.71	13.30**
Time X 10% AQ	vs.	Control	7	32.88	4.70	0.31
Time X 10% AQ/2.5% E-L30D	vs.	Control	7	384.12	54.87	3.64**
Time X 10% AQ/5% E-L30D	vs.	Control	7	419.03	59.86	3.97**
Time X 10% AQ/10% E-L30D	vs.	Control	7	1066.82	152.40	10.10**
Time X 5% AQ	vs.	Control	7	294.64	42.09	2.79**
Time X 5% AQ/2.5% E-L30D	vs.	Control	7	234.29	33.47	2.22*
Time X 5% AQ/5% E-L30D	vs.	Control	7	155.94	22.28	1.48
Time X 5% AQ/10% E-L30D	vs.	Control	7	308.68	44.10	2.92**
Time X 2.5% AQ	vs.	Control	7	58.47	8.35	0.55
Time X 2.5% AQ/2.5% E-L30D	vs.	Control	7	86.95	12.42	0.82
Time X 2.5% AQ/5% E-L30D	vs.	Control	7	46.61	6.66	0.44
Time X 2.5% AQ/10% E-L30D	vs.	Control	7	575.73	82.25	5.45**
Subplot Error			245	3697.14	15.09	
Suplot Total			364	89989.93		

[a]Control is uncoated acetaminophen powder.
* $p<0.05$
** $p<0.01$

amount of drug released and dissolution pattern in both dissolution mediums.

Statistically significant differences between several individual coated powders and uncoated drug were found for acetaminophen particles having a single Eudragit L30D coat or those having Eudragit L30D as the inner coat and Aquacoat as the outer coat. When compared to uncoated acetaminophen, all particles with 20 and 10% inner enteric coats and the 5% Eudragit L30D coated powder had a lower mean percent drug released in gastric fluid (Figures II.4a-II.4c and Table II.3a).

The dissolution pattern in gastric fluid (as determined by testing the individual time X treatment interactions) was significantly different from that of uncoated drug only for particles with 20% inner enteric coats and the single-coated 10 and 20% Eudragit L30D powders (Table II.3a). Inspection of Figures II.4a and II.4b reveals that dissolution from these coated particles was slower than from uncoated drug. Thus, powders having 20% or 10% enteric coats and overcoated powders with 20% inner enteric coats are effective in delaying drug release in gastric fluid. However, some drug release still occurs in this medium, as is evident in Figures II.4a and II.4b. It is interesting to note that the presence of Aquacoat as a layer over the enteric coat unexpectedly results in an increase in the

amount of drug released in gastric fluid relative to acetaminophen particles having only an enteric coat (Figures II.4a and II.4b). For overcoated powders with an inner coat of 10% Eudragit L30D, there were no significant differences when compared to uncoated drug particles (Table II.3a and Figure II.4b).

For acetaminophen particles having a single coat of Aquacoat and those having an inner Aquacoat layer and outer Eudragit L30D wall (Figures II.5a-d), most formulations were found to be significantly different from control with decreased mean percent drug released in gastric fluid (Table II.3b). Exceptions were 10% Aquacoat, 5% Aquacoat, 5% Aquacoat/5% Eudragit L30D, 2.5% Aquacoat, 2.5% Aquacoat/2.5% Eudragit L30D, and 2.5% Aquacoat/5% Eudragit L30D coated powders. The powder with a 5% Aquacoat/2.5% Eudragit L30D coat barely reached the 5% significance level (Table II.3b). If it is ignored, one observes a pattern of delayed drug release in gastric fluid for overcoated powders with the highest amounts of Aquacoat as the inner coat (10 or 20%) and for powders with 2.5% or 5% Aquacoat inner coats plus a 10% Eudragit L30D outer coat.

When dissolution patterns (time X treatment factor) for spray-coated powders in gastric fluid were compared to uncoated drug, significant differences were found for 20% Aquacoat/5% Eudragit L30D, 20% Aquacoat/10%

Eudragit L30D (Figure II.5a), 10% Aquacoat/ 5% Eudragit L30D, 10% Aquacoat/10% Eudragit L30D (Figure II.5b), and 5% Aquacoat particles (Figure II.5c, Table II.3b). With exception of the latter, the 5 and 10% outer enteric coats appear to be effective in retarding drug release when combined with inner Aquacoat layers of 20 or 10%. Slow release from the 5% Aquacoat powder relative to the control is unexpected since neither the 10% nor the 20% coats of Aquacoat alone delayed drug release relative to the uncoated drug (control) (Figures II.5a and II.5b). This particular coated powder was prepared separately from the rest of the powders, and thus its anomolous dissolution behavior may be due to some variation in production conditions.

In simulated intestinal fluid following gastric fluid pretreatment, treatment differences relative to uncoated particles were obtained for the 20% Eudragit L30D powder, for all overcoated powders with a 20% Eudragit L30D inner coat (Figure II.4a), and for 10% Eudragit L30D/10% Aquacoat (Figure II.4b), 5% Eudragit L30D/2.5% Aquacoat, 5% Eudragit L30D/10% Aquacoat (Figure II.4c), 2.5% Eudragit L30D/2.5% Aquacoat, and 2.5% Eudragit L30D/10% Aquacoat particles (Figure II.4d and Table II.3c). In addition, the powders with a single coat of 20 or 10% Eudragit L30D and all overcoated powders with a 20% inner enteric coat (Figure

II.4a) were also significantly different from uncoated drug particles with respect to dissolution pattern in simulated intestinal fluid, as was the 10% Eudragit L30D/10% Aquacoat formulation (Figure II.4b).

Thus, the inner enteric coat initially retards drug release in intestinal fluid when applied as a 20 or 10% single coat, and release is further slowed when increasing amounts of Aquacoat are applied over a 20% enteric inner coat. With a 10% Eudragit L30D inner coat, release in intestinal fluid is delayed only for particles overcoated with 10% Aquacoat.

For particles with single coats of Aquacoat and those having an inner Aquacoat layer and outer Eudragit L30D coat (Figures II.5a-d), the 20% Aquacoat, 20% Aquacoat/10% Eudragit L30D, 10% Aquacoat/ 5% Eudragit L30D, 10% Aquacoat/10% Eudragit L30D, 5% Aquacoat, 5% Aquacoat/2.5% Eudragit L30D, and 5% Aquacoat/5% Eudragit L30D coated powders were significantly different from uncoated drug with decreased mean percent drug released in intestinal fluid following gastric pretreatment (Table II.3d). The dissolution pattern in intestinal fluid differed significantly from uncoated drug for all coated powders with a 10% outer enteric coat and for 20% Aquacoat/ 2.5% Eudragit L30D, 20% Aquacoat/5% Eudragit L30D (Figure II.5a), 10% Aquacoat/2.5% Eudragit L30D, 10% Aquacoat/5%

Eudragit L30D (Figure II.5b), 5% Aquacoat, and 5% Aquacoat/2.5% Eudragit L30D (Figure II.5c) coated powders (Table II.3d). Application of only 2.5% Aquacoat as a single coat or inner coat was ineffective in delaying drug dissolution relative to uncoated acetaminophen.

The Eudragit L30D coat when applied alone, or when applied as an outer coat, appears to be retarding drug release in intestinal fluid at 20 and 10% coating levels based on the statistically significant differences in dissolution profiles compared to uncoated drug. Inspection of graphs in Figures II.4a, II.4b, and II.5a-d reveal that these statistically significant differences for some of the above-mentioned coatings occur only because the amount of drug released is lower than from uncoated drug at early time points following the switch to simulated intestinal fluid. It takes a while (lag time) for the enteric coat to break up and after about 2 hours in simulated intestinal fluid (4 hours elapsed time from start of dissolution test) the release pattern becomes the same as that for uncoated acetaminophen. The release rate of drug coated with 10 or 20% Eudragit L30D is initially more rapid than that of uncoated drug in simulated intestinal fluid following gastric fluid pretreatment, which is consistent for a coating which is entero-soluble.

Overall, it appears that the higher the amount of coating, the slower the drug release. This is as expected based on the literature but is the opposite of the results obtained for acetaminophen microcapsules with an ethylcellulose coat (Chapter I). An inner enteric coat is effective in slowing drug release, but only at the highest coating level of 20%. When compared to a single coat of 20% Eudragit L30D, overcoated powders with an inner coat of 20% Eudragit L30D were significantly different ($p<0.01$) with respect to mean percent drug released and dissolution pattern in simulated intestinal fluid. Inspection of Figure II.4a reveals that dissolution was significantly slower for these overcoated powders. Thus, the overcoat, even when it is only 2.5% Aquacoat, is having a marked effect on dissolution of drug from powders having a 20% inner enteric coat.

Acetaminophen powder with three separate layers of coating material dissolved at about the same rate as the double-coated powders irrespective of the total amount of coat (Figure II.6 and Table II.4). For example, powder coated with 10% Aquacoat/20% Eudragit L30D/ 10% Aquacoat (total coating of 40%) dissolved at the same rate as powder coated with 20% Eudragit L30D/ 10% Aquacoat (total coating of 30%) (Table II.4) which was unexpected. Thus, drug release is not further delayed

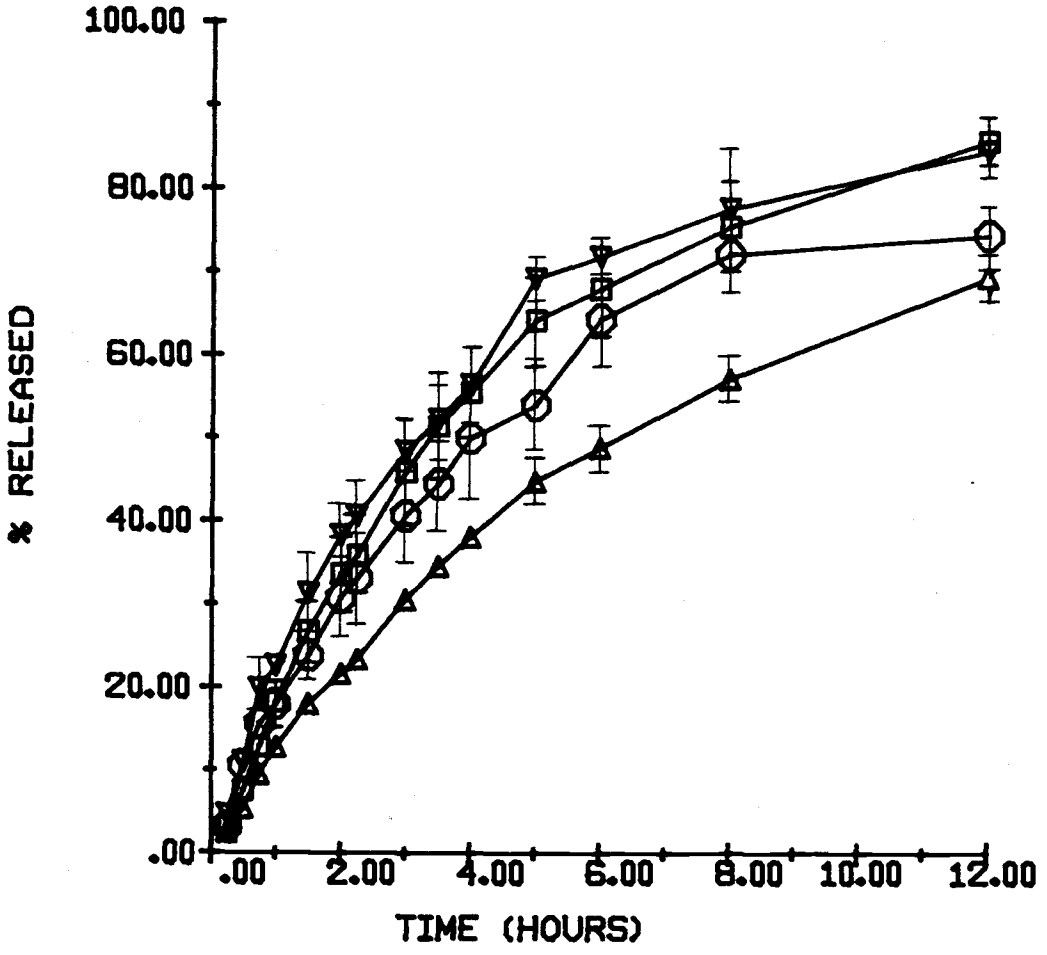

Figure II.6 In vitro dissolution of triple-coated acetaminophen powder. Key: (□) 5% Aquacoat/ 10% Eudragit L30D/5% Aquacoat; (▽) 5% Aquacoat/ 20% Eudragit L30D/5% Aquacoat; (○) 10% Aquacoat/ 10% Eudragit L30D/10% Aquacoat; (△) 10% Aquacoat/ 20% Eudragit L30D/10% Aquacoat. Each point is the mean ± standard deviation of three replications.

Table II.4 Time to 50% Dissolution of Selected Spray-Coated Acetaminophen Powders

Coating[a]	$d_{50\%}$[b], hr
20% AQ/10% E-L30D	3.98±0.11
10% AQ/10% E-L30D	3.17±0.30
20% E-L30D	3.03±0.01
20% E-L30D/2.5% AQ	3.75±0.53
20% E-L30D/5% AQ	4.80±0.01
20% E-L30D/10% AQ	6.31±0.98
5% AQ/10% E-L30D/5% AQ	3.44±0.67
5% AQ/20% E-L30D/5% AQ	3.28±0.60
10% AQ/10% E-L30D/10% AQ	4.26±0.89
10% AQ/20% E-L30D/10% AQ	6.31±0.83

[a] AQ is Aquacoat and E-L30D is Eudragit L30D. Inner coat is listed first.

[b] Each value is the mean ± standard deviation for 2-6 replications. Only coated powders with $d_{50\%}$ >3 hours are included in this table. See Table II.8a for $d_{50\%}$ of all powders studied.

by "sandwiching" the Eudragit L30D enteric coat between two layers of Aquacoat. Osmotic pressure from the dissolved polymeric salts in the Eudragit L30D coating (when exposed to intestinal fluid) may result in water being drawn into the center coating layer of the coated particles, thus causing swelling and possible rupturing of the rigid outer ethylcellulose coat.

The importance of the outer Aquacoat layer in delaying drug release can be futher illustrated by comparing dissolution of the 5% Aquacoat/10% Eudragit L30D/5% Aquacoat and 10% Aquacoat/10% Eudragit L30D/ 10% Aquacoat triple-coatings with that of the 5% Aquacoat/ 10% Eudragit L30D and 10% Aquacoat/10% Eudragit L30D coated powders, respectively. The dissolution pattern of the 5% Aquacoat/10% Eudragit L30D/5% Aquacoat powder was significantly different (slower dissolution) from that of the 5% Aquacoat/10% Eudragit L30D powder in both gastric fluid and intestinal fluid following gastric fluid pretreatment ($p<0.01$). Dissolution was also slower from the 10% Aquacoat/10% Eudragit L30D/ 10% Aquacoat coated powder compared to the 10% Aquacoat/10% Eudragit L30D particles, but the difference in dissolution pattern was significant only in intestinal fluid ($p<0.01$).

The time to 50% drug release ($d_{50\%}$) which was estimated by linear extrapolation, was 3 hours or less

for all coated powders except those listed in Table II.4. ($D_{50\%}$ values for other coated powders are given in Table II.8a). Delayed release of drug from formulations with an outer Eudragit L30D coat can be attributed primarily to the enteric coat slowing drug release in gastric fluid. It is interesting to note that a single coat of Aquacoat, even when applied at 20%, did not sufficiently delay drug release ($d_{50\%}$ <3 hours). However, when 5% Aquacoat/10% Eudragit L30D/5% Aquacoat was applied, drug release was delayed, even though the total coat was still 20%.

It was not particularly surprising that low coating levels of Eudragit L30D and Aquacoat were inadequate in delaying drug release due to the high surface area of the acetaminophen powder which results in a thin coat. These results confirm that delayed dissolution with thin coats produced by microencapsulation (Chapter I) are quite unexpected. This aspect will be further discussed in a subsequent section.

Visually, these ethylcellulose spray-coated drug particles were not quite as uniform and free flowing as those prepared with phase-separation coacervation as described in Chapter I. The smaller the particle size, the more difficult it is to effectively coat particles using air suspension techniques. 74 µm has been identified as the lowest practical particle size for

coating with air suspension (Bakan and Anderson, 1976). Acetaminophen powder is ≤75 μm. Agglomeration may occur when such fine particles are spray coated, but very few such agglomerates were found in 300 g batches of these coated particles. Another potential problem is that of using aqueous based coating materials for coating water soluble drugs. Unless the coating dries quickly, drug may partially dissolve and then reprecipitate on the outside of the particle, thus resulting in an incomplete coat. Without microscopic examination of coated drug particles, it is difficult to explain differences between these two methods of applying an ethylcellulose coat to small particles of acetaminophen. *In vitro* dissolution tests revealed one marked difference: microencapsulated acetaminophen dissolves very slowly because it does not wet when confined inside a basket while spray-coated acetaminophen (at the same coating amount) dissolves very quickly, and this observation could be due to differences in the nature of the coat (number and size of pores, channels, etc.).

Dissolution of Dosage Forms Containing Spray-Coated Acetaminophen Powder

Several spray-coated acetaminophen powders, most notably those exhibiting the slowest *in vitro* release, were incorporated into tablets. Mean *in vitro* dissolution profiles for intact, halved, and crushed

tablets are shown in Figures II.7a-d, and the corresponding $d_{50\%}$ values are given in Table II.5. Tablets containing particles having an outer enteric coat (Figure II.7a) and those with 2.5% Eudragit L30D/2.5% Aquacoat particles (Figure II.7b) had the fastest *in vitro* drug release. Note the break in the dissolution curves for the 5% Aquacoat/ 5% Eudragit L30D and 20% Aquacoat/10% Eudragit L30D formulations when the dissolution medium is changed from gastric to intestinal fluid (Figure II.7a). These tablets disintegrated in simulated intestinal fluid as the enteric coating material dissolved, resulting in rapid drug release. Tablets containing 20% Eudragit L30D/2.5% Aquacoat also disintegrated (Figure II.7b), but more slowly than the previously mentioned tablets. In contrast, the remaining tablets (Figures II.7b and II.7c) did not disintegrate during the dissolution period (24 hours), probably due to formation of a plastic matrix from which drug release occurs by leaching and diffusion (De Haan et al., 1984). These data show that the outer coating on the particles should not be ethylcellulose if a disintegrating tablet is desired. Likewise, ethylcellulose should not be the outermost coat if a product is desired which gives the same release pattern when crushed or chewed as when taken intact.

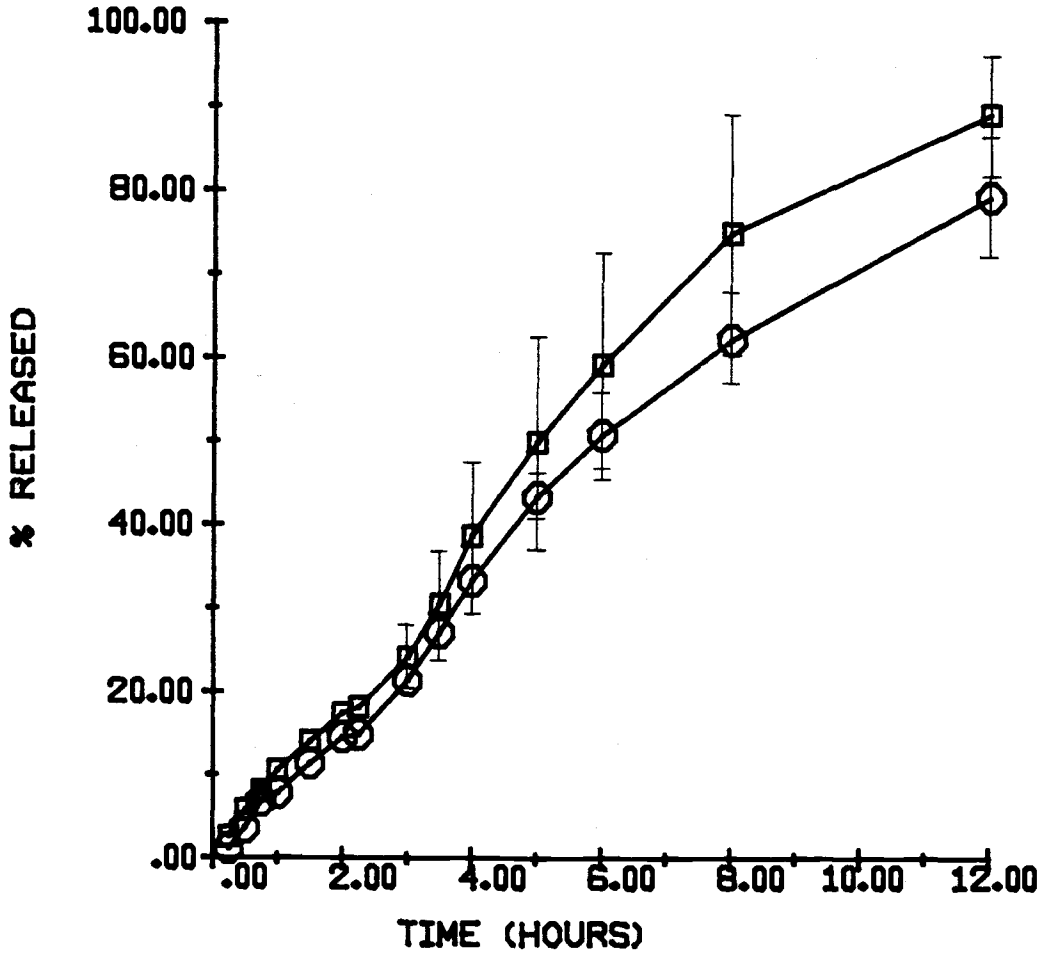

Figure II.7a *In vitro* dissolution of intact tablets containing spray-coated acetaminophen powder. Key: (□) 5% Aquacoat/5% Eudragit L30D; (○) 20% Aquacoat/10% Eudragit L30D. Each point is the mean ± standard deviation of two to three replications.

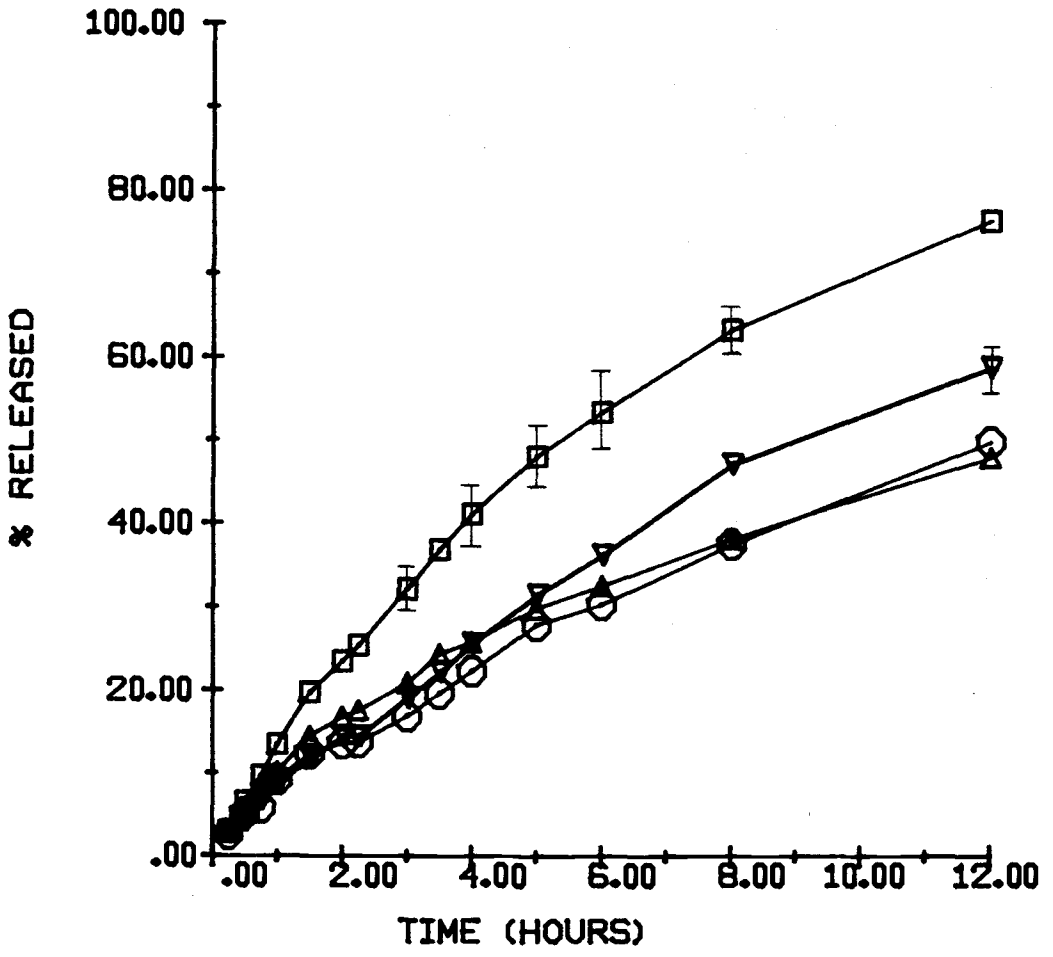

Figure II.7b In vitro dissolution of intact tablets containing spray-coated acetaminophen powder. Key: (□) 2.5% Eudragit L30D/2.5% Aquacoat; (△) 5% Eudragit L30D/5% Aquacoat; (◯) 20% Eudragit L30D/5% Aquacoat; (▽) 20% Eudragit L30D/2.5% Aquacoat. Each point is the mean ± standard deviation of two to three replications.

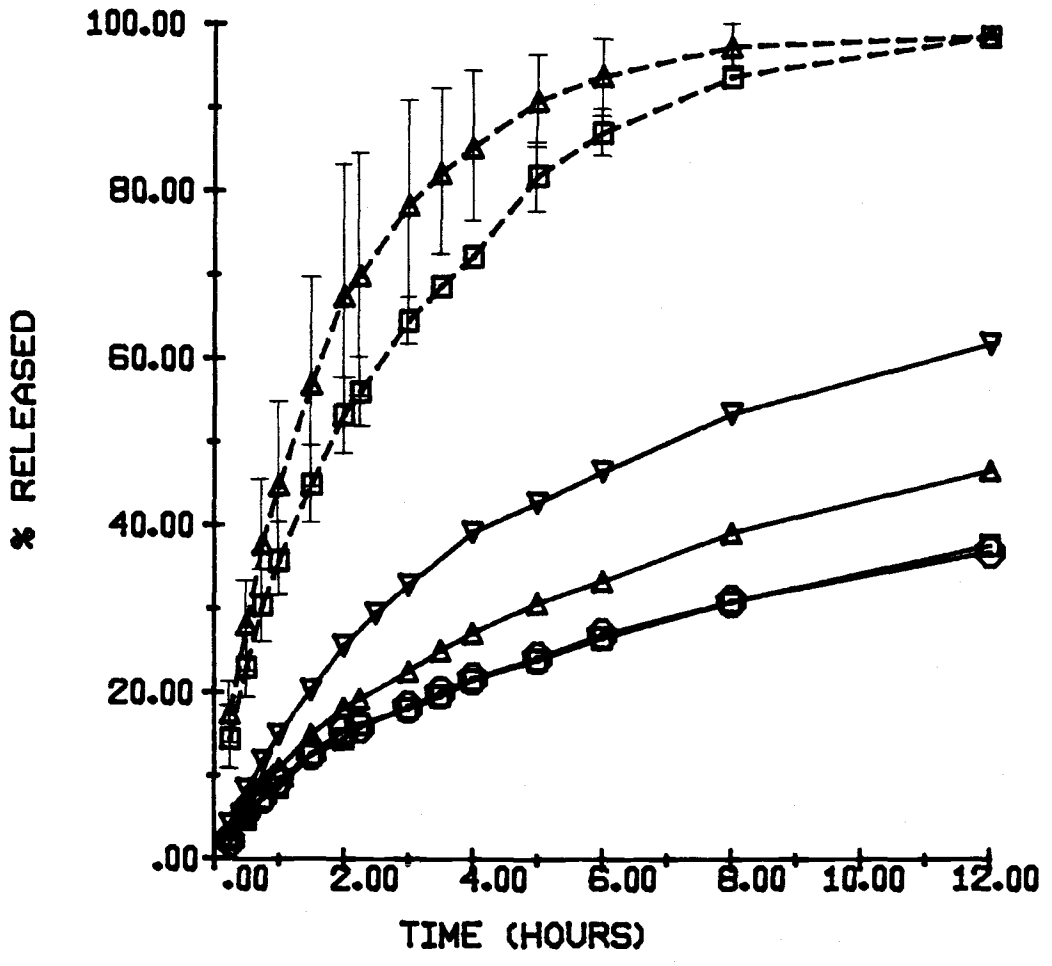

Figure II.7c In vitro dissolution of intact (———) and crushed (– – –) tablets containing spray-coated acetaminophen powder. Key: (▢) 20% Aquacoat plus acetaminophen granules; (◯) 20% Aquacoat; (△) 10% Aquacoat; (▽) 5% Aquacoat. Each point is the mean ± standard deviation of two to three replications.

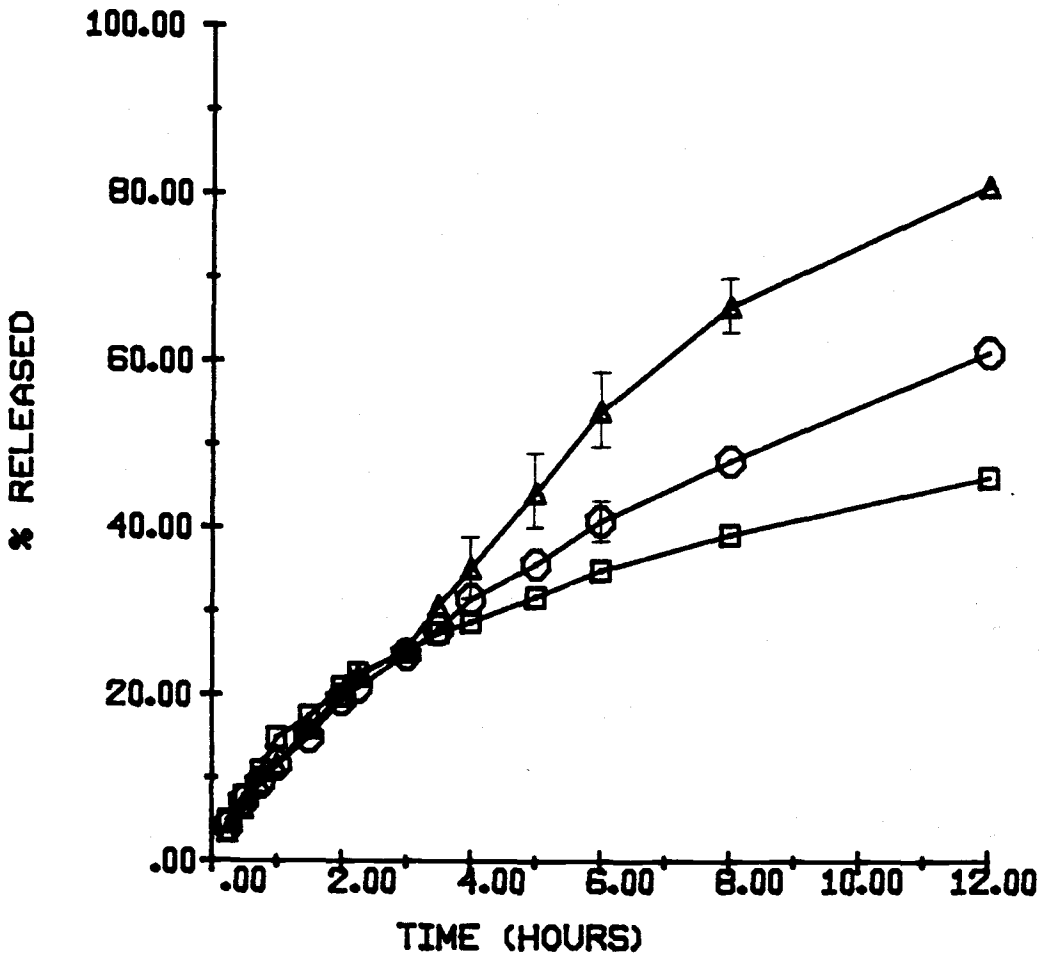

Figure II.7d *In vitro* dissolution of halved tablets containing spray-coated acetaminophen powder. Key: (△) 5% Eudragit L30D/5% Aquacoat; (□) 20% Aquacoat plus acetaminophen granules; (○) 20% Eudragit L30D/5% Aquacoat. Each point is the mean ± standard deviation of two to three replications.

Table II.5 Time to 50% Dissolution of Tablets Containing Spray-Coated Acetaminophen Powders[a]

Coating[c]	$d_{50\%}$[b], hr		
	Intact Tablet	Crushed Tablet	Halved Tablet
2.5% E-L30D/2.5% AQ	5.4±0.82		
5% E-L30D/5% AQ	13.6±1.1		5.6±0.49
20% E-L30D/2.5% AQ	9.1±0.78		
20% E-L30D/5% AQ	12.2±0.44		8.7±0.37
20% E-L30D/10% AQ	16.2±0.24		
5% AQ	7.1±0.34		
10% AQ	14.5±0.95	1.3±0.46	
20% AQ	22.6±1.2		
20% AQ + acetaminophen granules	22.6±1.5	1.8±0.31	15.9±2.3
5% AQ/5% E-L30D	5.3±1.4		
20% AQ/10% E-L30D	6.0±0.75		

[a] Composition of tablet formulation is given in Table II.1a.

[b] Each value is the mean ± standard deviation for 2-3 replications. $D_{50\%}$ values for coated powders are listed in Table II.8a.

[c] AQ is Aquacoat and E-L30D is Eudragit L30D. Inner coat is listed first.

Drug release from tablets made with 2.5% Eudragit L30D/2.5% Aquacoat was fairly rapid ($d_{50\%}$ = 5.4±0.82 hours) especially when compared to tablets containing 5% Eudragit L30D/5% Aquacoat ($d_{50\%}$ = 13.6±1.1 hours) (Figure II.7b). This slight increase in the amount of coating greatly influenced the dissolution rate of drug from such tablets. This effect is most likely due to the increase in the amount of ethylcellulose outer coat which, when compressed, resulted in a more extensive plastic matrix. This same result was observed for tablets containing acetaminophen particles with a fixed amount of Eudragit L30D (20%) as the inner coating. As the outer Aquacoat level was increased from 2.5% to 5%, $d_{50\%}$ increased from 9.1±0.78 to 12.2±0.4 hours (Figure II.7b). This increase was not as great as that mentioned above, which may be due to the high amount of enteric coating present. A small increase in the amount of outer ethylcellulose may not entirely block any channeling effect that occurs when the polymeric enteric coating dissolves in simulated intestinal fluid.

Dissolution profiles for some intact and crushed tablets made with acetaminophen coated only with ethylcellulose (Aquacoat) are given in Figure II.7c. The dissolution rate was clearly dependent on the amount of ethylcellulose present since dissolution rate

increased as the amount of ethylcellulose decreased, and this effect was less marked at higher amounts of ethylcellulose. $D_{50\%}$ doubled as the amount of Aquacoat in these tablets increased from 5 to 10% and then increased by only about 35% as the amount of Aquacoat was again doubled to 20% (Table II.5). This can again be attributed to the formation of a more extensive plastic matrix. However, it appears that once the ethylcellulose coat increases beyond a certain amount, the corresponding decrease in dissolution rate diminishes.

The similarity of the dissolution profiles for intact tablets made with 20% Aquacoat drug particles mixed with a chewable tablet excipient blend or containing acetaminophen granules instead of the excipient mixture indicated that the ethylcellulose matrix traps the drug granules inside the tablet and does not allow for immediate drug release or even an increase in the release rate (Figure II.7c). Any free drug that dissolved within the matrix still has to be leached out of the tablet, and this process was impeded by the ethylcellulose shell.

Halving some of these tablets resulted in faster drug release, and the magnitude of the effect was least for tablets made from 20% Aquacoat particles combined with acetaminophen granules (Figure II.7d compared to

II.7c). Reasons for this faster release are probably two-fold. First, cracking the tablet in half results in the inner part of the plastic matrix being exposed to the dissolution fluid, thus exposing free drug. Secondly, the total surface area is increased and the dissolution rate is expected to increase as given by the Noyes-Whitney equation (Noyes and Whitney, 1897). With a higher ethylcellulose content, the first effect (that of exposing free drug from a freshly broken surface) has a smaller influence, and this may explain the finding that halving had only a slight effect on the rate of dissolution from tablets containing 20% Aquacoat drug particles and acetaminophen granules.

Tablets with the slowest in vitro release (those with 10% and 20% Aquacoat drug particles, respectively) were crushed by cracking between two spoons. Such crushing may be desirable for some elderly or pediatric patients. Release of drug from crushed tablets was extremely rapid (Figure II.7c). Thus, crushing the tablets destroys the plastic matrix formed upon compression. This finding was also observed for compressed ethylcellulose microscapsules in Chapter I. This implies that chewing these tablets would result in rapid drug release in vivo.

Dissolution tests of tablets, crushed tablets, tablet formulation and tablet formulation packed into

hard gelatin capsules were performed for the 20% Eudragit L30D/10% Aquacoat particles in order to determine what effect crushing compressed tablets has on spray-coated acetaminophen particles (Figure II.8). Release from crushed tablets was much more rapid than from intact tablets. However, the release rate from crushed tablets is only slightly faster than from the tablet formulation, indicating that crushing tablets destroys the matrix, but probably does not crack individual particle coats. Thus, a formulation of coated particles which produces delayed release independent of polymer matrix formation may be useful for crushable controlled release tablets. Coated powders tested to date do not meet these criteria.

Release profiles of drug from the tablet formulation and tablet formulation packed into hard gelatin capsules were virtually identical, as expected, with a slight lag time for the capsules to dissolve. $D_{50\%}$ for the tablet formulation in capsules (2.68$\pm$0.2 hours) is faster than that from coated acetaminophen particles in capsules (6.31$\pm$0.98 hours, Table II.4) and may be attributed to the presence of soluble sugar in the excipient blend which increase wetting of acetaminophen particles.

Dissolution of Spray-Coated Acetaminophen Pellets

In vitro dissolution profiles for acetaminophen

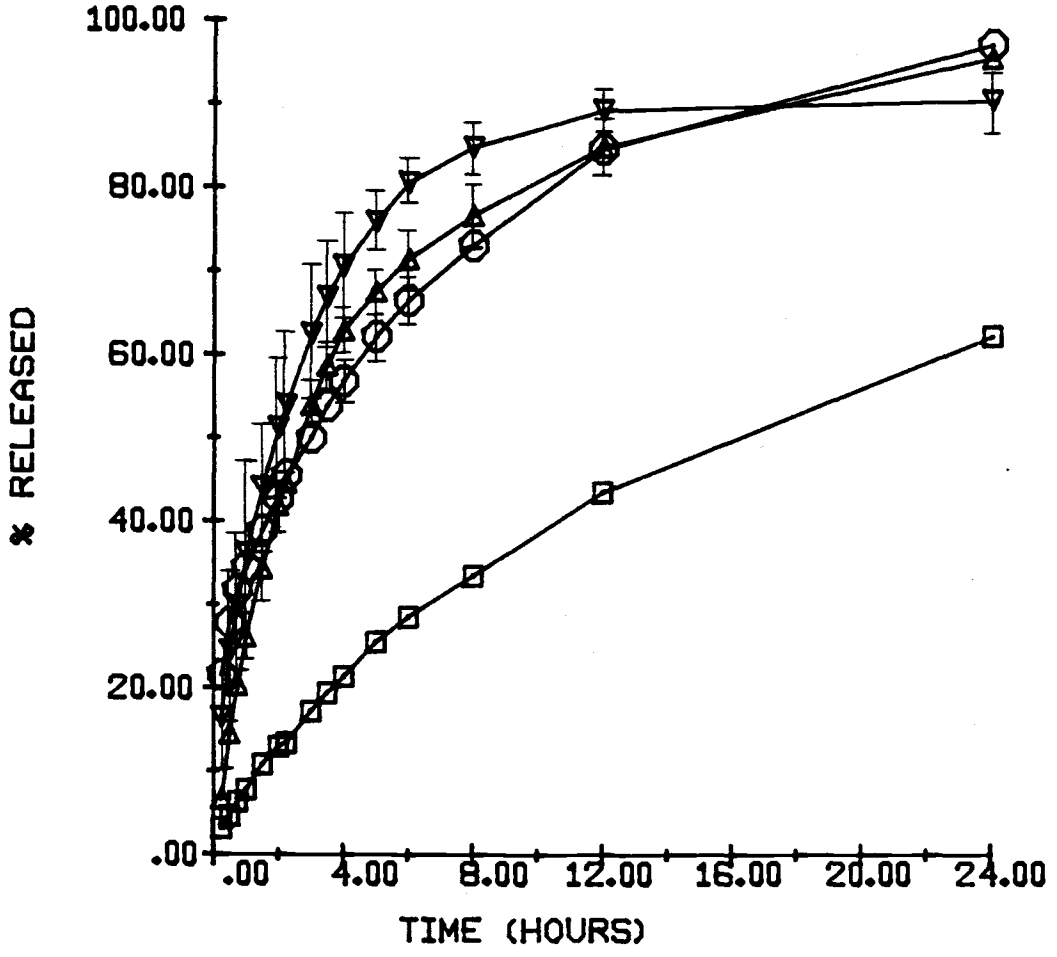

Figure II.8 In vitro dissolution of dosage forms containing spray-coated acetaminophen powder: 20% Eudragit L30D/10% Aquacoat. Key: (□) intact tablets; (▽) crushed tablets; (△) tablet formulation in hard gelatin capsules; (○) uncompressed tablet formulation. Each point is the mean ± standard deviation of three replications.

pellets coated with Aquacoat alone are given in Figure II.9a. Release was extrememly slow from pellets with 4, 5, and 10% Aquacoat, with less than 25% of the drug released after 48 hours. The release rate from 0.5% and 1.0% Aquacoat drug pellets was extremely rapid, which implies that such small amounts of coating material are insufficient to completely coat the pellets or that the coats are too thin. The dissolution profile for the 2% Aquacoat pellets lies midway between the 1 and 3% coated pellets. Thus, the release rate of drug from pellets coated with Aquacoat is affected markedly by slight changes in the amount of coating in this region. Release of drug from these pellets appears to be zero order for coatings $\geq$ 3%. The dissolution profile for the 2% drug pellets is also linear on this scale but only over the first 8 hours of the dissolution test.

A mixture of Aquacoat and Eudragit E30D was applied as a "combination coat" to pellets at 2, 3, and 4% amounts. Dissolution profiles are given in Figure II.9b. Release of drug from pellets with the 2% combination coat was virtually the same as that from the 2% Aquacoat pellets (Figure II.9a). However, at higher coating levels, drug release from pellets with a combination coat was more rapid than from the analagous single Aquacoat layer. It is quite unexpected that the 2% "combination coat" gives the same release as 2%

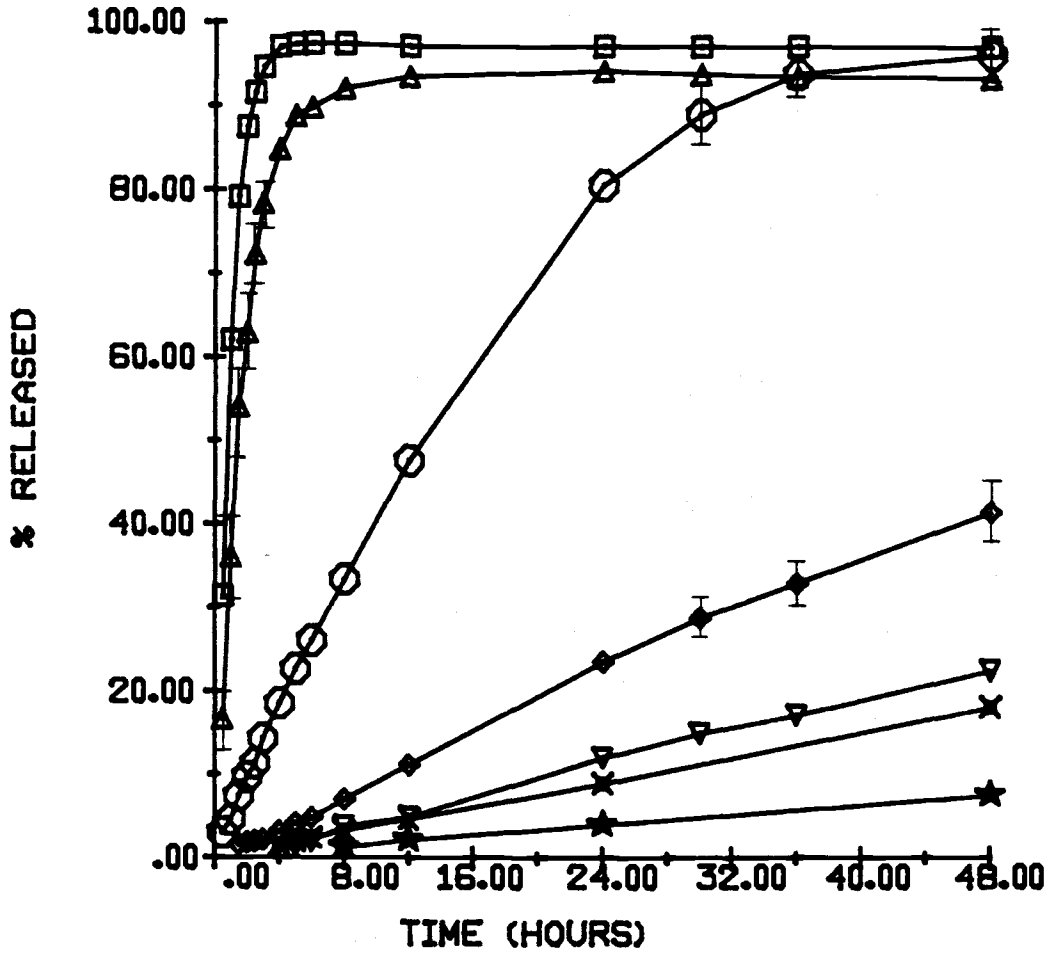

Figure II.9a *In vitro* dissolution of spray-coated acetaminophen pellets. Key: (□) 0.5%; (△) 1%; (⬡) 2%; (◇) 3%; (▽) 4%; (✕) 5%; (★) 10% Aquacoat. Each point is the mean ± standard deviation of two to three replications.

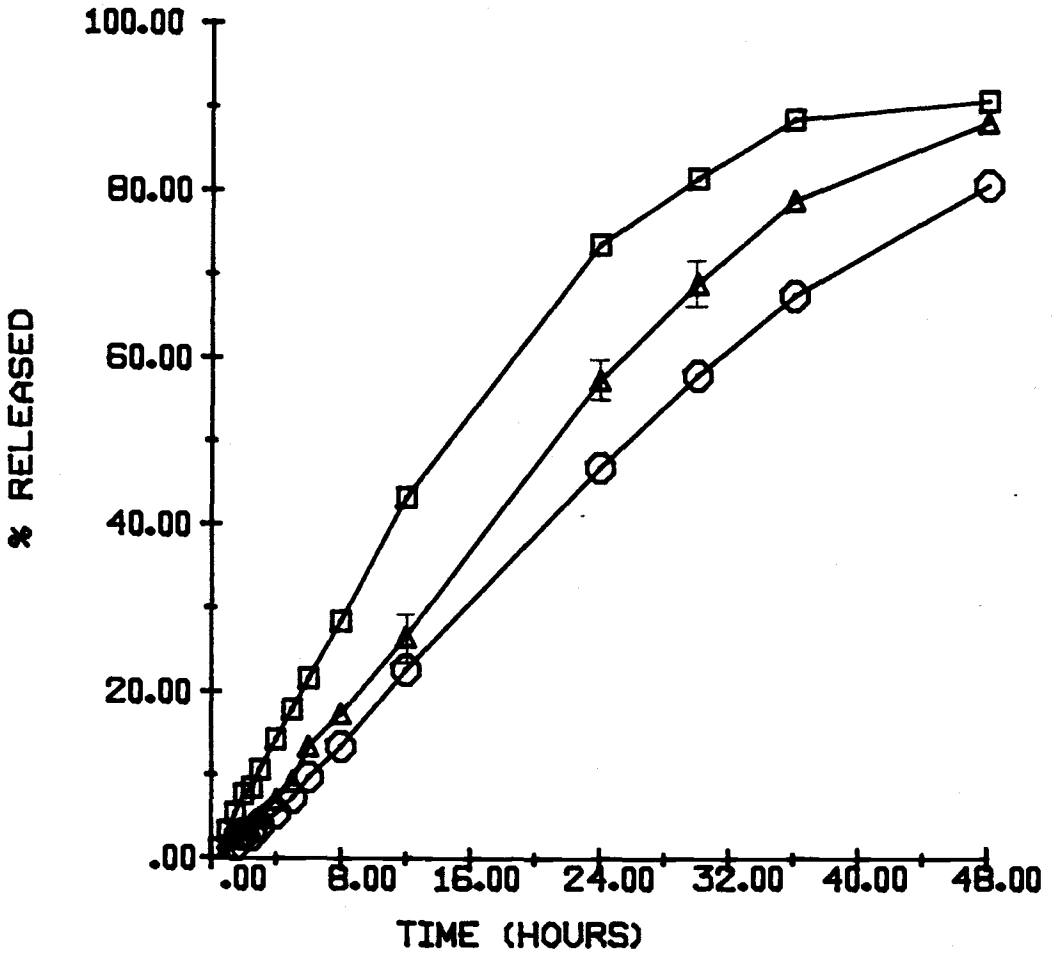

Figure II.9b *In vitro* dissolution of spray-coated acetaminophen pellets. Key: (□) 2%; (△) 3%; (○) 4% Aquacoat and Eudragit E30D "combination coat". Each point is the mean ± standard deviation of two to three replications.

Aquacoat, but the 3% and 4% "combination coats" provide faster release than the 3% and 4% Aquacoat pellets. A practical application of this finding is that the "combination coat" is not as sensitive to the amount applied as pure Aquacoat which would allow for less difficulty in manufacturing. It was observed visually that at completion of the dissolution test period, "combination coats" did not retain their original pellet shape, but rather had broken apart. This is quite different from pellets coated with Aquacoat alone which retain their shape, leaving intact opaque beads in the basket after all the drug has been released.

Dissolution profiles for triple-coated acetaminophen pellets are given in Figure II.9c. Release was more rapid than from the 4, 5, and 10% single-coated Aquacoat pellets which means that the inner enteric coat, rather than slowing drug release, serves to increase it. As the enteric coating material is dissolved due to passage of intestinal fluid into the pellet, the polymeric salts formed may act as an osmotic attractant since they are trapped in between two Aquacoat layers. Thus, fluid is drawn into the pellet faster, leading to an increased dissolution rate. The additional water drawn into the bead may also cause the outer coat to partially rupture by swelling of the center layer. However, even if this occurred, the 5%

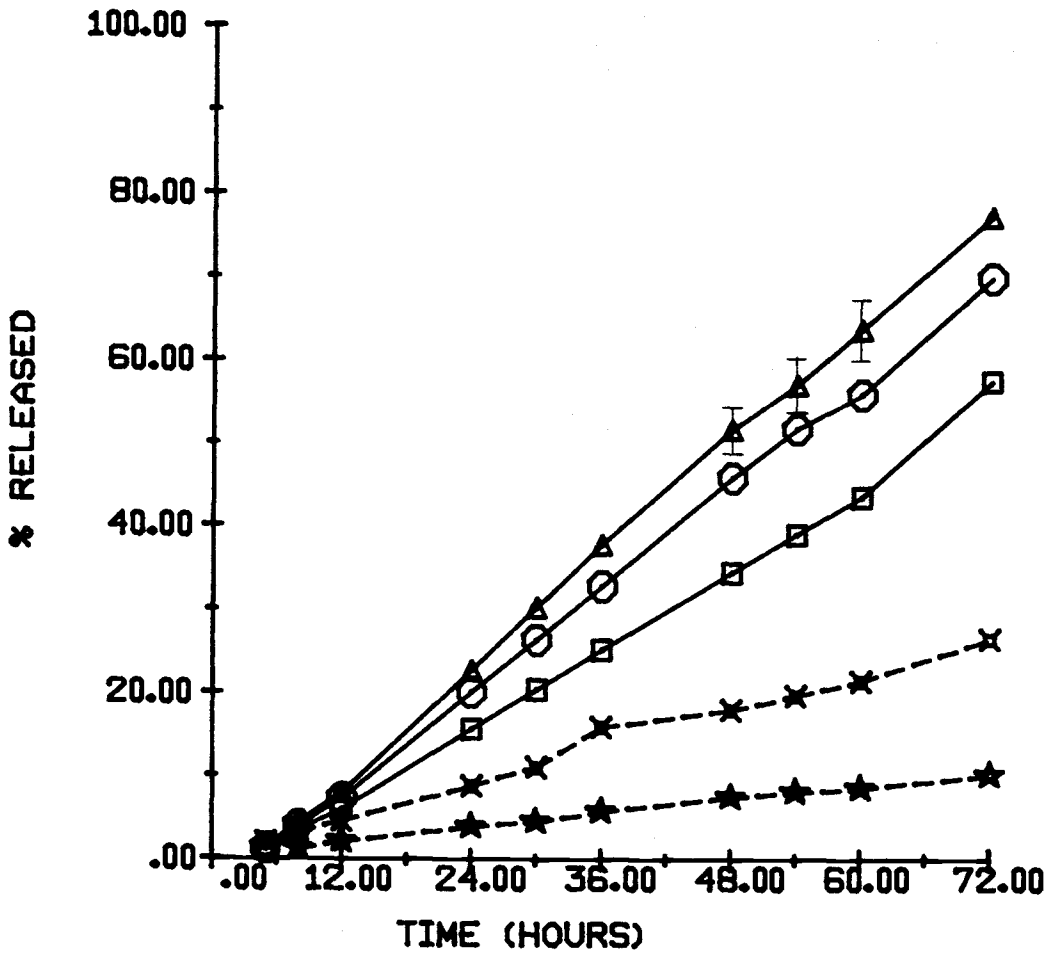

Figure II.9c *In vitro* dissolution of spray-coated acetaminophen pellets. Key: (———) triple coat; (□) 5% Aquacoat/5% Eudragit L30D/5% Aquacoat; (△) 5% Aquacoat/10% Eudragit L30D/5% Aquacoat; (⬡) 5% Aquacoat/15% Eudragit L30D/5% Aquacoat; (– – –) single coat; (✕) 5% Aquacoat; (★) 10% Aquacoat. Each point is the mean ± standard deviation of two to three replications.

inner Aquacoat layer should be unaffected and thus should delay drug release at least as much as the single 5% Aquacoat wall. The absence of an extensive delayed release effect for the triple-coated pellets when compared to single-coated pellets seems to suggest that Eudragit L30D does not form a hydrogel when trapped by overcoating with Aquacoat, because a hydrogel should delay, not increase, the rate of drug release. The results are quite unexpected and cannot be fully explained at this time.

The 2, 3, and 4% Aquacoat-coated drug pellets were also tested in a 50 rpm paddle apparatus (Figure II.9d). The release profiles were virtually identical to those obtained from testing with the rotating basket apparatus (Figure II.9a). This is somewhat surprising but also useful since it means that *in vitro* drug release from such pellets is independent of the type of apparatus used. This implies that the transfer of dissolved drug from the core through the Aquacoat barrier is the rate limiting step in this dissolution process. Otherwise, one would expect that drug release would be faster in the paddle apparatus since dissolved drug in the diffusion layer at the surface of the pellet would be dispersed into the bulk of the dissolution fluid more rapidly under more vigorous agitation conditions, resulting in an increase in dissolution (Hanson, 1982).

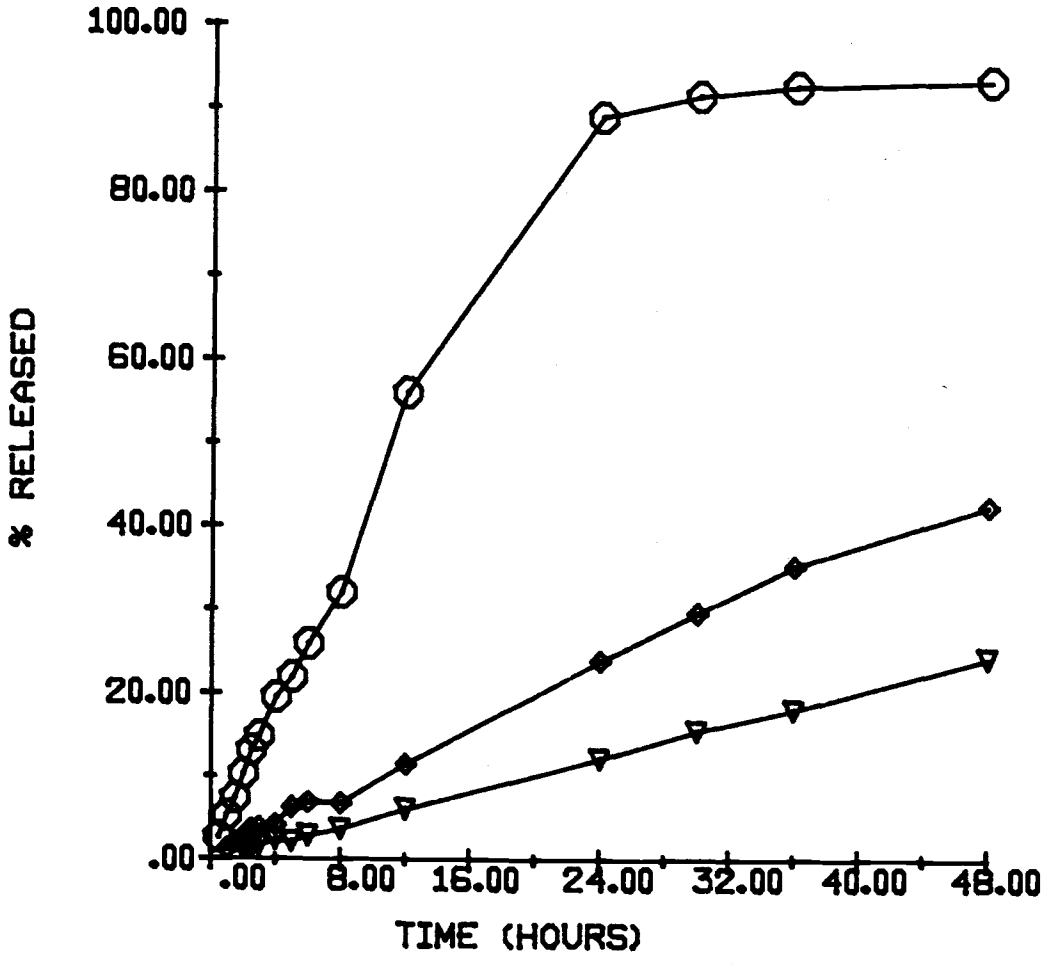

Figure II.9d *In vitro* dissolution of spray-coated acetaminophen pellets in paddle apparatus at 50 rpm. Key: (◯) 2%; (◇) 3%; (▽) 4% Aquacoat. Each point is the mean ± standard deviation of two to three replications.

Dissolution of Tablets Containing Spray-Coated Acetaminophen Pellets

Dissolution testing of uncompressed tablet formulation revealed that the presence of the chewable tablet excipient blend does not affect release of drug from coated pellets (Figure II.10a compared to Figure II.9a). This is in contrast to coated powders from which drug release is increased in the presence of sugar due to increased wetting. This suggests that release of drug from pellets occurs primarily by a diffusion or leaching process.

Release of acetaminophen from tablets containing compressed coated pellets (Figure II.10b) was more rapid than from the coated pellets alone (Figure II.10a). This effect must be due to cracking of the pellet coats during compression. This increase in dissolution was most pronounced for the thinnest coat (5% Aquacoat), as expected, since surface cracks would disrupt a thin coat more so than a thick coat. Visual inspection of the tablets over the course of the dissolution tests revealed that they do not disintegrate, and the pellet shape is retained within the tablets as they are depleted of drug. When these tablets were crushed (Figure II.10c) release was more rapid than for intact tablets (Figure II.10b), which can be explained by the pellets being spread apart. However, the extent of this

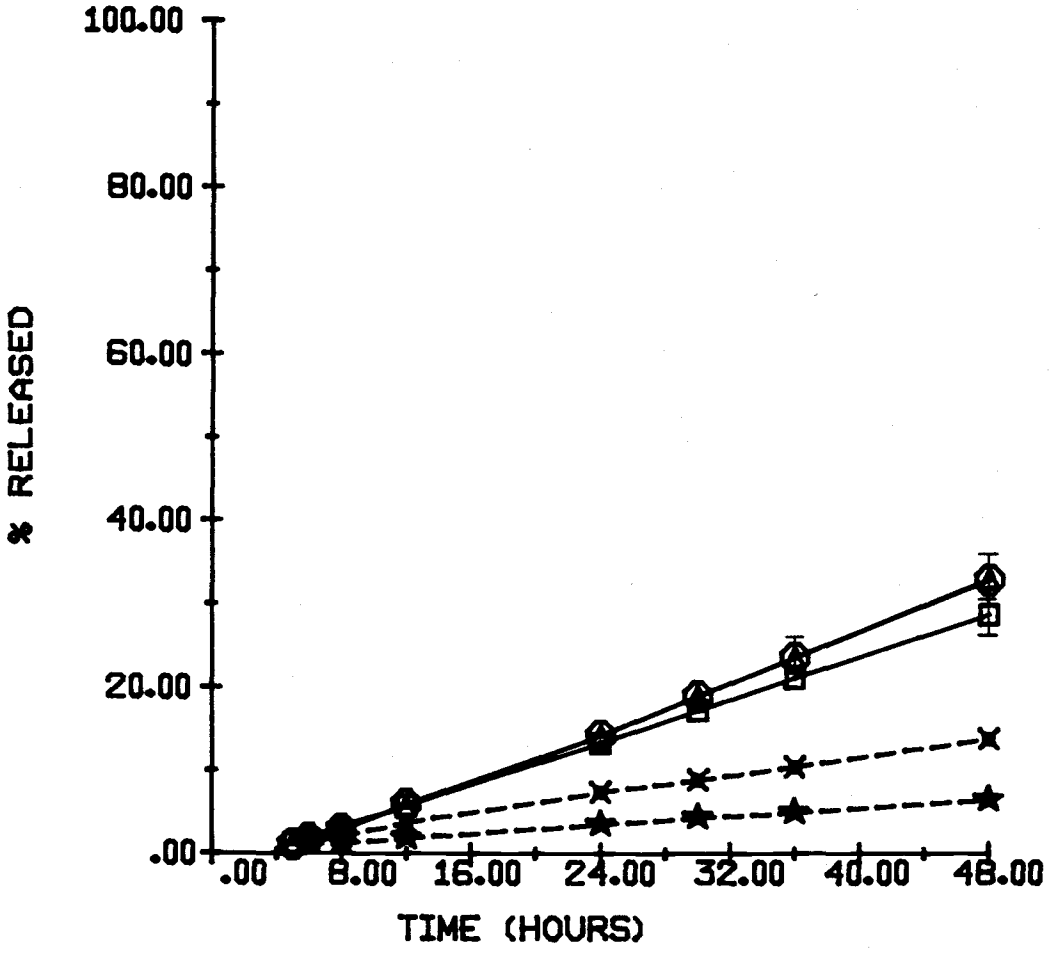

Figure II.10a In vitro dissolution of tablet formulation containing spray-coated acetaminophen pellets. Key: (———) triple coat; (□) 5% Aquacoat/ 5% Eudragit L30D/5% Aquacoat; (△) 5% Aquacoat/ 10% Eudragit L30D/5% Aquacoat; (⬡) 5% Aquacoat/ 15% Eudragit L30D/5% Aquacoat; (– – –) single coat; (✕) 5% Aquacoat; (★) 10% Aquacoat. Each point is the mean ± standard deviation of two to three replications.

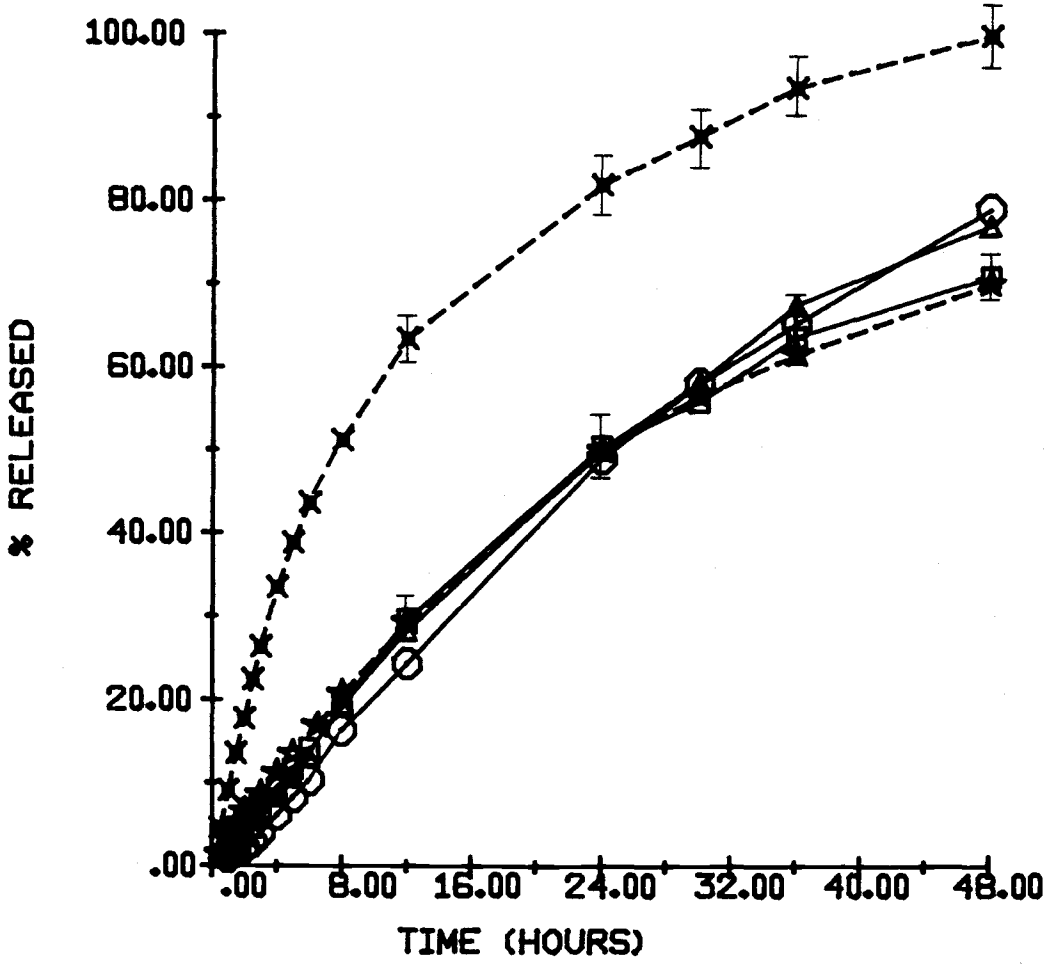

Figure II.10b *In vitro* dissolution of intact tablets containing spray-coated acetaminophen pellets. Key: (———) triple coat; (□) 5% Aquacoat/ 5% Eudragit L30D/5% Aquacoat; (△) 5% Aquacoat/ 10% Eudragit L30D/5% Aquacoat; (⬡) 5% Aquacoat/ 15% Eudragit L30D/5% Aquacoat; (– – –) single coat; (✕) 5% Aquacoat; (★) 10% Aquacoat. Each point is the mean ± standard deviation of two to three replications.

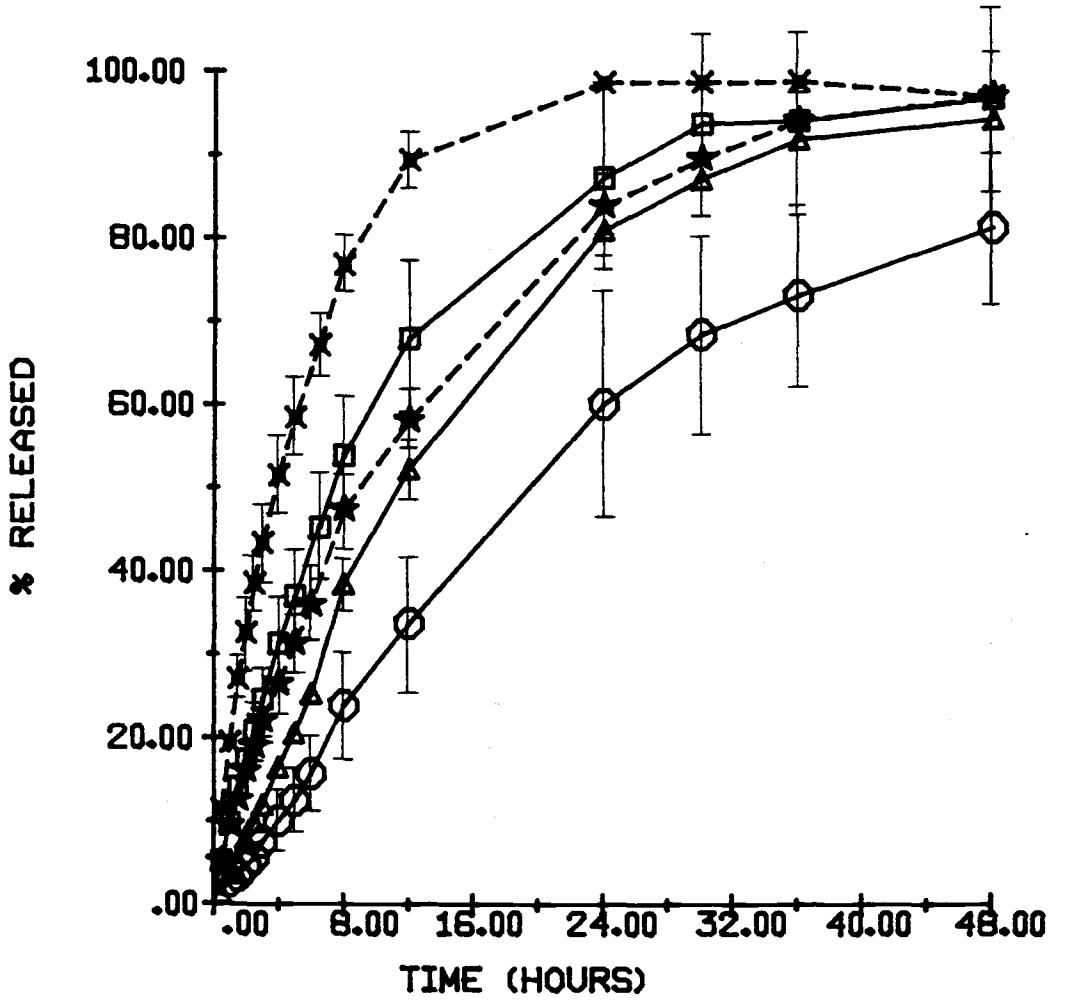

Figure II.10c In vitro dissolution of crushed tablets containing spray-coated acetaminophen pellets. Key: (——) triple coat; (□) 5% Aquacoat/ 5% Eudragit L30D/5% Aquacoat; (△) 5% Aquacoat/ 10% Eudragit L30D/5% Aquacoat; (○) 5% Aquacoat/ 15% Eudragit L30D/5% Aquacoat; (– – –) single coat; (✕) 5% Aquacoat; (★) 10% Aquacoat. Each point is the mean ± standard deviation of two to three replications.

effect was least for tablets containing the 5% Aquacoat/15% Eudragit L30D/5% Aquacoat pellets. The finding that these triple-coated pellets give about the same release pattern from intact tablets as from crushed tablets is different from any previous findings.

With the exception of tablets made with 10% Aquacoat pellets, addition of a disintegrant to the tablet formulation had little effect on drug release from such tablets (Figure II.10d). It was visually observed that after 2 hours in simulated gastric fluid, tablets containing 5% Aquacoat pellets and triple-coated pellets had only slightly disintegrated and after an additional 22 hours in simulated intestinal fluid, the pellets were still not completely spread apart as for a crushed tablet. Thus, it appears that 2.5% Ac-Di-Sol is incapable of fully breaking apart the tablet. This could be due to uneven distribution of disintegrant in the tablet formulation, since the disintegrant is composed of fine particles relative to the size of the pellets and excipient granules. Another possibility is that the plastic matrix effect of the ethylcellulose overcoat cannot be overcome by a disintegrant. Release of drug from tablets containing only 10% Aquacoat pellets was more rapid with the disintegrant than without it. This finding was inconsistent with results for the other tablets and perhaps could be explained by

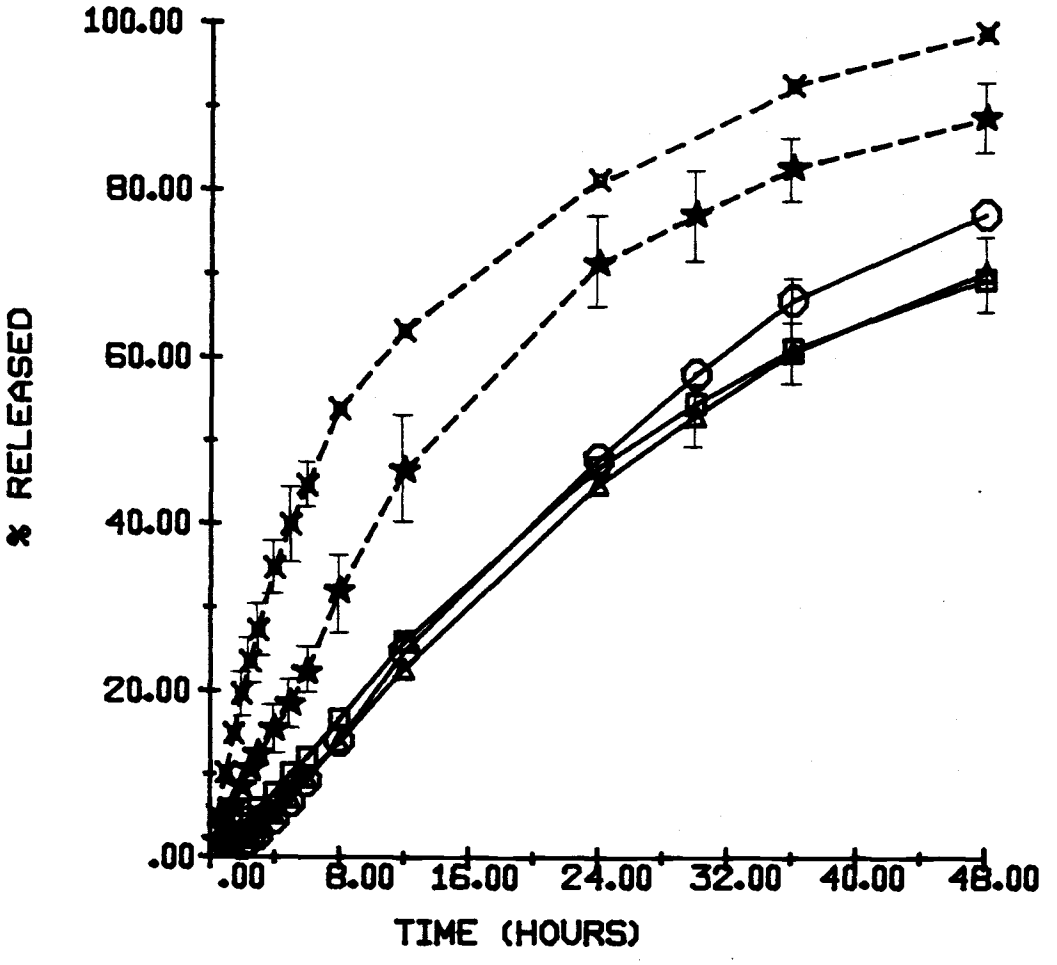

Figure II.10d *In vitro* dissolution of disintegrating tablets containing spray-coated acetaminophen pellets. Key: (———) triple coat; (□) 5% Aquacoat/ 5% Eudragit L30D/5% Aquacoat; (△) 5% Aquacoat/ 10% Eudragit L30D/5% Aquacoat; (⬡) 5% Aquacoat/ 15% Eudragit L30D/5% Aquacoat; (— — —) single coat; (✱) 5% Aquacoat; (★) 10% Aquacoat. Each point is the mean ± standard deviation of two to three replications.

uneven distribution of the disintegrant, resulting in differences in the extent of tablet disintegration. $D_{50\%}$ values for the triple-coated formulations and the 5 and 10% Aquacoat formulations are given in Table II.6 as a summary of the results discussed above.

Pellets coated with the "combination coat" composed of a mixture of Aquacoat and Eudragit E30D gave very rapid release when compressed into tablets. Crushing these tablets further increased the release rate (Figure II.11a and Table II.7). This finding is surprising because it was anticipated that a more flexible coating would be less likely to crack upon compression. However, it was observed that these pellets are ruptured by compression. They deformed inside the tablet, not retaining their original shape as do Aquacoat pellets. In addition, this coating material does not form an extensive plastic matrix when compressed. At completion of the dissolution test, the insoluble coating material is spread apart in the basket, rather than in the form of a tablet-shaped skeleton. In addition, crushing these tablets exposes free drug present inside the tablet and thus results in faster drug release and dissolution. Addition of a disintegrant to the tablets did not have much of an effect on drug release, although the mean $d_{50\%}$ values were lower for tablets with the disintegrant compared to those without it for 3 and 4%

Table II.6 Time to 50% Dissolution of Spray-Coated Acetaminophen Pellets

Coating[b]	$t_{50\%}$[a], hr			
	Pellets	Intact Tablets[d]	Crushed Tablets	Tablets with Disintegrant
5% AQ/15% E-L30D/5% AQ	>48	24.6±0.6	20.0±5.7	25.4±1.1
5% AQ/10% E-L30D/5% AQ	46.7±2.9	23.9±0.1	11.4±1.1	28.2±2.7
5% AQ/5% E-L30D/5% AQ	>48	24.1±2.6	7.5±1.4	26.5±0.4
5% AQ	>84	7.7±0.6	3.8±0.6	7.2±0.4
10% AQ	>84	24.3±1.5	9.0±1.7	13.9±3.2

[a]Each value is the mean ± standard deviation for 2-3 replications.

[b]AQ is Aquacoat and E-L30D is Eudragit L30D. Inner coat is listed first.

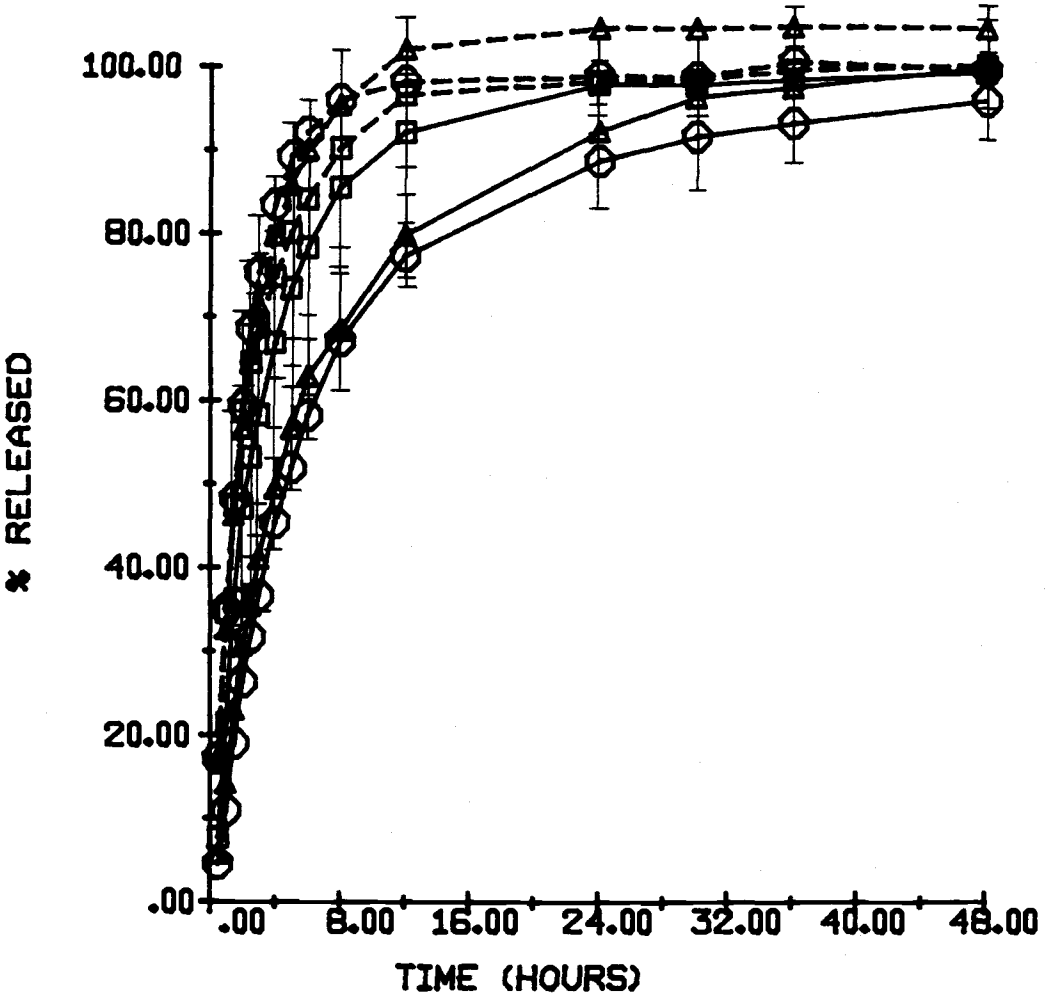

Figure II.11a *In vitro* dissolution of intact (———) and crushed (– – –) tablets containing spray-coated acetaminophen pellets. Key: (□) 2%; (△) 3%; (○) 4% Aquacoat and Eudragit E30D "combination coat". Each point is the mean ± standard deviation of two to three replications.

Table II.7 Time to 50% Dissolution of Acetaminophen Pellets Spray Coated with "Combination Coat"

Coating[b]	$t_{50\%}$[d], hr[a] Pellets	Intact Tablets	Crushed Tablets	Tablets With Disintegrant
2% AQ & E-E30D	14.7±0.5	2.5±1.2	1.7±0.6	4.0±1.9
3% AQ & E-E30D	21.2±1.1	4.1±1.0	1.7±0.1	3.4±1.1
4% AQ & E-E30D	25.8±0.1	4.7±0.5	1.6±0.0	2.9±0.7

[a] Each value is the mean ± standard deviation for 2 replications.

[b] AQ is Aquacoat and E-E30D is Eudragit E30D.

combination coats, and were higher for tablets containing pellets with a 2% "combination coat" (Figures II.11a and II.11b; Table II.7).

Results described in the above paragraph were consistent with expectation based on the literature. That is, compression forces applied to the tablet ruptured the pellets and destroyed the controlled drug release. Crushing of tablets further destroyed any residual controlled release effects. These results, consistent with expectation, make the results with some of the previously described coated pellets quite surprising. For example, Table II.6 shows some coated pellets which gave extended controlled drug release from intact and crushed tablets.

Wall Thickness of Spray-Coated Powders and Pellets

Tables II.8a and II.8b give the estimated thickness of the ethylcellulose and Eudragit L30D coats on the spray-coated powders and pellets. For drug particles having more than one coat, the diameter was adjusted to account for the thickness of the first coat by adding the thickness of the inner coat to the drug particle radius and then multiplying this value by 2 to obtain the new diameter. This diameter was then used to determine the thickness of the second coat. However, no adjustment was made with regard to particle density. The assumption was made that the density of the first

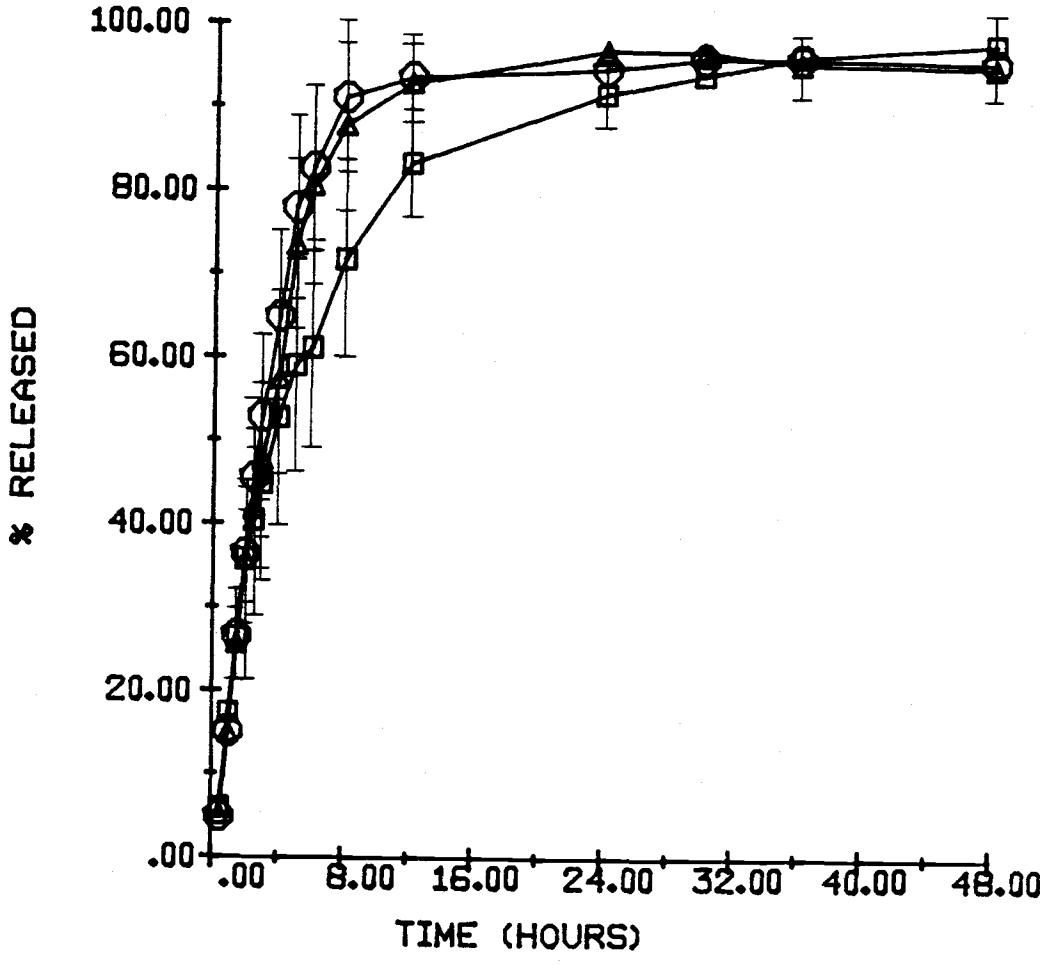

Figure II.11b In vitro dissolution of disintegrating tablets containing spray-coated acetaminophen pellets. Key: (□) 2%; (△) 3%; (⬡) 4% Aquacoat and Eudragit E30D "combination coat". Each point is the mean ± standard deviation of two to three replications.

Table II.8a Approximate Wall Thickness and Time to 50% Dissolution of Spray-Coated Acetaminophen Powders

Coating[a]	Thickness, μm Inner	Center	Outer	Total	$d_{50\%}$, hr
uncoated acetaminophen					1.3
2.5% AQ				0.37	1.8
5.0% AQ				0.75	2.5
10% AQ				1.59	1.7
20% AQ				3.58	2.7
2.5% E-L30D				0.49	1.4
5.0% E-L30D				1.01	2.0
10% E-L30D				2.14	2.5
20% E-L30D				4.81	3.0
20% E-L30D/2.5% AQ	4.81		0.41	5.22	3.8
20% E-L30D/5% AQ	4.81		0.85	5.66	4.8
20% E-L30D/10% AQ	4.81		1.79	6.60	6.3
10% E-L30D/2.5% AQ	2.14		0.39	2.53	1.9
10% E-L30D/5% AQ	2.14		0.80	2.94	1.7
10% E-L30D/10% AQ	2.14		1.68	3.82	2.2
5% E-L30D/2.5% AQ	1.01		0.38	1.39	2.0
5% E-L30D/5% AQ	1.01		0.77	1.78	2.0
5% E-L30D/10% AQ	1.01		1.63	2.64	2.1
2.5% E-L30D/2.5% AQ	0.49		0.37	0.86	1.9
2.5% E-L30D/5% AQ	0.49		0.76	1.25	1.9
2.5% E-L30D/10% AQ	0.49		1.61	2.10	1.7
20% AQ/2.5% E-L30D	3.58		0.54	4.12	2.2
20% AQ/5% E-L30D	3.58		1.11	4.69	2.7
20% AQ/10% E-L30D	3.58		2.34	5.92	4.0
10% AQ/2.5% E-L30D	1.59		0.51	2.10	2.5
10% AQ/5% E-L30D	1.59		1.06	2.65	2.6
10% AQ/10% E-L30D	1.59		2.23	3.82	3.2
5% AQ/2.5% E-L30D	0.75		0.50	1.25	2.4
5% AQ/5% E-L30D	0.75		1.03	1.78	2.1
5% AQ/10% E-L30D	0.75		2.18	2.93	2.3
2.5% AQ/2.5% E-L30D	0.37		0.50	0.87	1.1
2.5% AQ/5% E-L30D	0.37		1.02	1.39	1.6
2.5% AQ/10% E-L30D	0.37		2.16	2.53	2.3
5% AQ/10% E-L30D/5% AQ	0.75	2.18	0.81	3.74	3.4
5% AQ/20% E-L30D/5% AQ	0.75	4.91	0.87	6.53	3.3
10% AQ/10% E-L30D/10% AQ	1.59	2.23	1.75	5.57	4.3
10% AQ/20% E-L30D/10% AQ	1.59	5.01	1.87	8.47	6.3

[a] AQ is Aquacoat and E-L30D is Eudragit L-30D. Inner coat is listed first.

Table II.8b Approximate Wall Thickness and Time to 50% Dissolution of Spray-Coated Acetaminophen Pellets[a]

Coating[b]	Thickness, μm Inner	Center	Outer	Total	$d_{50\%}$, hr
0.5% AQ				1.24	0.8
1.0% AQ				2.48	1.4
2.0% AQ				5.02	12.9
3.0% AQ				7.61	>48
4.0% AQ				10.3	>48
5.0% AQ				12.9	>84
10.0% AQ				27.3	>84
5% AQ/5% E-L30D/5% AQ	12.9	17.8	13.6	44.3	>48
5% AQ/10% E-L30D/5% AQ	12.9	37.5	14.0	64.4	46.7
5% AQ/15% E-L30D/5% AQ	12.9	59.6	14.4	86.9	>48

[a] Uncoated pellet size is 1.29±0.09 from sampling of 25 pellets.

[b] AQ is Aquacoat and E-L30D is Eudragit L30D. Inner coat is listed first.

coat has little effect on the overall density of the particle, so the drug density was used in calculations of overcoat thicknesses. For Aquacoat-coated pellets, the density of acetaminophen was also used to calculate the coating thickness, although the pellet is composed of a non-pareil sugar seed. However, the exact content of this seed is not known and thus no correction for the contribution of the density of this material could be made. Representative calculations are given in Appendix A. Because several assumptions were made in calculating the coating thickness, the values given in Tables II.8a and II.8b represent only approximate wall thicknesses and are useful in making comparisons among various coated pellets rather than statements about the actual magnitude of the values.

As expected, the wall thickness of coated acetaminophen powders was quite thin, and this accounts for the fairly rapid release observed from most of these powders. The thickest coat obtained for double-coated powders was 6.6 μm for the 20% Eudragit L30D/10% Aquacoat particles. Even the highest coating combination of the triple-coated powders (10% Aquacoat/ 20% Eudragit L30D/10% Aquacoat) had a total coat thickness of only about 8.5 μm. As discussed in Chapter I, such coating thicknesses should have little effect on retarding drug release from small particles. However,

$d_{50\%}$ for both of these formulations was about five times that of uncoated acetaminophen powder (6.3 versus 1.3 hours) which is quite surprising.

Comparisons between $d_{50\%}$ and coating thickness for coated powders (Table II.8a) revealed that a total thickness of at least 3.8 µm was necessary to achieve a $d_{50\%}$ of $\geq$3 hours. The double-coated powder having a 20% Eudragit L30D/10% Aquacoat wall and the 5% Aquacoat/ 20% Eudragit L30D/5% Aquacoat triple-coated powder both had a total coating thickness of 6.6 µm, yet the double-coated powder dissolved more slowly ($d_{50\%}$ of 6.31 hours versus 3.28 hours). Thus, such a triple coating for powders does not retard drug release relative to double-coated powders having equivalent total coating thicknesses. Note that the triple-coated powder (10% Aquacoat/20% Eudragit L30D/10% Aquacoat) having the thickest total coat of 8.5 µm had a $d_{50\%}$ of 6.31 hours, which is equivalent to that of the 20% Eudragit L30D/ 10% Aquacoat formulation having a 6.6 µm coat.

Coatings for the pellets (Table II.8b) were thicker than for powders at the same weight percentages of coating, as expected, since the total surface area is lower for larger sized particles. Thus, larger particles may be more effectively and uniformly coated (as expected), which is also demonstrated by the *in vitro* dissolution results. For coated pellets there was

no delay in drug release until the coating thickness was greater than 2.5 µm (Table II.8b). Also, release was faster from triple-coated pellets with thicker total coats (44 to 87 µm versus <27 µm for single coats of ≤10% Aquacoat). This establishes that the center enteric coat is somehow unexpectedly increasing the rate of drug release rather than delaying it. Thus, the process of dissolution can no longer be considered to be simply diffusion controlled.

Release Patterns

Theoretical aspects regarding drug release from small, spherical particles, as well as actual findings from the literature, were discussed in Chapter I. Some *in vitro* dissolution data for spray-coated acetaminophen powders and pellets and dosage forms containing these formulations were plotted as log of percent drug unreleased versus time to determine whether drug release could be described by a first order process since many of these formulations did not exhibit zero order release patterns. In addition, percent released versus square root of time plots were made since such a dependency has been described for monolithic devices which consist of drug homogeneously dispersed in a release-rate-controlling membrane (Baker and Lonsdale, 1974). Release from coated particles and pellets should not follow such a pattern. However, such a relationship may

exist for tablets containing these formulations since ethylcellulose may form a plastic matrix when compressed, and it has already been shown that several of these tablets do not disintegrate, but leave a hollow, ethylcellulose shell at completion of dissolution.

Release patterns for several of the spray-coated powders do not appear to follow either first order or square root of time relationships (Figures II.12-II.14). However, for particles with outer ethylcellulose coats (Figure II.13) the log of percent unreleased versus time plots are approaching linearity for the higher coating levels (20% Eudragit L30D/ 10% Aquacoat and 20% Eudragit L30D/5% Aquacoat) which indicates that first order release may apply for said particles. This was also observed for the triple-coated acetaminophen powders with outer ethylcellulose coats from which the release of drug appears to be a sum of at least two first order processes over the first 12 hours of dissolution (Figure II.14).

Release from intact and crushed tablets containing coated acetaminophen powders are adequately described by a combination of first order processes, as well (Figures II.15 and II.16). Square root of time plots were curved.

Many coated pellets produced zero order release

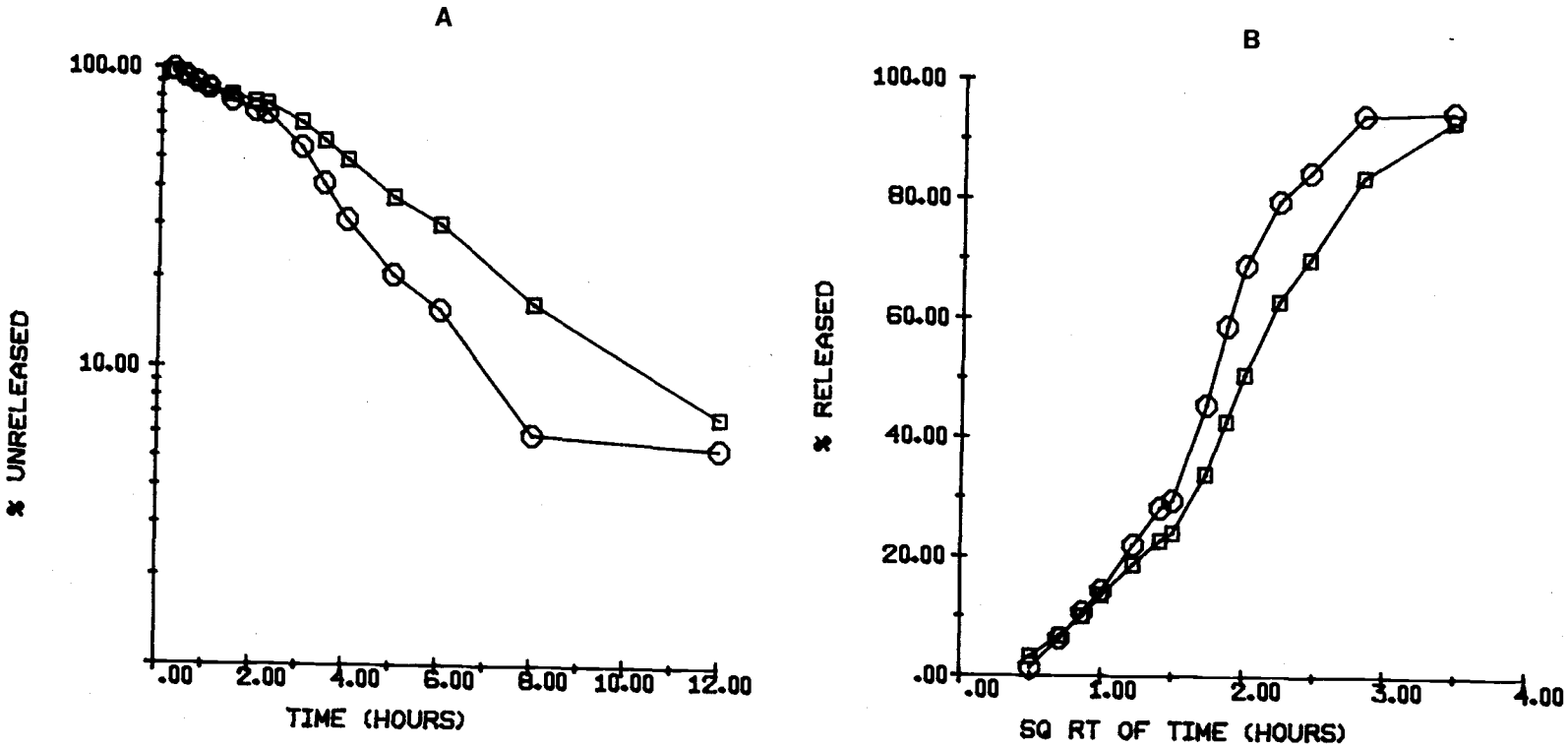

Figure II.12 In vitro dissolution of spray-coated acetaminophen powders: (A) percent acetaminophen unreleased versus time; (B) percent acetaminophen released versus square root of time. Key: (□) 20% Aquacoat/10% Eudragit L30D; (◯) 10% Aquacoat/10% Eudragit L30D. Each point is the mean of two to six replications.

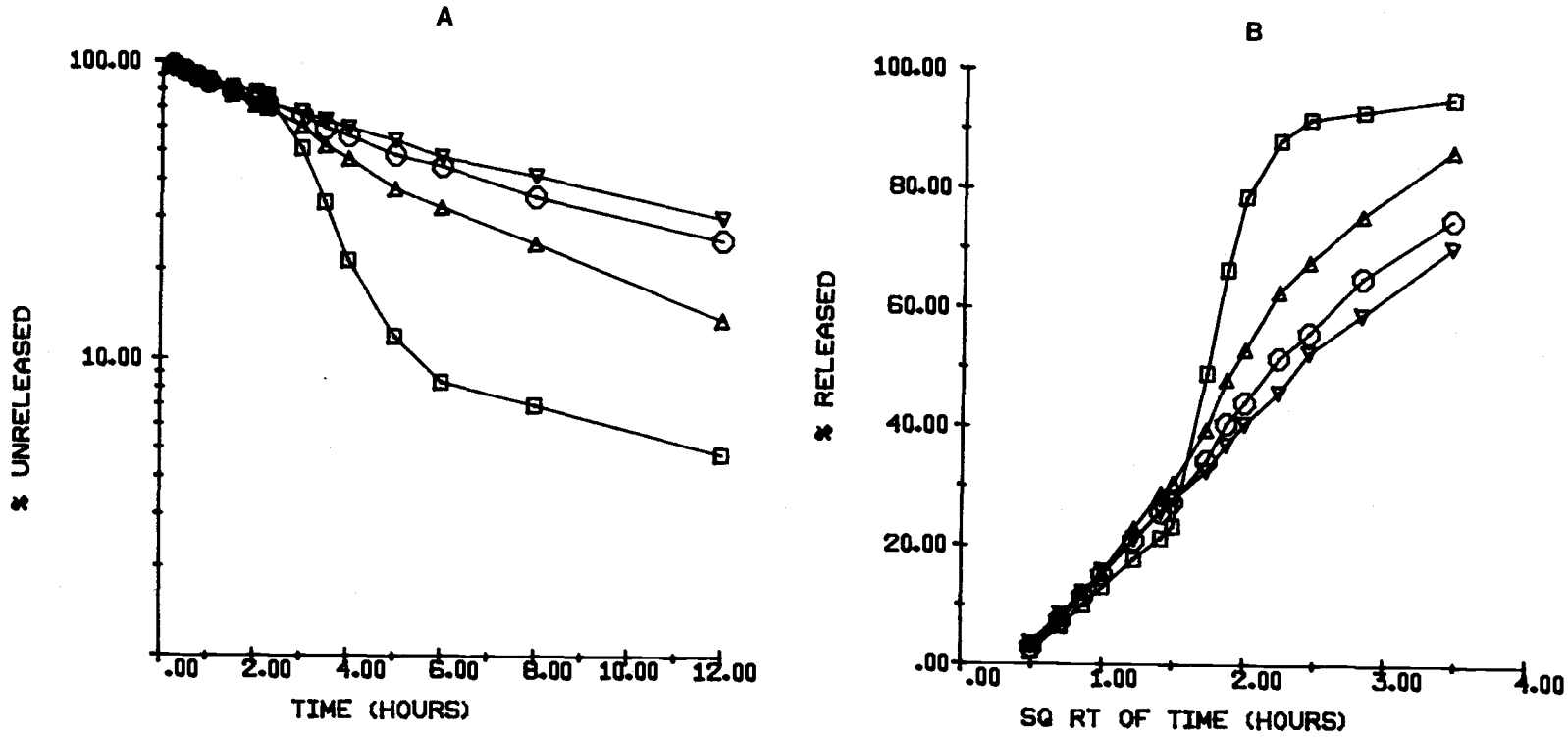

Figure II.13 In vitro dissolution of spray-coated acetaminophen powders with 20% Eudragit L30D inner coat: (A) percent acetaminophen unreleased versus time; (B) percent acetaminophen released versus square root of time. Key: (□) 0%; (△) 2.5%; (◯) 5%; (▽) 10% Aquacoat overcoat. Each point is the mean of two to six replications.

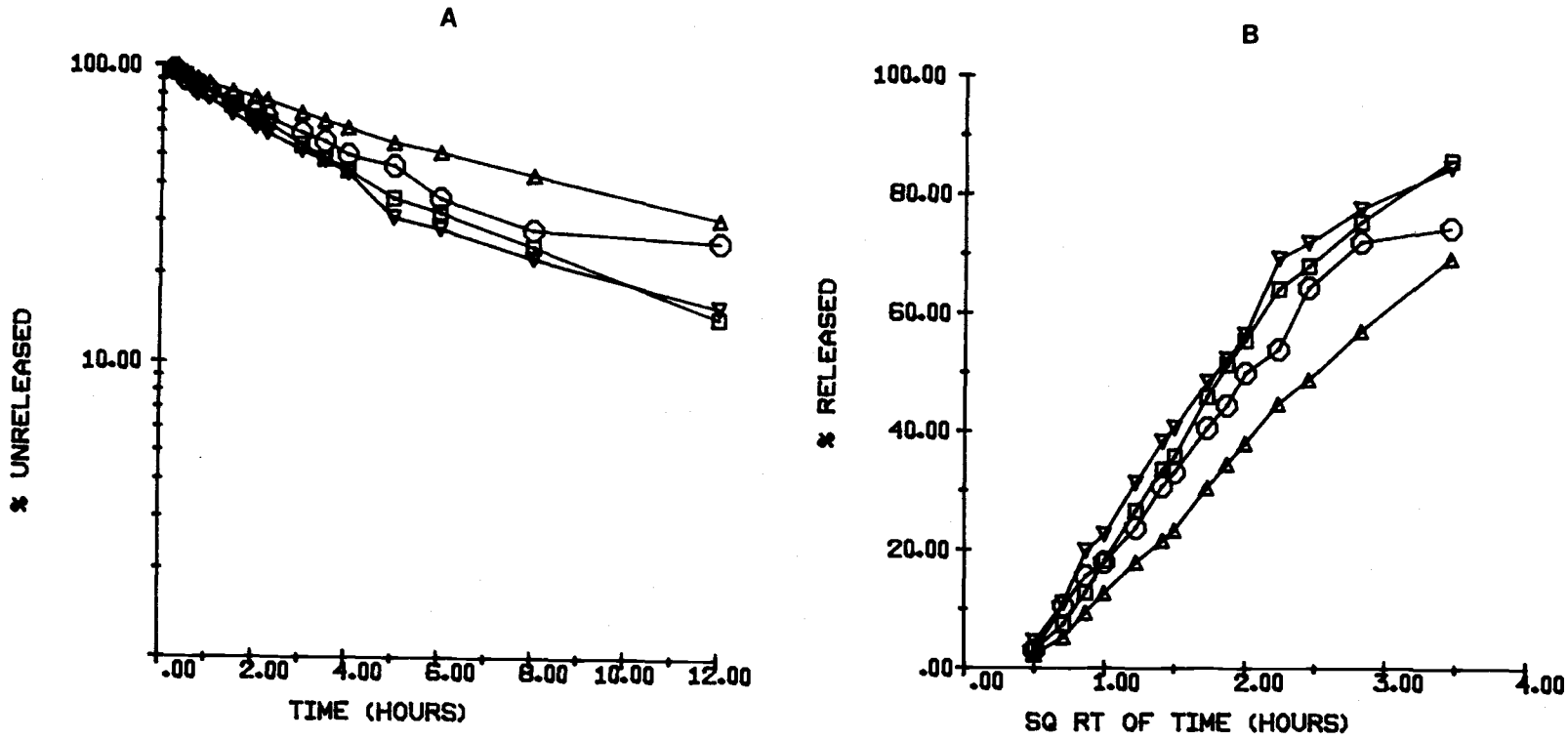

Figure II.14 In vitro dissolution of triple-coated acetaminophen powders: (A) percent acetaminophen unreleased versus time; (B) percent acetaminophen released versus square root of time. Key: (□) 5% Aquacoat/ 10% Eudragit L30D/5% Aquacoat; (▽) 5% Aquacoat/20% Eudragit L30D/5% Aquacoat; (○) 10% Aquacoat/10% Eudragit L30D/10% Aquacoat; (△) 10% Aquacoat/ 20% Eudragit L30D /10% Aquacoat. Each point is the mean of three replications.

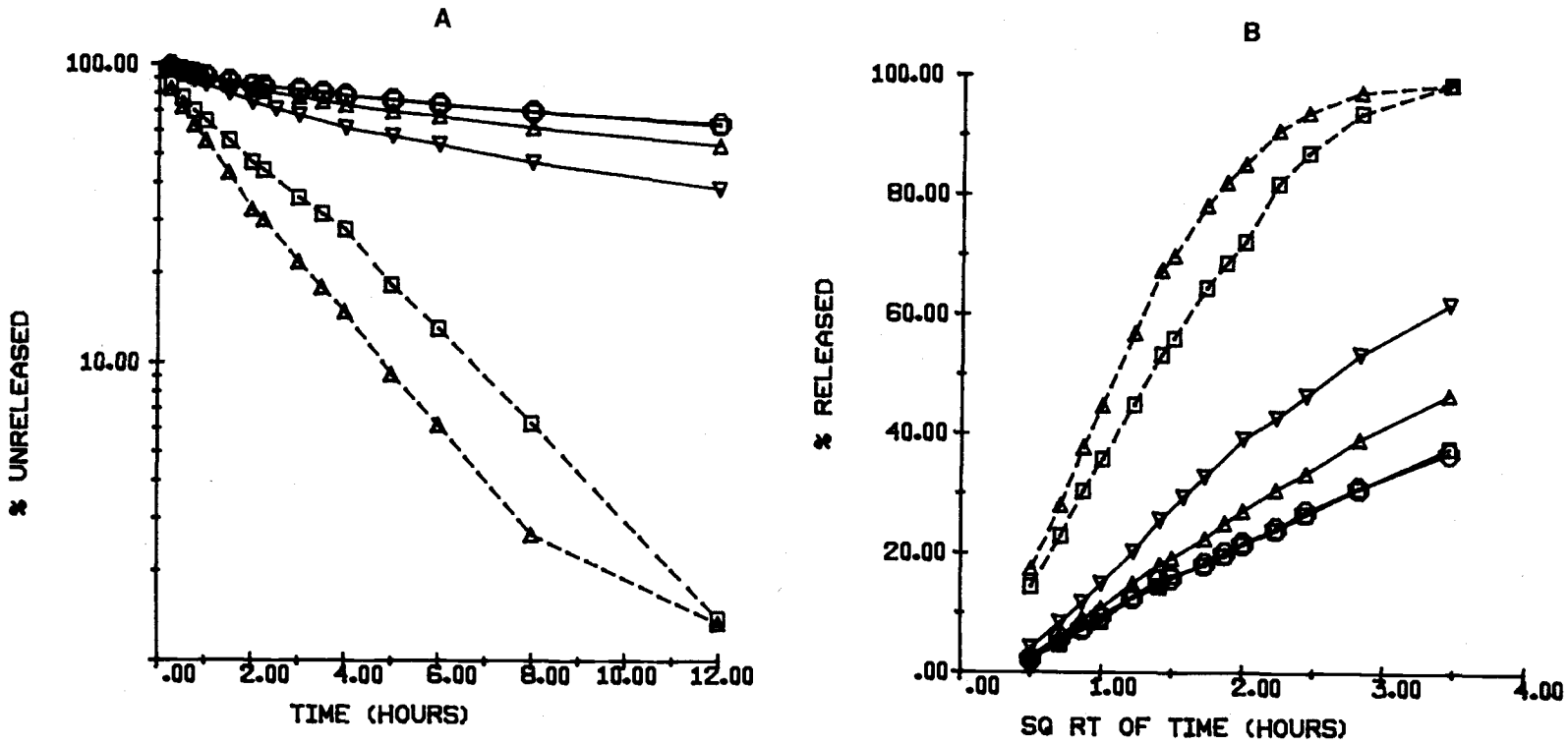

Figure II.15 In vitro dissolution of intact (———) and crushed (– – –) tablets containing spray-coated acetaminophen powder: (A) percent acetaminophen unreleased versus time; (B) percent acetaminophen released versus square root of time. Key: (□) 20% Aquacoat plus acetaminophen granules; (◯) 20% Aquacoat; (△) 10% Aquacoat; (▽) 5% Aquacoat. Each point is the mean of two to three replications.

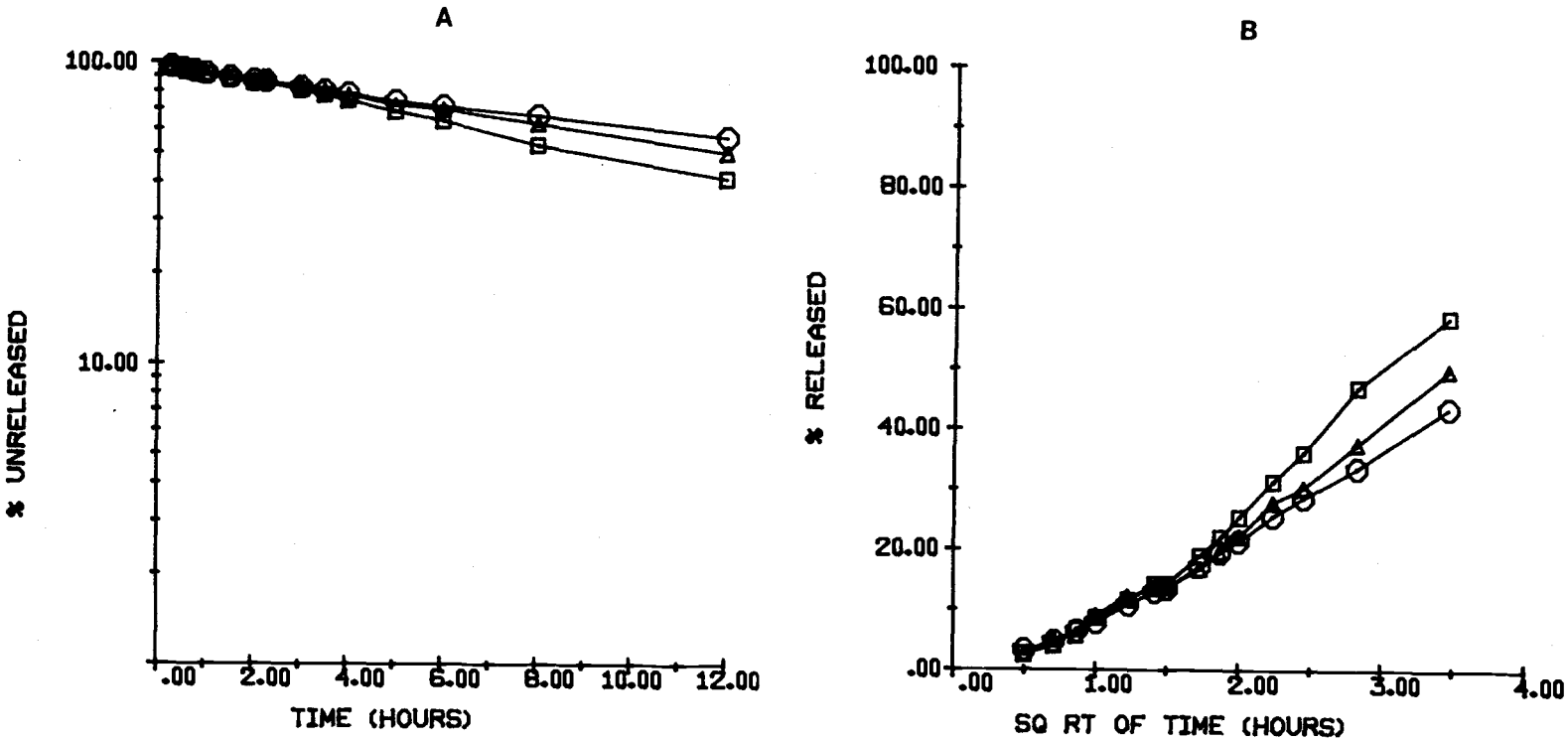

Figure II.16 In vitro dissolution of intact tablets containing spray-coated acetaminophen powder with 20% Eudragit L30D inner coat: (A) percent acetaminophen unreleased versus time; (B) percent acetaminophen released versus square root of time. Key: (□) 2.5%; (△) 5%; (○) 10% Aquacoat overcoat. Each point is the mean of two to three replications.

patterns, as seen previously in Figures II.9a and II.9c. This is as expected for spherical, reservoir controlled release devices (Baker and Lonsdale, 1974; Bakan, 1980). However, Aquacoat pellets with thin coats (0.5 and 1.0%) gave rapid first order release of drug over the first 90% of drug release (Figure II.17) while release from the 2% Aquacoat pellets was not first order. Release from pellets with a combination coating of Aquacoat and Eudragit E30D could not be described by either a first order or zero order process (Figures II.9b and II.18).

Compression of pellets which had apparent zero order *in vitro* drug release into tablets altered the release pattern considerably as seen in Figure II.19. The release is apparently a combination of several processes since a square root of time plot gave nonlinear dissolution profiles while first order plots were somewhat linear. This was also observed for tablets containing pellets coated with the Aquacoat and Eudragit E30D "combination coat" (Figure II.20), although in this case the drug release from pellets alone was not zero order.

In summary, the release patterns from spray-coated acetaminophen formulations are complex and cannot be described by any one process. This was also found to be true for microencapsulated acetaminophen in Chapter I.

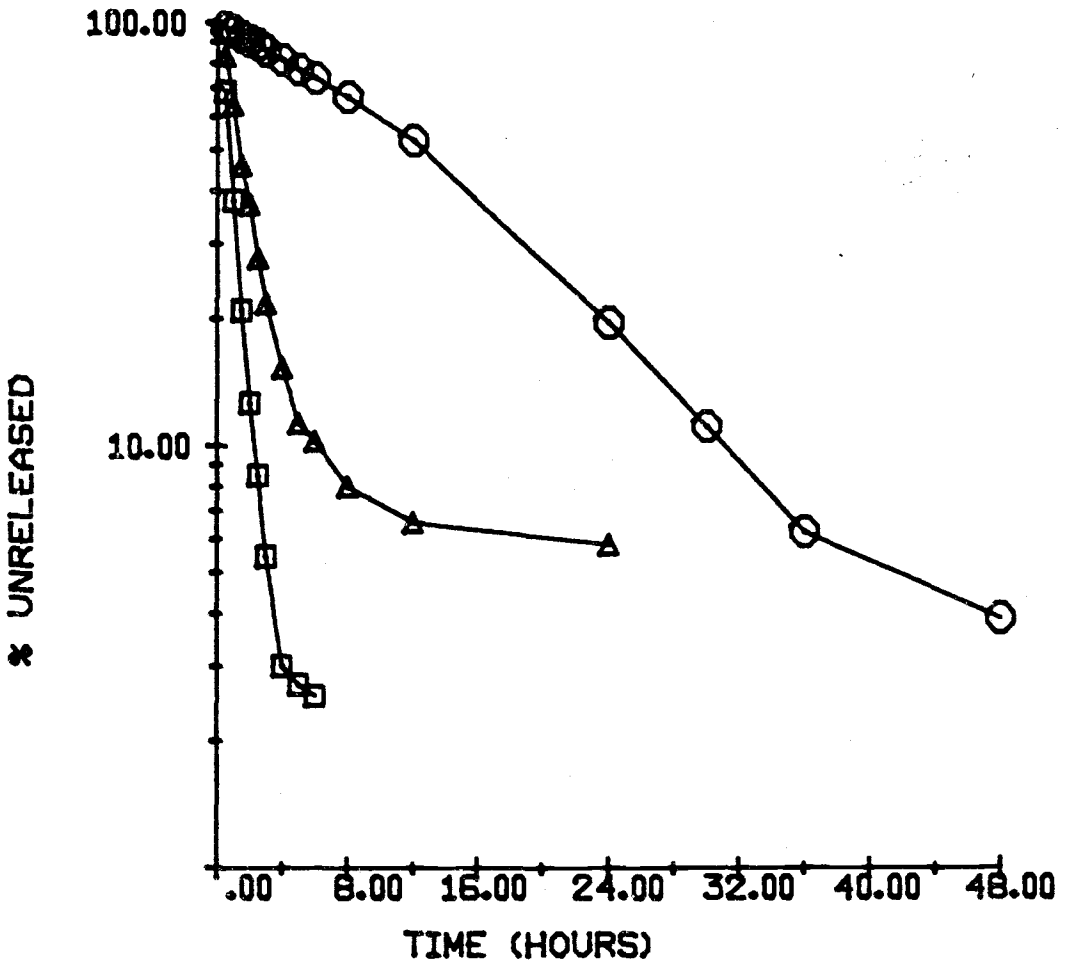

Figure II.17 In vitro dissolution of spray-coated acetaminophen pellets: percent acetaminophen unreleased versus time. Key: (□) 0.5%; (△) 1%; (○) 2% Aquacoat. Each point is the mean of two to three replications.

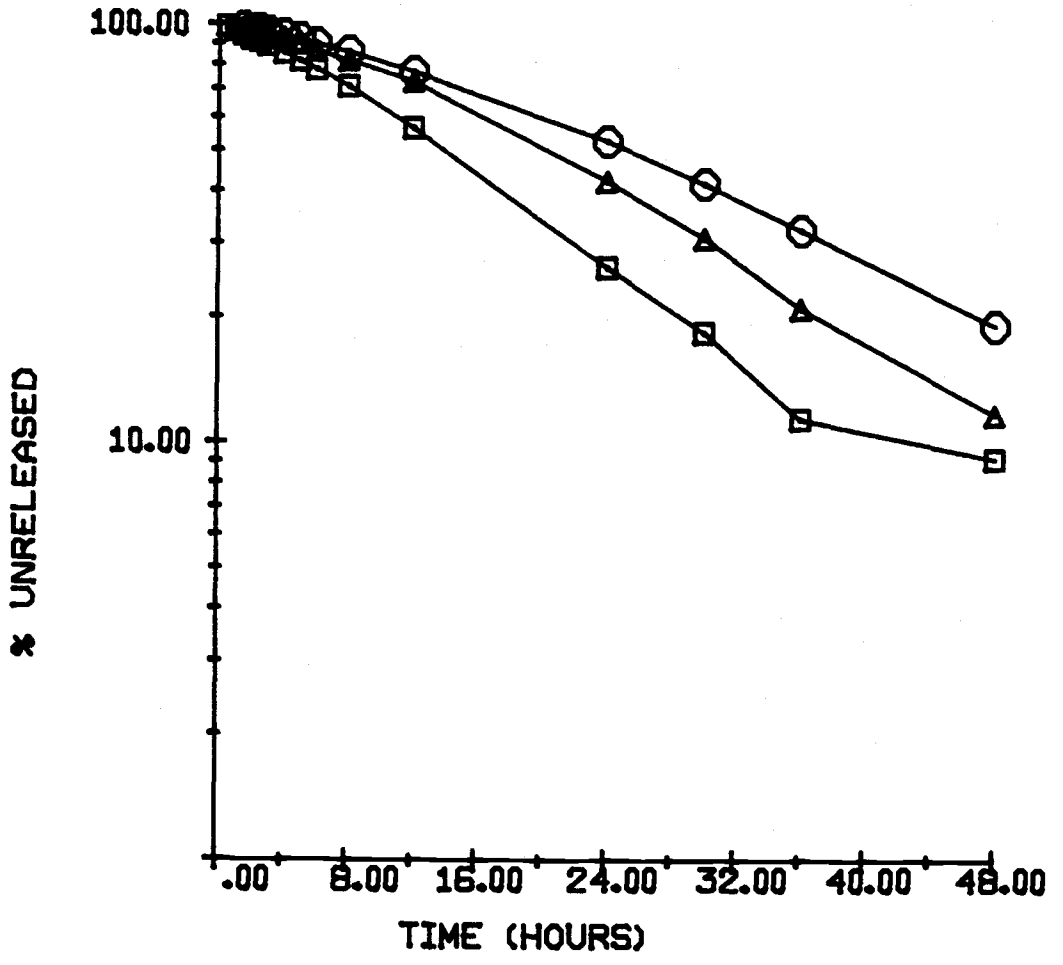

Figure II.18 In vitro dissolution of spray-coated acetaminophen pellets: percent acetaminophen unreleased versus time. Key: (□) 2%; (△) 3%; (⬡) 4% Aquacoat and Eudragit E30D "combination coat". Each point is the mean of two to three replications.

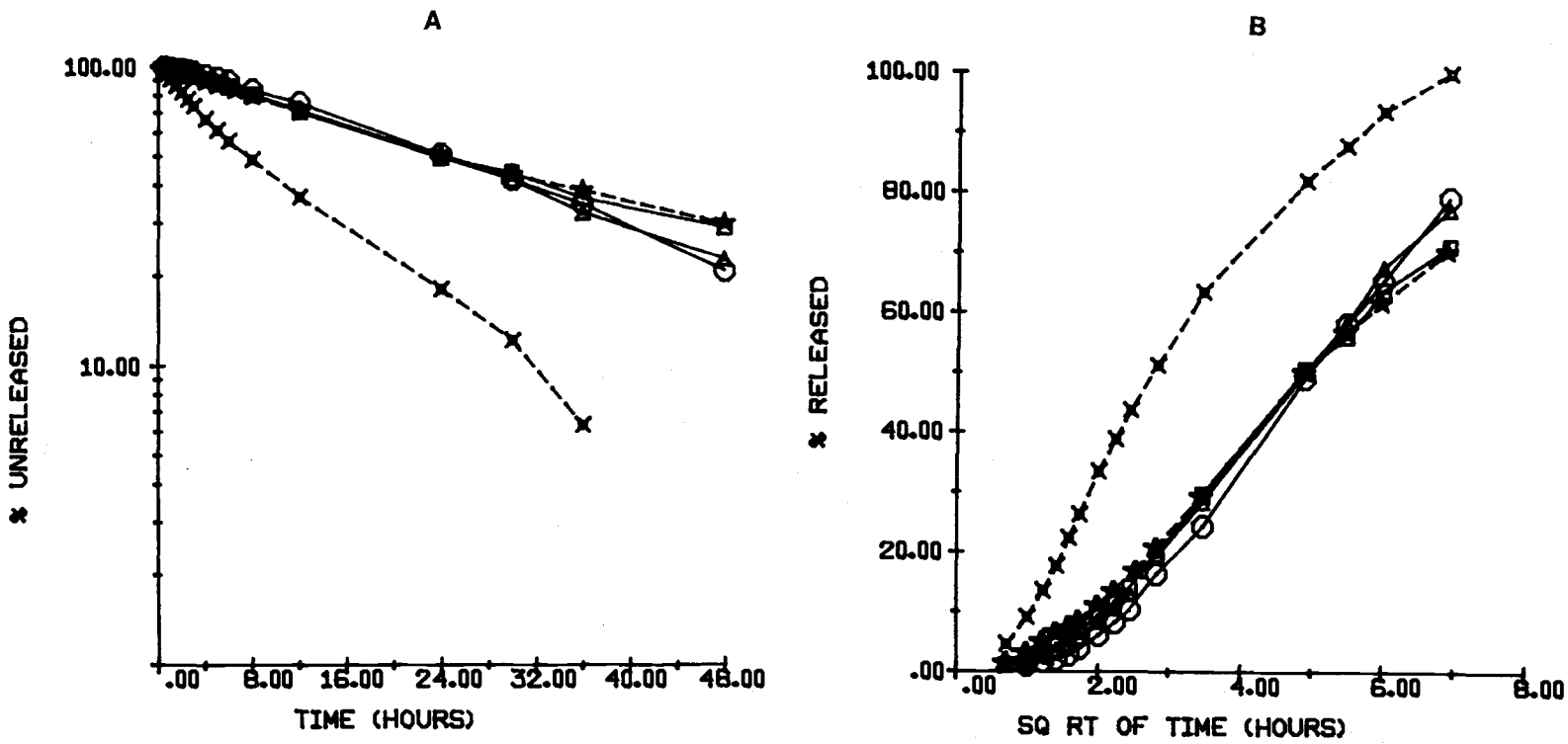

Figure II.19 In vitro dissolution of intact tablets containing spray-coated acetaminophen pellets: (A) percent acetaminophen unreleased versus time; (B) percent acetaminophen released versus square root of time. Key: (———) triple coat; (□) 5% Aquacoat/5% Eudragit L30D/5% Aquacoat; (△) 5% Aquacoat/10% Eudragit L30D/5% Aquacoat; (⬡) 5% Aquacoat/15% Eudragit L30D/5% Aquacoat; (– – –) single coat; (✕) 5% Aquacoat; (★) 10% Aquacoat. Each point is the mean of two to three replications.

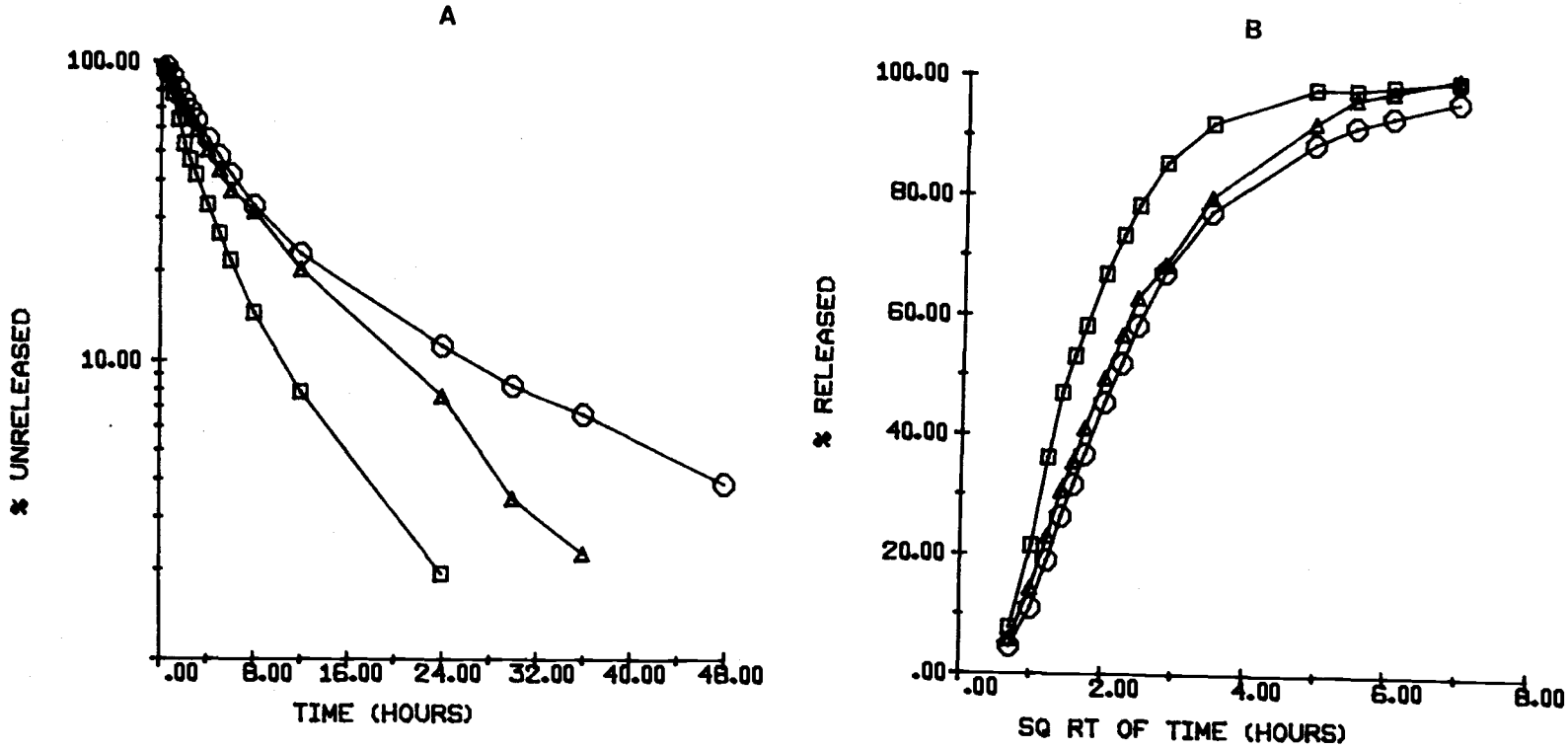

Figure II.20 In vitro dissolution of intact tablets containing spray-coated acetaminophen pellets: (A) percent acetaminophen unreleased versus time; (B) percent acetaminophen released versus square root of time. Key: (□) 2%; (△) 3%; (○) 4% Aquacoat and Eudragit E30D "combination coat". Each point is the mean of two to three replications.

Bioavailability and Pharmacokinetics of Spray-Coated Acetaminophen Dosage Forms

Saliva acetaminophen concentrations in one subject following oral administration of several dosage forms containing spray-coated acetaminophen powder and pellets are given in Figures II.21a and II.21b. This data provides some preliminary information only regarding drug release from spray-coated formulations *in vivo* and is meant as a tool. It may be useful when taken in combination with *in vitro* dissolution data to indicate trends.

Dosage forms containing the highest and lowest coating combinations of spray-coated acetaminophen powder showed differences in saliva drug levels. *In vivo* release of drug from the 2.5% Eudragit L30D/2.5% Aquacoat powder administered in two size 00 hard gelatin capsules (Figure II.21a) was similar to that of commercial immediate release tablets (Figure I.13 in Chapter I) and thus no sustained release of drug occurred. This is consistent with rapid dissolution *in vitro* ($d_{50\%}$ approximately 2 hours). The apparent elimination half-life of 3.5 hours was also equivalent to the value obtained for commercial tablets.

The spray-coated product with a double coat of 20% Eudragit L30D/10% Aquacoat provided a peak saliva drug concentration of 8.5 µg/ml at 90 minutes post dosing

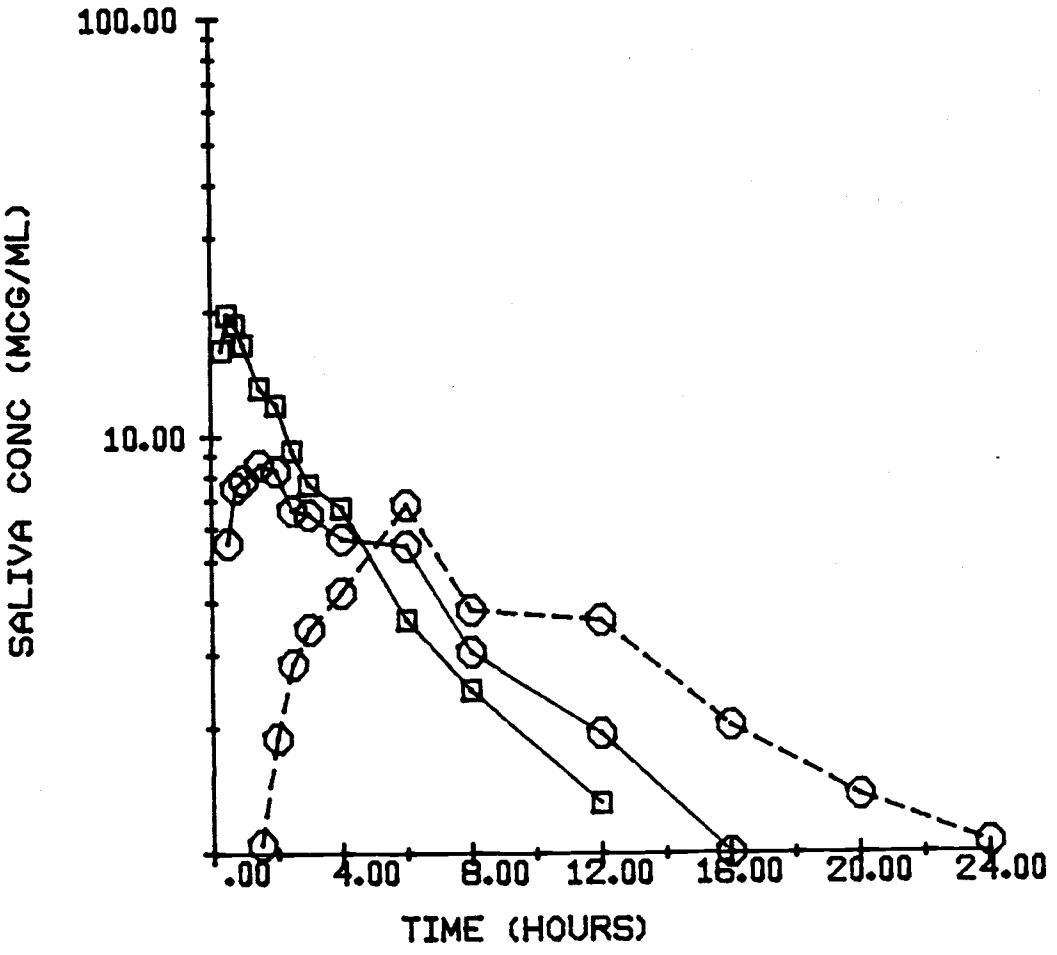

Figure II.21a Saliva acetaminophen concentrations in one subject following administration of spray-coated acetaminophen powder formulations. Key: (———) fasting conditions; (– – –) with food; (▢) 2.5% Eudragit L30D/2.5% Aquacoat in two size 00 capsules (1250 mg dose); (◯) 20% Eudragit L30D/10% Aquacoat in two size 00 capsules (1300 mg dose).

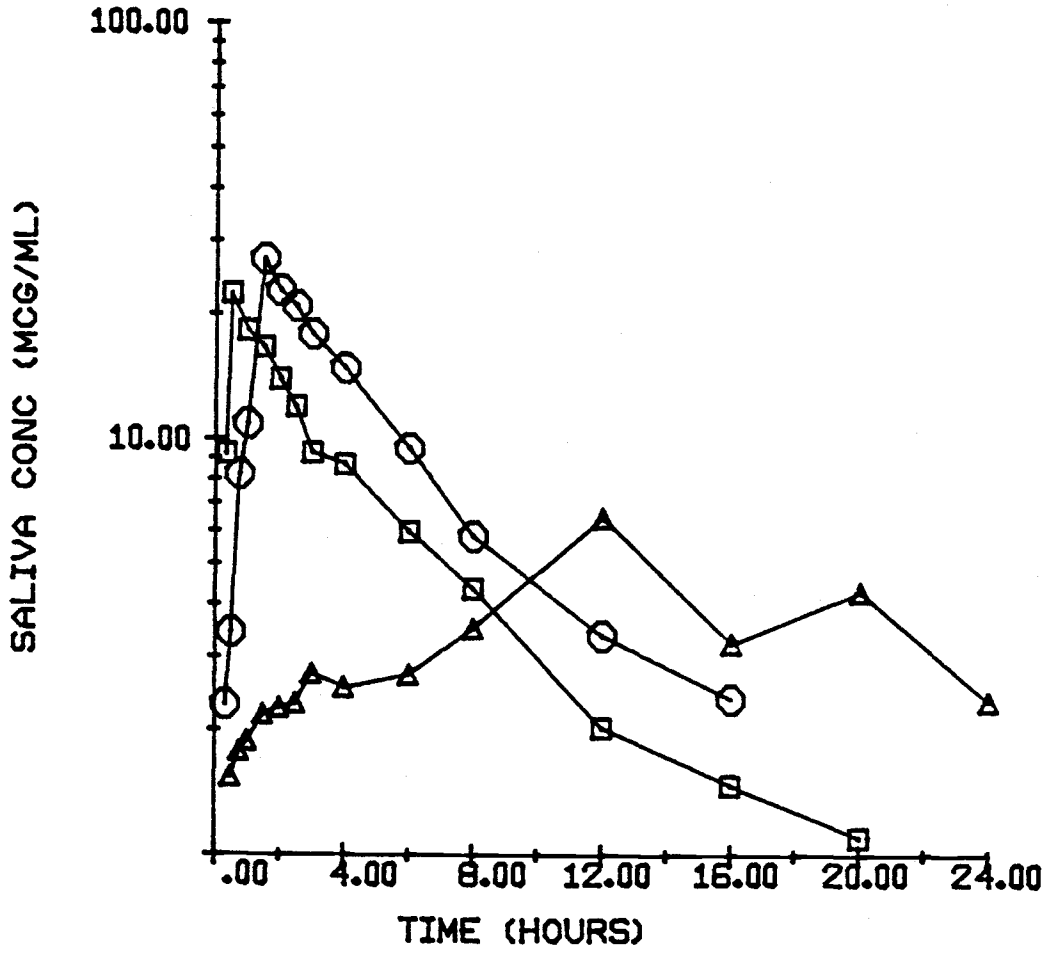

Figure II.21b Saliva acetaminophen concentrations in one subject following administration of spray-coated acetaminophen powder formulations. Key: (□) 20% Eudragit L30D/10% Aquacoat tablet formulation in two size 00 capsules (1530 mg dose); (△) 20% Eudragit L30D/ 10% Aquacoat tablets (1500 mg dose); (◯) 2.5% Eudragit L30D/2.5% Aquacoat tablets (2000 mg dose).

(Figure II.21a). This level decreased slowly to approximately 5 µg/ml at 6 hours post dosing and then declined according to first order kinetics over the next 10 hours. Thus, a sustained release effect was achieved, and absorption was delayed since the apparent elimination rate constant increased to 5 hours (Table II.9). This is consistent with dissolution results which indicated delayed release of drug ($d_{50\%}$ of 6.3 hours). When this treatment was administered immediately after a high calorie, high carbohydrate meal, absorption was delayed (Figure II.21a). A peak saliva drug concentration of 6.9 µg/ml was not attained until 6 hours post dosing and was less than the peak concentration achieved for administration under fasting conditions (8.5 µg/ml at 90 minutes post dosing). In addition, the apparent elimination half-life was prolonged even more from 5 to 8.5 hours (Table II.9), which reflects continued absorption occurring throughout the terminal portion of the curve. The area under the curve for the two treatments was virtually equivalent and actually slightly higher for capsules administered with food (Table II.9). Thus, food delayed the rate, but not the extent, of acetaminophen absorption, as has been reported in the literature (Jaffe et al., 1971; McGilveray and Mattock, 1972).

In vivo release of drug from the tablet formulation

Table II.9 Pharmacokinetic Parameters Following Administration of Spray-Coated Acetaminophen Powder Formulations

Treatment[a]	Dose, g	k_{el}[b], hr^{-1}	$t_{1/2}$[c], hr	t_p[d], hr	C_p[e], µg/ml	$AUC_{0\rightarrow\infty}$, µg-hr/ml	F[f]
2.5% E-L30D/2.5% AQ in two size 00 capsules	1.25	0.198	3.50	0.5	19.7	76.37	0.96
20% E-L30D/10% AQ in two size 00 capsules	1.30	0.139	4.99	1.5	8.5	67.14	0.81
20% E-L30D/10% AQ in capsules with food	1.30	0.082	8.45	6.0	6.9	73.47	0.88
20% E-L30D/10% AQ tablet formulation in two size 00 capsules	1.53	0.076	9.12	0.5	22.4	107.20	1.10
20% E-L30D/10% AQ tablets	1.50	0.069	10.04	12.0	6.5	99.99	1.04
2.5% E-L30D/2.5% AQ tablets	2.00	0.112	9.96	1.5	27.1	146.50	0.91

[a] AQ is Aquacoat and E-L30D is Eudragit L30D. Inner coat is listed first.
[b] Apparent elimination rate constant.
[c] Apparent half-life.
[d] Time to peak.
[e] Peak saliva acetaminophen concentration.
[f] F is the ratio of the AUC (adjusted for dose) for each treatment to the AUC for the commercial product, Tylenol, at the 1.5 g or 2.0 g dose.

containing 20% Eudragit L30D/10% Aquacoat powder was somewhat different than from coated powder alone when administered in gelatin capsules (Figure II.21b). A peak drug concentration of 22 µg/ml was achieved for the capsule at only 30 minutes post dosing with a subsequent decline in the saliva drug concentration. However, when the formulation was compressed into tablets, there was a dramatic decrease in saliva acetaminophen levels, and a peak drug concentration of 6 µg/ml was not attained until 12 hours post dosing (Figure II.21b). Thus, there is a definite sustained release effect provided by these intact tablets, and this *in vivo* behavior correlates with *in vitro* dissolution tests, since $d_{50\%}$ values for the tablet formulation and intact tablets were about 2.5 and 16 hours, respectively. Tablets containing the 2.5% Eudragit L30D/2.5% Aquacoat formulation showed little delay in drug release, with a peak concentration being achieved at 90 minutes post dosing followed by a biphasic decline in drug concentration (Figure II.21b). These tablets had a $d_{50\%}$ of approximately 5 hours, which suggests that an *in vitro* time to 50% dissolution of >5 hours is necessary to obtain sustained release of acetaminophen *in vivo*. Further work with more than one subject is needed to confirm this trend.

Several pharmacokinetic parameters for these dosage forms are given in Table II.9. They were calculated as

described in Chapter I. The bioavailability was determined relative to that of commercial acetaminophen tablets which were administered to this same subject as part of a different study, which is the topic of Chapter III. The area under the curve ($AUC_{0\rightarrow\infty}$) for the spray-coated formulations was divided by AUC of the commercial tablets at the 1.5 g dose and then corrected to account for differences in the dose, giving the relative bioavailability which is listed in the last column of the table. The AUC for a 2.0 g dose of the commercial tablets was used to determine the relative bioavailability of the tablets containing the 2.5% Eudragit L30D/2.5% Aquacoat powder.

Peak concentrations were lower for formulations exhibiting sustained release and for the formulation administered with food (Table II.9). The apparent elimination half-life was prolonged for all treatments, even those for which no apparent decrease in absorption rate was observed from saliva concentration curves. This probably means that some absorption is still occurring through the terminal portion of the curve. However, the actual magnitude of these values does not correlate well with the time to peak which is also an estimate of the rate of absorption. The bioavailability was virtually equivalent to that of commercial tablets, with exception of the 20% Eudragit L30D/10% Aquacoat

formulation in hard gelatin capsules which had a bioavailability of 0.80. With only one subject and a single administration of this treatment, it is difficult to ascertain whether this decrease in bioavailability is a true effect or one that is due to single study or intrasubject variability, such as an increase in GI transit time, particularly because the same treatment administered with food gave a higher bioavailability (0.88). A decrease in bioavailability would seem to be more likely for intact tablets, since they exhibited slower *in vitro* release and are a non-disintegrating dosage form. However, the 20% Eudragit L30D/10% Aquacoat formulation compressed into tablets was bioequivalent to the commercial tablets (F=1.04). In Chapter I it was found that when acetaminophen microcapsules with a 2.5% ethylcellulose coat were compressed into tablets, the relative bioavailability was quite low (F=0.56). Thus, with only these preliminary results, the question of bioequivalency cannot be further addresssed. The trends however, are quite useful since $d_{50\%}$ correlates with *in vivo* effects as discussed earlier.

Tablets containing 5% Aquacoat/10% Eudragit L30D/ 5% Aquacoat or 5% Aquacoat/15% Eudragit L30D/ 5% Aquacoat pellets (3 tablets, 500 mg acetaminophen per tablet, giving a total dose of 1.5 g) were administered

to this same subject. The subject chewed the tablets quite thoroughly and commented that he felt the pellets collapsing between his teeth, and that the taste was quite bitter (indicating that drug has been released in the mouth). Acetaminophen saliva concentrations are given in Figure II.22 and pharmacokinetic parameters in Table II.10. There was some sustained drug release from these thoroughly chewed tablets. Apparent bioavailability was variable (1.0 for one dose and 0.72 for the other). The apparent half-life was 4.2 to 5.2 hours versus about 3.8 hours for this subject following administration of immediate release commercial tablets (1.5 g). The low bioavailability for one formulation may be an artifact due to underestimation of AUC at the early time points where acetaminophen concentrations cannot be measured in saliva because of residual drug in the mouth.

Based on *in vitro* data alone, it would be expected that chewed tablets containing triple-coated acetaminophen pellets would provide extensive sustained drug release, but such an effect was not observed *in vivo*. The slight prolongation in apparent half-life and the shape of the saliva drug concentration-time curve indicates continuing absorption at later times, which could have been due to sustained drug release from pellets which were not completely destroyed by chewing.

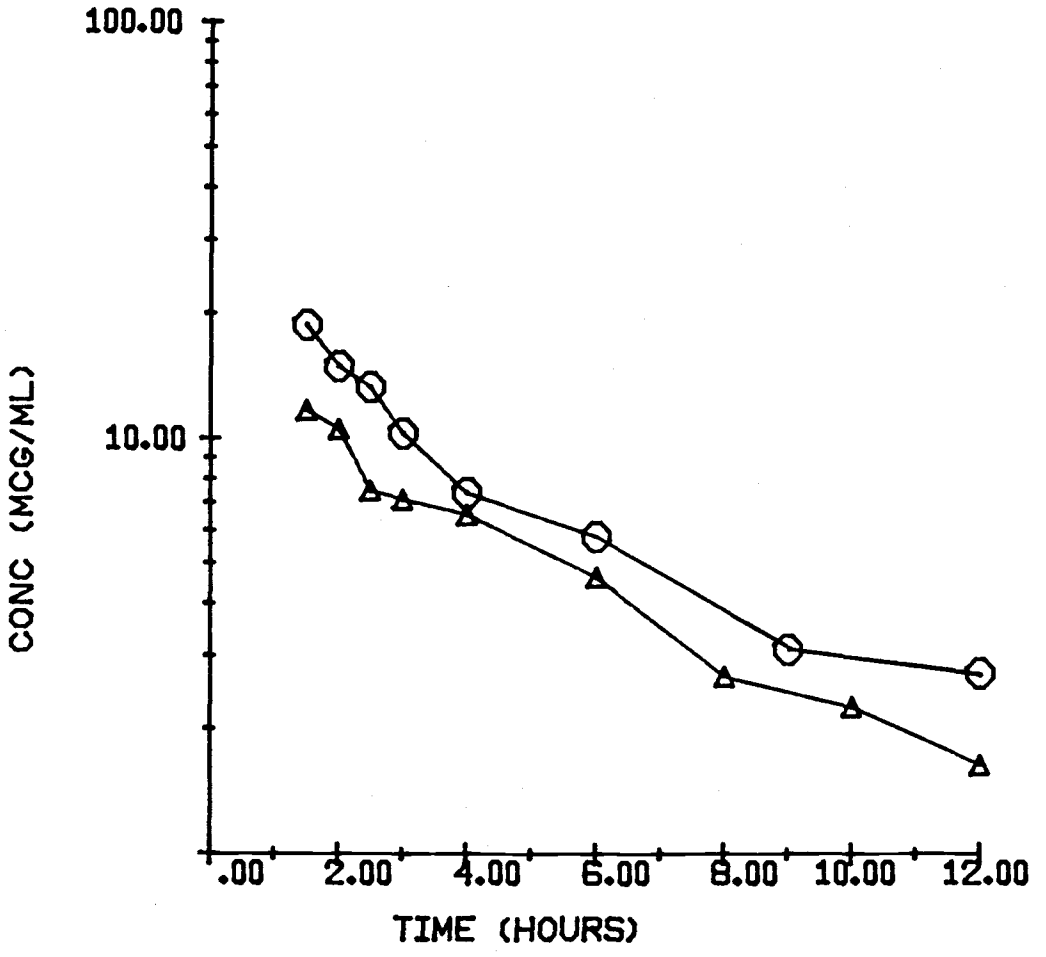

Figure II.22 Saliva acetaminophen concentrations in one subject following administration of chewable tablets containing triple-coated acetaminophen pellets. Key: (◯) 5% Aquacoat/10% Eudragit L30D/5% Aquacoat; (△) 5% Aquacoat/15% Eudragit L30D/5% Aquacoat.

Table II.10 Pharmacokinetic Parameters Following Administration of Chewable Tablets Containing Triple-Coated Acetaminophen Pellets

Treatment[a]	Dose, g	k_{el}[b], hr^{-1}	$t_{1/2}$[c], hr	$AUC_{0\rightarrow\infty}$, µg-hr/ml	F[d]
5% AQ/15% E-L30D/5% AQ	1.5	0.164	4.23	69.63	0.73
5% AQ/10% E-L30D/5% AQ	1.5	0.133	5.21	93.18	0.97

[a] AQ is Aquacoat and E-L30D is Eudragit L30D.

[b] Apparent elimination rate constant.

[c] Apparent half-life.

[d] F is the ratio of the AUC for each treatment to the AUC for the commercial product, Tylenol, at the 1.5 g dose.

CONCLUSION

Several spray-coated acetaminophen powders, pellets, and dosage forms provided delayed drug release *in vitro*. Powder having a 20% Eudragit L30D inner coat and a 10% outer ethylcellulose coat or triple-coated powder having the 10% Aquacoat/20% Eudragit L30D/10% Aquacoat had the slowest *in vitro* release. Not surprisingly, they also had the thickest total coatings, but the coats were still so thin that no delay in drug release would be expected based on literature reports. There appears to be no advantage to applying an additional 10% inner coat of Aquacoat prior to application of the enteric coat since dissolution profiles were similar for double- and triple-coated powders. When spray-coated powders were incorporated into tablets, drug release was slowest from tablets containing powder having 20% Aquacoat, and drug release increased as the amount of coating decreased. Crushing these tablets destroyed the plastic matrix formed by compression of a polymer, thus resulting in extremely rapid release. This suggested that spray coating acetaminophen powder cannot provide sustained release chewable tablets. Spray-coated acetaminophen pellets had very slow *in vitro* drug release, but when incorporated into tablets, drug release was more rapid,

presumably due to cracking of the outer pellet coat. When a disintegrant was added, drug release was about the same because the tablet did not completely break up. Crushing such tablets resulted in further increases in dissolution rate. However, tablets containing 5% Aquacoat/15% Eudragit/5% Aquacoat had similar *in vitro* release profiles when tested intact or crushed. The "combination coat" of Aquacoat and Eudragit L30D on acetaminophen pellets at coating levels of 3 and 4% provided faster drug release than that from pellets with single ethylcellulose coats of 3 and 4%, respectively. In addition, tablets containing these pellets gave rapid drug release due to deformation and rupturing of the coating upon compression, which is quite different from what occurred with the previously described pellets. Preliminary *in vivo* data for several of these dosage forms was in agreement with *in vitro* dissolution data. Sustained release was achieved for intact tablets containing 20% Eudragit L30D/10% Aquacoat coated powder. Chewing tablets containing triple-coated pellets provided only a slight prolonged release effect, and this was quite different from expectations based on *in vitro* dissolution of these crushed tablets. However, such tablets could still be useful as a crushed, rather than chewed, dosage form.

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CHAPTER III

DOSE DEPENDENT PHARMACOKINETICS AND BIOAVAILABILITY OF ACETAMINOPHEN

ABSTRACT

Saliva acetaminophen concentrations were determined in 15 subjects after administration of five different doses of commercial acetaminophen tablets (325 to 2000 mg acetaminophen). Saliva acetaminophen concentration-time profiles for individuals were adequately described with bi- or triexponential equations. Statistically significant differences ($p<0.05$) in elimination rate, mean residence time, and the ratio of area under the curve to dose were found between treatments (doses), suggestive of dose-dependent pharmacokinetics and metabolism. These findings can be explained by saturation of presystemic hepatic biotransformation at doses >500 mg. To offset any significant losses in the amount of drug systemically available, a sustained release dosage form for acetaminophen should include an immediate release portion.

INTRODUCTION

The objective of this study was to determine whether the pharmacokinetics and metabolism of acetaminophen are dose dependent. This research topic was of particular interest since it has important implications regarding the development and testing of sustained release acetaminophen oral dosage forms. If saturation of presystemic biotransformation occurs at higher doses of acetaminophen, as has been suggested by Rawlins et al. (1977), then slowing drug release from a dosage form would slow drug input, which would prevent saturation of presystemic metabolism from occurring. Thus, therapeutic drug concentrations might not be achieved and apparent bioavailability of acetaminophen from a sustained release preparation would be significantly reduced. This could explain why tablets containing microencapsulated acetaminophen had low bioavailability (Chapter I).

The systemic availability study conducted by Rawlins et al. (1977) suggested that saturation of presystemic biotransformation occurs at doses greater than 500 mg since the apparent bioavailability was significantly less after 500 mg than after 1000 mg or 2000 mg orally. Reduced bioavailability at an oral dose of 625 mg was also reported by Ameer et al. (1983). In

Rawlins' study, no difference in half-life was observed between doses. The study was conducted with only six subjects and three oral doses. In addition, plasma acetaminophen concentrations were monitored for only 6 hours post dosing.

The present study was conducted with 15 subjects, each of whom received five different oral doses of acetaminophen. Saliva samples were collected for 16 hours post dosing. Four of these subjects had participated in a pilot study which examined the feasibility of using saliva acetaminophen levels in determination of pharmacokinetic parameters. Mean saliva acetaminophen levels have been reported to be proportional and virtually equivalent to serum levels (Glynn and Bastain, 1973; Ahmed and Enever, 1981; Adithan and Thangam, 1982). An HPLC method for measuring acetaminophen concentration in saliva was developed which was a modification of an assay used by Gwilt (1984).

MATERIALS AND METHODS

Fifteen healthy male and female volunteers (Table III.1) participated in this study after giving informed written consent. All participants were taking no other medications during and one week prior to study initiation and had no history of chronic disease. In addition, no alcohol was allowed on treatment days. Each volunteer received five different doses of commercial acetaminophen tablets: 1) one 325 mg tablet Tylenol, Lot No. SF0099S (McNeil, Fort Washington, PA); 2) one 500 mg tablet Tylenol Extra-Strength, Lot No. SSF187 (McNeil, Fort Washington, PA); 3) two Tylenol Extra-Strength 500 mg tablets (1000 mg dose); 4) three Tylenol Extra-Strength 500 mg tablets (1500 mg dose); 5) four Tylenol Extra-Strength 500 mg tablets (2000 mg dose). Treatments were administered on five separate occasions separated by at least three days according to a randomized block design (Snedecor and Cochran, 1980a). Subjects fasted at least 12 hours prior to dosing and for an additional two hours post dosing. Tablet(s) were swallowed with six fluid ounces of water, immediately followed by a mouthwash rinse with 20 ml Scope mouthwash (Proctor and Gamble, Cincinnnati, OH) in an attempt to remove any drug that may have adsorbed to the buccal mucosa. Saliva samples were collected by chewing on

Table III.1 Vital Statistics of Subjects Participating in Bioavailability Study

Subject No.	Sex	Age, yrs	Weight, kg
1	F	25	50.8
2	F	34	50.8
3	M	44	77.1
4	M	24	77.1
5	F	23	56.7
6	F	29	43.1
7	M	26	60.8
8	F	30	68.0
9	M	27	68.0
10	M	27	63.5
11	M	45	81.6
12	M	35	73.5
13	M	28	77.1
14	F	28	53.1
15	M	29	72.6
Mean		30.3	64.9
SD[a]		6.6	11.9
Range		23-45	43.1-81.6

[a]Standard deviation.

Parafilm (American Can Co., Greenwich, CT) squares (one-inch by one-inch) for one minute with simultaneous spitting into 12 ml centrifuge tubes. Samples were collected by each subject at 0, 10, 20, 30, 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 16 hours. Saliva was centrifuged at 3000 rpm for 25 minutes to remove mucous and particulate matter. Salivary supernatant was transferred to a polypropylene container with a lock cap and frozen at $-20^{o}C$ until analyzed.

Concentrations of acetaminophen in saliva were determined by the HPLC method described in Chapter I. The sensitivity of this assay was about 1 µg/ml.

Data were analyzed by AUTOAN2 (Sedman and Wagner, 1972) except where noted otherwise. Data from a pilot study (four subjects), which was conducted under the same conditions as described above, was included in the analysis. Saliva concentrations were fitted to a linear sum of two or three exponential terms. Coefficients and exponents from fitted functions were used to calculate pharmacokinetic parameters and the mean residence time (MRT) which involves a composite of drug release, absorption, and disposition processes (Riegelman and Collier, 1980). The mathematical description of MRT and equations used to calculate it are given in Appendix C. Possible differences in bioavailability between treatments were examined by comparing the ratios of AUC

to dose (AUC/D). Statistical methods used included ANOVA and LSD for multiple comparisons (Snedecor and Cochran, 1980b,c).

RESULTS AND DISCUSSION

The mean saliva acetaminophen concentrations after 325, 500, 1000, 1500, and 2000 mg doses are shown in Figure III.1. Maximum saliva concentrations were reached at 30 to 45 minutes post dosing for all doses, indicating rapid absorption. Concentration-time curves and data for each individual at each dose are given in Appendices D and E. Saliva acetaminophen concentration-time curves were well described by a one or two compartment open pharmacokinetic model with rapid first-order absorption (Appendix F). Pharmacokinetic parameters for acetaminophen following oral administration are given in Tables III.2a,b-III.6a,b. The data for Subject 6 for the 325 mg dose and Subject 12 for the 500 mg dose were fitted to a two compartment open model with instantaneous input because they could not be fit to a model with first order absorption as there were no detectable saliva drug concentrations prior to the peak concentration. This procedure provided estimates of the distribution and elimination rate constants. However, AUC was calculated with the linear trapezoidal rule (Gibaldi and Perrier, 1982a) since use of the equation based on the pharmacokinetic parameters would result in an overestimate of the AUC between time zero and the time to peak concentration

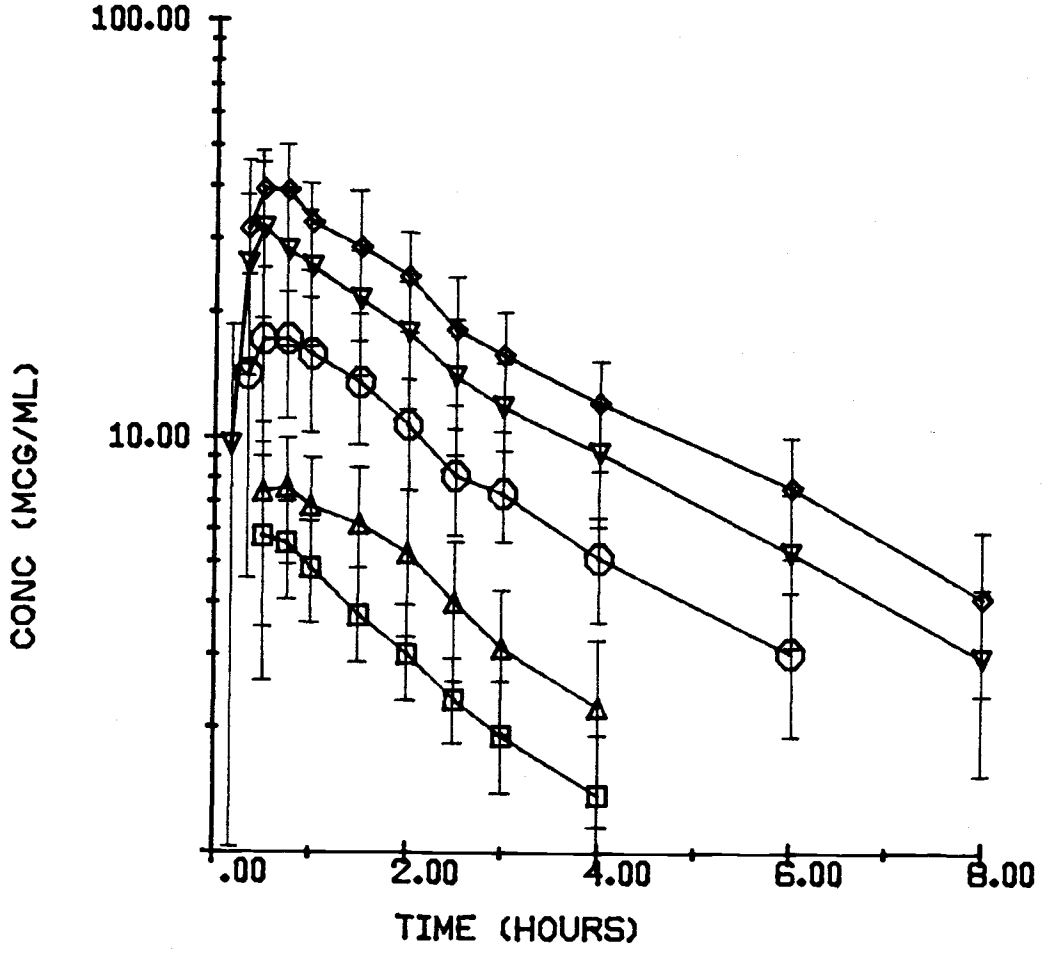

Figure III.1 Mean saliva acetaminophen concentrations following oral administration of commercial acetaminophen tablets to 15 subjects. Key: (□) 325 mg tablet; (△) 500 mg tablet; (⬡) two 500 mg tablets (1000 mg dose); (▽) three 500 mg tablets (1500 mg dose); (◇) four 500 mg tablets (2000 mg dose).

Table III.2a Pharmacokinetic Parameters[a] for Two Compartment Open Model Following Oral Administration of 325 mg Acetaminophen Tablet

Subject No.	α, hr^{-1}	ß, hr^{-1}	$t_{½}$, hr	k_a, hr^{-1}	k_{el}, hr^{-1}	k_{12}, hr^{-1}	k_{21}, hr^{-1}	t_1[b], hr	MRT, hr	AUC, µg-hr/ml
1	2.843	0.2822	2.46	5.702	0.675	1.262	1.188	0.15	3.229	23.46
2	1.331	0.1765	3.93	14.401	0.415	0.527	0.566	0.14	4.720	30.76
3	4.221	0.3475	1.99	7.543	0.676	1.722	2.171	0.15	2.787	13.73
4	1.888	0.2951	2.35	13.088	0.538	0.609	1.036	0.13	3.029	13.50
6[c]	1.103	0.1647	4.21	----	0.377	0.409	0.482	0.00	4.902	30.37[d]
10	3.894	0.3670	1.89	9.685	0.509	0.943	2.810	0.12	2.729	18.24
13	1.016	0.1742	3.98	8.097	0.342	0.331	0.517	0.12	4.914	21.97
15	2.533	0.2464	2.81	9.680	0.643	1.166	0.971	0.13	3.526	15.13
Mean	2.354	0.2567	2.70*	9.742	0.522	0.697	1.218	0.12	3.730	20.90
SD[e]	1.239	0.0796		3.076	0.135	0.390	0.845	0.05	0.958	6.98
CV(%)[f]	52.65	31.01		31.57	25.82	55.93	69.38	41.63	25.70	33.41

[a] From AUTOAN2.
[b] Lag time.
[c] Data was fit to a two compartment open model with instantaneous input since there were no data points on the upslope to define an absorption phase.
[d] Caculated using linear trapezoidal rule.
[e] Standard deviation.
[f] Coefficient of variation.
* 0.693/ß.

Table III.2b Pharmacokinetic Parameters[a] for One Compartment Open Model Following Oral Administration of 325 mg Acetaminophen Tablet

Subject No.	k_a, hr^{-1}	k_{el}, hr^{-1}	$t_{1/2}$, hr	t_l[b], hr	MRT, hr	AUC, µg-hr/ml
5	2.216	1.0160	0.68	0.00	1.436	6.76
7	4.609	0.5234	1.32	0.00	2.128	12.96
9	4.869	0.7856	0.88	0.46	1.478	12.07
11	4.411	0.3675	1.89	0.43	2.948	10.63
14	11.470	0.4607	1.50	0.47	2.258	15.22
Mean	5.515	0.6306	1.10*	0.27	2.050	11.43
SD[c]	3.493	0.2656		0.25	0.624	3.14
CV(%)[d]	63.34	42.11		91.45	30.47	27.26

[a] From AUTOAN2.
[b] Lag time.
[c] Standard deviation.
[d] Coefficient of variation.
* $0.693/k_{el}$.

Table III.3a Pharmacokinetic Parameters[a] for Two Compartment Open Model Following Oral Administration of 500 mg Acetaminophen Tablet

Subject No.	α, hr^{-1}	ß, hr^{-1}	$t_{½}$, hr	k_a, hr^{-1}	k_{el}, hr^{-1}	k_{12}, hr^{-1}	k_{21}, hr^{-1}	t_l[b], hr	MRT, hr	AUC, µg-hr/ml
2	1.434	0.2834	2.45	13.579	0.337	0.175	1.205	0.15	3.470	43.58
3	2.179	0.1737	3.99	4.620	0.516	1.103	0.734	0.15	5.069	34.75
6	1.130	0.2848	2.43	12.145	0.503	0.272	0.640	0.00	2.915	33.25
8	4.250	0.5210	1.33	11.720	0.834	1.283	2.654	0.00	1.863	18.52
12[c]	0.935	0.1714	4.04	----	0.446	0.301	0.360	0.00	4.123	28.98[d]
14	1.910	0.2444	2.84	11.014	0.666	0.788	0.701	0.15	3.278	21.52
15	2.901	0.2449	2.83	2.489	0.993	1.437	0.715	0.00	3.432	19.22
Mean	2.106	0.2748	2.52*	9.261	0.614	0.766	1.001	0.06	3.450	28.55
SD[e]	1.158	0.1180		4.549	0.232	0.523	0.770	0.08	0.992	9.34
CV(%)[f]	55.00	42.93		49.12	37.73	68.31	76.91	124.7	28.77	32.73

[a] From AUTOAN2.
[b] Lag time.
[c] Data was fit to a two compartment open model with instantaneous input since there were no data points on the upslope to define an absorption phase.
[d] Calculated using linear trapezoidal rule.
[e] Standard deviation.
[f] Coefficient of variation.
* 0.693/ß.

Table III.3b Pharmacokinetic Parameters[a] for One Compartment Open Model Following Oral Administration of 500 mg Acetaminophen Tablet

Subject No.	k_a, hr^{-1}	k_{el}, hr^{-1}	$t_{1/2}$, hr	t_l[b], hr	MRT, hr	AUC, µg-hr/ml
1	2.242	0.4337	1.60	0.67	2.752	29.31
4	5.812	0.3084	2.25	0.17	3.415	20.62
7	2.743	0.7753	0.89	0.28	1.654	18.18
9	7.538	0.5119	1.35	0.27	2.086	20.16
10	1.559	0.4584	1.51	0.13	2.823	29.36
11	2.349	0.4027	1.72	0.21	2.909	13.35
13	2.498	0.3675	1.89	0.29	3.121	21.98
Mean	3.534	0.4654	1.49*	0.29	2.680	21.85
SD[c]	2.232	0.1513		0.18	0.608	5.80
CV(%)[d]	63.15	32.52		61.87	22.69	26.56

[a] From AUTOAN2.
[b] Lag time.
[c] Standard deviation.
[d] Coefficient of variation.
* $0.693/k_{el}$.

Table III.4a Pharmacokinetic Parameters[a] for Two Compartment Open Model Following Oral Administration of Two 500 mg Acetaminophen Tablets (1000 mg dose)

Subject No.	α, hr^{-1}	ß, hr^{-1}	$t_{1/2}$, hr	k_a, hr^{-1}	k_{el}, hr^{-1}	k_{12}, hr^{-1}	k_{21}, hr^{-1}	t_1[b], hr	MRT, hr	AUC, µg-hr/ml
2	1.141	0.1473	4.71	11.847	0.385	0.467	0.437	0.16	5.459	106.60
3	1.090	0.1475	4.70	1.586	0.388	0.435	0.415	0.13	5.916	62.82
6	0.628	0.1527	4.54	8.762	0.293	0.161	0.328	0.09	5.205	92.69
8	0.587	0.1264	5.48	4.625	0.368	0.144	0.211	0.30	4.872	57.90
9	1.574	0.3350	2.07	4.458	0.547	0.398	0.964	0.00	2.807	65.64
10	0.791	0.0730	9.49	1.938	0.424	0.304	0.136	0.00	8.138	91.03
11	4.505	0.3797	1.83	7.478	0.650	1.602	2.633	0.11	2.609	37.72
12	2.748	0.2112	3.28	5.135	0.512	1.314	1.133	0.15	4.411	44.79
13	0.818	0.0286[c]	24.23	14.526	0.193	0.533	0.121	0.16	28.05[c]	145.78[c]
14	1.045	0.1529	4.53	3.757	0.516	0.372	0.310	0.28	4.532	64.89
15	4.923	0.2853	2.43	7.932	0.828	2.684	1.696	0.08	3.244	53.75
Mean	1.805	0.2011	3.45[*]	6.549	0.464	0.765	0.762	0.13	4.719	67.78
SD[d]	1.561	0.0997		4.039	0.175	0.787	0.792	0.10	1.645	22.19
CV(%)[e]	86.48	49.57		61.67	37.61	102.84	103.94	72.19	34.85	32.74

[a] From AUTOAN2.
[b] Lag time.
[c] Value omitted in calculation of mean.
[d] Standard deviation.
[e] Coefficient of variation.
[*] 0.693/ß.

Table III.4b Pharmacokinetic Parameters[a] for One Compartment Open Model Following Oral Administration of Two 500 mg Acetaminophen Tablets (1000 mg dose)

Subject No.	k_a, hr^{-1}	k_{el}, hr^{-1}	$t_{1/2}$, hr	t_l[b], hr	MRT, hr	AUC, µg-hr/ml
1	7.546	0.4613	1.50	0.45	2.300	58.85
4	3.325	0.4233	1.64	0.11	2.663	34.26
5	10.498	0.4649	1.49	0.15	2.246	52.58
7	0.914	0.2690	2.58	0.36	4.811	57.87
Mean	5.571	0.4046	1.71*	0.27	3.005	50.89
SD[c]	4.278	0.0924		0.16	1.218	11.42
CV(%)[d]	76.80	22.82		61.23	40.54	22.45

[a] From AUTOAN2.
[b] Lag time.
[c] Standard deviation.
[d] Coefficient of variation.
* $0.693/k_{el}$.

Table III.5a Pharmacokinetic Parameters[a] for Two Compartment Open Model Following Oral Administration of Three 500 mg Acetaminophen Tablets (1500 mg dose)

Subject No.	α, hr^{-1}	ß, hr^{-1}	$t_{½}$, hr	k_a, hr^{-1}	k_{el}, hr^{-1}	k_{12}, hr^{-1}	k_{21}, hr^{-1}	t_l[b], hr	MRT, hr	AUC, µg-hr/ml
1	1.210	0.1868	3.71	4.852	0.363	0.411	0.623	0.26	4.780	164.30
3	1.183	0.1831	3.79	5.244	0.380	0.416	0.569	0.15	4.742	93.29
4	7.116	0.3616	1.92	10.103	0.982	3.875	2.621	0.14	2.623	62.87
6	0.529	0.1167	5.94	2.555	0.355	0.117	0.174	0.00	5.109	161.09
8	0.534	0.1004	6.90	10.474	0.337	0.138	0.159	0.15	5.647	111.38
10	1.035	0.1709	4.06	7.026	0.388	0.362	0.456	0.16	4.766	155.21
12[c]	---	0.3535	1.96	---	---	---	---	--	2.374[d]	75.06[e]
14	0.823	0.2071	3.35	38.591	0.414	0.205	0.412	0.16	3.639	120.83
15	1.290	0.2075	3.34	10.380	0.434	0.447	6.158	0.08	4.068	90.61
Mean	1.715	0.2097	3.30*	11.153	0.457	0.746	1.397	0.14	4.194	114.96
SD[f]	2.202	0.0916		11.468	0.215	1.271	2.082	0.07	1.119	38.07
CV(%)[g]	128.41	43.67		102.82	46.99	170.28	149.06	53.97	26.69	33.12

[a] From AUTOAN2.
[b] Lag time.
[c] Pharmacokinetic paramaters are from NONLIN since this data was best described by a three compartment open model which is indeterminate.
[d] AUMC/AUC.
[e] Calculated using linear trapezoidal rule.
[f] Standard deviation.
[g] Coefficient of variation.
* 0.693/ß.

Table III.5b Pharmacokinetic Parameters[a] for One Compartment Open Model Following Oral Administration of Three 500 mg Acetaminophen Tablets (1500 mg dose)

Subject No.	k_a, hr^{-1}	k_{el}, hr^{-1}	$t_{½}$, hr	t_l[b], hr	MRT, hr	AUC, µg-hr/ml
2	6.466	0.2535	2.73	0.13	4.099	150.73
5	2.811	0.3507	1.98	0.11	3.207	95.47
7	2.511	0.3745	1.85	0.27	3.068	74.30
9	25.038	0.3836	1.81	0.16	2.647	67.78
11	5.142	0.3788	1.83	0.13	2.834	53.56
13	7.244	0.2029	3.42	0.10	5.067	95.41
Mean	8.202	0.3240	2.14*	0.15	3.487	89.53
SD[c]	8.464	0.0768		0.06	0.923	34.11
CV(%)[d]	103.19	23.69		41.53	26.46	38.10

[a] From AUTOAN2.
[b] Lag time.
[c] Standard deviation.
[d] Coefficient of variation.
* $0.693/k_{el}$.

Table III.6a Pharmacokinetic Parameters[a] for Two Compartment Open Model Following Oral Administration of Four 500 mg Acetaminophen Tablets (2000 mg dose)

Subject No.	α, hr^{-1}	ß, hr^{-1}	$t_{1/2}$, hr	k_{a_1}, hr^{-1}	k_{el_1}, hr^{-1}	k_{12_1}, hr^{-1}	k_{21_1}, hr^{-1}	t_l[b], hr	MRT, hr	AUC, µg-hr/ml
1	1.834	0.2596	2.67	2.397	0.550	0.678	0.865	0.09	3.660	175.70
3	2.023	0.1944	3.57	19.758	0.380	0.802	1.036	0.15	4.724	159.22
4	1.138	0.2299	3.01	14.251	0.457	0.338	0.573	0.06	3.553	83.46
5	0.477	0.1389	4.99	2.200	0.346	0.078	0.191	0.10	4.523	136.85
6	0.595	0.1985	3.49	22.407	0.293	0.098	0.403	0.15	4.281	190.82
8	0.743	0.1690	4.10	5.371	0.450	0.183	0.279	0.00	3.871	112.26
9	2.674	0.2800	2.48	9.892	0.699	1.184	1.071	0.11	3.114	131.81
11	1.456	0.3259	2.13	8.535	0.477	0.310	0.995	0.15	2.868	78.48
12	1.672	0.3562	1.95	6.128	0.474	0.298	1.256	0.31	2.773	111.46
13	0.495	0.0995	6.97	10.770	0.184	0.142	0.268	0.14	8.430	194.47
14	1.038	0.1781	3.89	5.062	0.466	0.354	0.397	0.15	4.254	163.10
15	1.223	0.2390	2.90	14.556	0.386	0.319	0.757	0.26	3.749	116.14
Mean	1.281	0.2224	3.12*	10.111	0.430	0.399	0.674	0.14	4.150	137.81
SD[c]	0.680	0.0750		6.537	0.129	0.329	0.368	0.08	1.485	39.18
CV(%)[d]	53.10	33.73		64.65	30.07	82.61	54.55	59.21	35.79	28.43

[a] From AUTOAN2.
[b] Lag time.
[c] Standard deviation.
[d] Coefficient of variation.
* 0.693/ß.

Table III.6b Pharmacokinetic Parameters[a] for One Compartment Open Model Following Oral Administration of Four 500 mg Acetaminophen Tablets (2000 mg dose)

Subject No.	k_a, hr^{-1}	k_{el}, hr^{-1}	$t_{1/2}$, hr	t_l[b], hr	MRT, hr	AUC, µg-hr/ml
2	11.521	0.2526	2.74	0.30	4.046	205.14
7	4.399	0.2991	2.32	0.16	3.571	127.88
9	7.637	0.2597	2.67	0.00	3.982	143.17
Mean	7.852	0.2705	2.56*	0.15	3.866	158.73
SD[c]	3.566	0.0251		0.15	0.258	40.91
CV(%)[d]	45.41	9.26		97.90	6.67	25.78

[a] From AUTOAN2.
[b] Lag time.
[c] Standard deviation.
[d] Coefficient of variation.
* $0.693/k_{el}$.

(the first detectable drug concentration). Data for subjects 8 and 12 for the 325 mg dose and Subject 5 for the 500 mg dose are missing because the saliva acetaminophen concentrations fluctuated radically over time, resulting in illogical profiles which could not and should not be fit to a smooth curve for estimation of pharmacokinetic parameters (Figures D.5, D.8, D.12). Such fluctuations are probably due to experimental error, particularly when subjects are required to collect their own samples, or may be due to intrasubject variability in the distribution of the drug in the saliva (Danhof and Breimer, 1978). Some of the concentration-time curves for Subject 13 were also "atypical" over the terminal portion of the curves (Figure D.13), although the data could still be described by a bi- or triexponential equation. However, some of the pharmacokinetic parameters for the 1000 mg dose fell well outside the range of observed values for all other subjects and were omitted in calculation of mean values (Table III.4a). Because of the extremely long observed half-life (24.3 hours) in Subject 13 for this dose, the AUC at 1000 mg was 50% greater than at 1500 mg (Tables III.4a and III.5b), which is inconsistent with expected and observed results. The concentration-time curve for Subject 12 for the 1500 mg dose was best fit by a linear sum of four exponential

terms (a three compartment open model). Since such a model is indeterminate, the only pharmacokinetic parameter obtained from this data was the elimination rate constant (slope of the terminal phase), which was obtained from NONLIN. AUC was calculated with the linear trapezoidal rule. To obtain MRT, the area under the moment curve (AUMC) was also calculated with the linear trapezoidal rule and used to obtain the ratio of AUMC to AUC, which is a model-independent estimate of MRT. The equations are described in Appendix C.

The distribution phase was fairly rapid for data that was best fitted by a triexponential equation but tended to increase with dose (mean $t_{\frac{1}{2}\alpha}$ = 0.29 hr for 325 mg dose and 0.54 hr for 2000 mg dose). However, values for α were quite variable between subjects (CV ranged between 53% and 128%). The mean elimination half-life also tended to increase with dose and was shorter for data fit to a one compartment model than for a two compartment model (which is reasonable). However, as the dose increased, the difference between mean elimination half-life for the one and two compartment models became smaller ($t_{\frac{1}{2}kel}$ = 1.10 hr and $t_{\frac{1}{2}\beta}$ = 2.70 hr for 325 mg dose; $t_{\frac{1}{2}kel}$ = 2.56 hr and $t_{\frac{1}{2}\beta}$ = 3.12 hr for 2000 mg dose). These differences were also reflected in MRT and AUC values which were calculated from the parameters in the model, one of which is the elimination

rate constant. Average MRT values were higher for data fit to a two compartment model. This was also true for average AUC values, except at the 2000 mg dose.

Values for the absorption rate constant were extremely variable, as reflected by the high coefficient of variation associated with the estimated values (CV ranged between 32% and 103%). Estimates of k_a are probably not reliable for most of the data because there were not enough data points prior to the peak concentration to characterize the absorption phase. Mean drug absorption was quite rapid at all doses, but somewhat slower in subjects whose data was described by a one compartment model. (For example, mean k_a = 5.5 hr^{-1} for one compartment model and 9.7 hr^{-1} for two compartment model data for the 325 mg dose). However, rate of absorption appeared to be independent of dose. For many of the concentration-time curves there was a lag time between administration of the drug and onset of absorption. Mean lag time was longer for data described by a one compartment than a two compartment model.

At lower oral doses (325 and 500 mg), acetaminophen exhibits both one compartment and two compartment behavior, while at higher doses (1000 to 2000 mg) more of the concentration-time profiles are better described by the two compartment model. Acetaminophen is known to display two compartment characteristics after

intravenous injection (Clements and Prescott, 1976; Rawlins et al., 1977; Ameer et al., 1983). The distributive phase may not be observed following oral administration, which results in plasma concentration-time curves which appear to be biexponential rather than multiexponential (Gibaldi and Perrier, 1982b). Also, limitations imposed by the sensitivity of the assay did not allow for concentrations to be followed beyond a certain time at lower doses, while at higher doses, detectable saliva drug levels were observed for as long as 16 hours post dosing. There may be another exponential phase at later times which cannot be seen at low doses. Therefore, estimates of half-life for data best described as a one compartment model are expected to be shorter than for two compartment behavior and are most likely underestimates of the true half-life.

Elimination rate constants (ß and k_{el}), MRT, AUC, and AUC/D were combined for all the data, and mean values for each dose are given in Table III.7. Although the study was designed as a randomized block experiment, the pharmacokinetic parameters in this table were compared according to a one-way ANOVA (completely randomized design) because of missing data in four of the blocks (subjects). It was recognized that analyzing the data in such a manner would result in decreased

Table III.7 Mean Pharmacokinetic Parameters[a] Following Administration of Commercial Acetaminophen Tablets to 15 Subjects

Dose, mg	k^b, hr^{-1}	$t_{1/2}^c$, hr	MRT, hr	AUC, µg-hr/ml	AUC/D[d], µg-hr/ml-mg
325	0.4005 (0.2511)	1.73	3.083 (1.179)	17.29 (7.36)	0.0532 (0.0226)
500	0.3701 (0.1636)	1.87	3.065 (0.886)	25.20 (8.24)	0.0504 (0.0165)
1000	0.2593 (0.1340)	2.67	4.230 (1.691)	62.96 (20.83)	0.0630 (0.0208)
1500	0.2554 (0.1013)	2.71	3.911 (1.072)	104.79 (37.55)	0.0699 (0.0208)
2000	0.2320 (0.0700)	2.99	4.093 (1.325)	142.00 (38.99)	0.0710 (0.0195)

[a] From AUTOAN2. Values in parentheses are standard deviations.

[b] Slope of the terminal portion of the saliva acetaminophen concentration-time curve as determined by AUTOAN2. One compartment (k_{el}) and two compartment (ß) values were averaged together.

[c] 0.693/k.

[d] AUC divided by the dose (D).

precision. However, the estimated efficiency of a randomized block relative to a completely randomized design for this set of data was only 1.3, meaning that analysis with blocking would have resulted in only a slight increase in precision.

Statistically significant differences in elimination rate constants, MRT, and AUC/D were found between treatments (dose levels) ($p<0.05$). The difference in MRT with dose reflects *in vivo* differences in absorption and disposition processes. Elimination appears to be dose-dependent since the half-life is increasing with dose. The differences in AUC/D indicate that AUC is increasing disproportionately with dose. This is apparent from the trends observed in the mean pharmacokinetic parameters in Table III.7. Pairwise comparisons (LSD) revealed that the elimination rate constant after 2000 mg was significantly less than after 325, 500, or 1000 mg orally ($p<0.05$). The elimination rate constant after 1500 mg was also significantly less than after 325 mg. Thus, the apparent half-life of acetaminophen in saliva is prolonged at higher doses. This is contrary to what Rawlins et al. (1977) observed after oral administration of 500, 1000 and 2000 mg doses. However, drug concentrations were monitored for only 6 hours post dosing and thus, for the higher doses, the calculated elimination rate constant for the Rawlins

data would have been a hybrid constant obtained during the distributive phase and the first part of the post-distributive phase of drug decline, and would be greater than the elimination rate constant measured solely in the post-distributive phase.

An increase in acetaminophen half-life with dose is consistent with a reduced first-pass hepatic effect which results in greater amounts of unchanged drug in the body (Forrest et al., 1979). Acetaminophen metabolism is altered following overdosage (Prescott, 1980) due to liver damage, and prolongation of half-life is related to the severity of hepatic injury (Gazzard et al., 1977; Prescott and Wright, 1973; Prescott et al., 1971). Although 2000 mg is below toxic doses for healthy subjects, saturation of metabolism (sulfate and glucuronide conjugation) in some of the subjects could account for slower elimination. Thus, nonlinearity in disposition of drug in the body may be occurring at higher doses of acetaminophen. Within a given subject acetaminophen half-life in saliva varied considerably but was usually longer at higher doses (Tables III.2-III.6).

Increases in half-life with dose for acetaminophen could also be due to slower in vivo dissolution at higher doses which would result in prolonged absorption. Thus, the true elimination half-life of acetaminophen

would be distorted by a longer absorption half-life. Sotiropoulus et al. (1981) reported that acetaminophen absorption may be dissolution rate controlled based on their findings that acetaminophen half-life was prolonged for tablets which exhibited delayed *in vitro* disintegration and dissolution. *In vitro* dissolution of 500 mg Tylenol tablets was found to be dependent on dose; four tablets (2000 mg acetaminophen) dissolved more slowly than one tablet (500 mg acetaminophen) when tested in a 50 rpm rotating basket apparatus (Borin, 1984). If *in vitro* dissolution under these conditions correlates with *in vivo* dissolution, then this would indicate a prolongation of absorption which would be reflected in an increased apparent half-life. Estimated k_a values do not reflect such a trend. However, as discussed previously, these estimates may be inaccurate because of too few data points prior to the peak concentration.

Significant differences in MRT were found between 2000 mg and 325 or 500 mg doses, respectively, and between 1000 mg and 325 or 500 mg doses, respectively ($p<0.05$). Inspection of the mean values in Table III.7 reveals that MRT increased considerably between 500 mg and 1000 mg doses and then remained about the same at higher doses. MRT has been interpreted as "the mean time for intact drug molecules to transit through the

body" (Riegelman and Collier, 1980), and because elimination is slower at higher doses, transit of drug molecules will be slower as reflected in the magnitude of MRT. It has been reported that differences in MRT of drug concentration-time curves with dose may suggest saturation of drug disposition (i.e., nonlinearity) (Yamaoka et al., 1978).

The observation that AUC/D values varied with dose is indicative of differences in apparent bioavailability (F) with dose which have been reported by Rawlins et al. (1977) for acetaminophen. However, since volume of distribution is also directly related to AUC, differences in AUC with dose, which would be reflected in bioavailability, could also occur if the apparent volume of distribution was changing with dose. AUC/D values were examined in our study because an IV reference dose was not administered to determine absolute bioavailability. In Rawlins' study, bioavailability decreased from 0.90 at 1000 and 2000 mg oral doses to 0.63 for a 500 mg oral dose. Such incomplete systemic availability could be explained by presystemic biotransformation either by first-pass hepatic extraction or metabolism in the epithelium and/or lumen of the GI tract, or by a combination of these processes (George, 1981; Ameer et al., 1983).

Statistically significant differences in AUC/D were

found between 2000 mg and 325 or 500 mg doses, respectively, and between 1500 mg and 325 or 500 mg doses, respectively ($p<0.05$). Although the differences between the ratios for 1000 mg and 500 or 325 mg doses, respectively, were not statistically significant, they may be clinically significant because the average AUC/D increased by 25% in going from 500 mg to 1000 mg orally. Thus, it appears that apparent bioavailability is decreased at doses less than 1000 mg.

Nonlinearity in drug disposition with dose can be detected from plots of AUC versus dose. These plots should be linear for drugs eliminated by first order kinetics and curved for those exhibiting nonlinear kinetics (Wagner, 1975a). Figure III.2 shows the relationship between AUC and dose (adjusted for subject weight) in this study. The data was adequately described by a line with zero intercept (correlation coefficient, r, of 0.976; Figure III.2). The coefficient of the quadratic term (dose squared) was not significantly different from zero ($p=0.07$), and the correlation coefficient did not improve ($r=0.977$). Thus, a deviation from linearity is not readily apparent from such a mathematical representation of the data. However, visually, the data appears to be better described by a quadratic equation since the residuals from a linear fit are biased downwards at low doses and upwards at higher

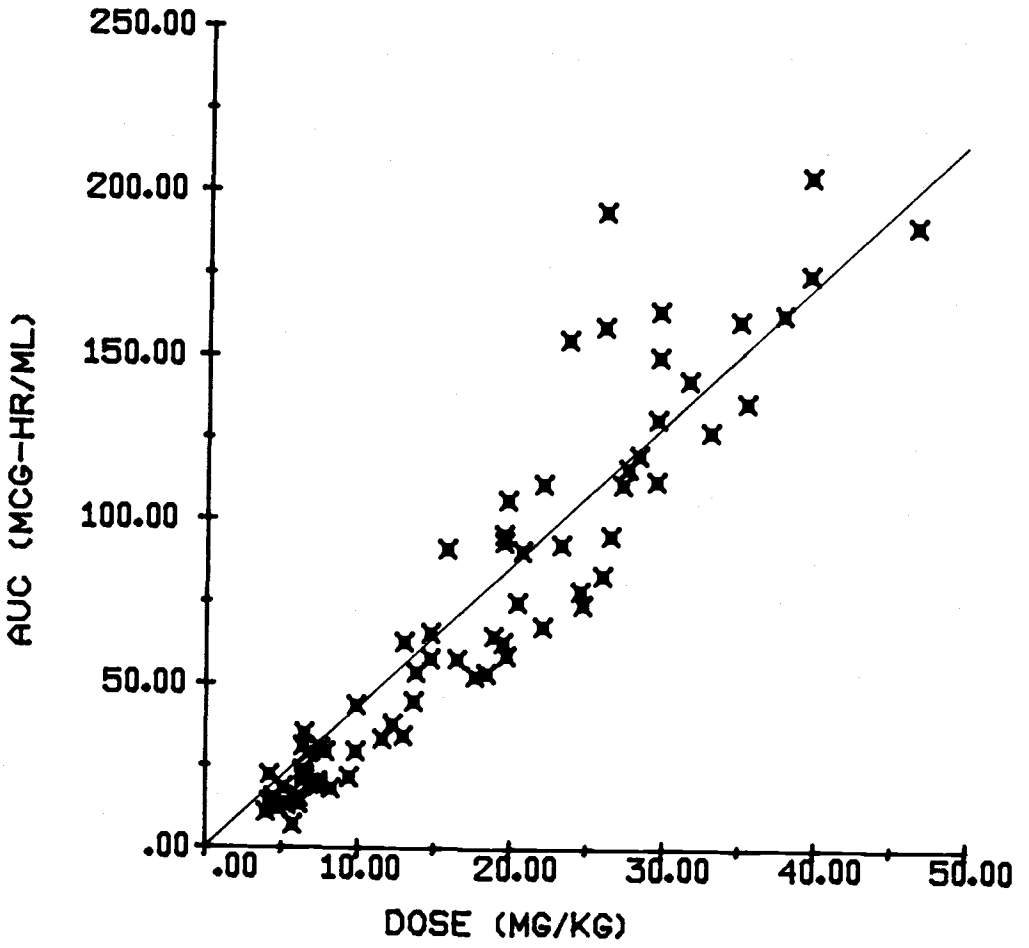

Figure III.2 Area under the curve versus dose adjusted for subject weight.

doses. This curvature in AUC versus dose indicates nonlinearity in acetaminophen disposition.

Differences in bioavailability with dose have a direct impact on development of a sustained release oral dosage form for acetaminophen with regard to selection of the appropriate dose, presence or absence of a loading dose, and bioavailability trials. In conducting a bioavailability trial, it is necessary to define a reference standard against which to compare the sustained release dosage forms. If presystemic metabolism occurs at lower doses, then it may be substantial with slower drug input from a sustained release oral dosage form. Thus, it would be inappropriate to compare the bioavailability of the sustained release product with an equivalent dose of an immediate release product, since the latter would have greater apparent bioavailability due to saturation of presystemic biotransformation. Slower drug input could be simulated by a multiple dosing regimen of low oral doses. For example, 325 mg tablets could be administered every 2 hours over a 12 hour period, providing a total dose of 1950 mg which would serve as a reference standard for a bioavailability study of a 2000 mg sustained release tablet.

Therapeutic concentrations for acetaminophen have not been well documented in the literature. However, it

is possible to evaluate sustained release dosage forms by comparison of published dose-response curves for total change in pain intensity at effective doses. Maximum analgesic effectiveness of acetaminophen has been reported to occur following 1000 mg doses (Beaver, 1965; Hopkinson et al., 1974) and further dosage increases will result in little increment in analgesia (Beaver, 1965). Peak plasma concentrations following oral dosing of 1000 mg acetaminophen have been reported to be 15 µg/ml in a study with six subjects (Rawlins et al., 1977) and 10 µg/ml in a study with 10 subjects (Adithan and Thangam, 1982). Adithan and Thangam also simultaneously obtained saliva samples from these subjects and reported a peak salivary acetaminophen concentration of about 12 µg/ml. The overall mean saliva to serum concentration ratio in their study was 1.14 but showed wide inter- and intra-individual variation. For a 20 mg/kg oral dose, a peak plasma concentration of about 18 µg/ml was observed in a study by Prescott (1980) with eight subjects. The concentration was maintained between 10 and 20 µg/ml for 0.25 to 3 hours post dosing. Effective plasma acetaminophen levels appear to lie in the range of 10 to 20 µg/ml as has been reported by Wagner (1975b). Effective saliva acetaminophen concentrations are probably similar or somewhat higher, based on reported

mean saliva to serum ratios of 1.0 to 1.4 (Glynn et al., 1973; Ahmed and Enever, 1981; Adithan and Thangam, 1982).

Therefore, our results indicate that in order to achieve and maintain therapeutic concentrations of acetaminophen, the sustained release formulation must provide some immediate release of drug in an amount sufficient to saturate presystemic metabolism. This dose should produce an initial peak saliva acetaminophen concentration greater than 7.5 µg/ml (average peak saliva drug concentration for the 500 mg dose) and preferably greater than 10 µg/ml since the literature indicates that this is the minimum effective acetaminophen plasma concentration. Based on our results suggesting dose-dependent bioavailability, it can be proposed that combination of an immediate release portion of drug with a sustained release portion may result in acetaminophen concentrations higher than those predicted by addition of the curves from separate administration of each portion. This hypothesis is supported by Ahmed and Enever's report (1981) that compression coating of 200 mg acetaminophen onto a 500 mg sustained release acetaminophen tablet core provides a dosage form having saliva acetaminophen levels higher than those predicted by addition of the curves obtained from separate administration of the compression coated

portion and the sustained release core when two such tablets are taken (total dose of 1400 mg). Therefore, the ideal sustained release dosage form should contain an immediate release component of at least 500 mg, and the dose in the sustained release portion would depend on the mechanism and rate of drug release.

CONCLUSION

Acetaminophen pharmacokinetics was found to be dose-dependent based on statistically significant differences in elimination half-life, MRT, and AUC/D between treatments (doses). These findings can be explained by saturation of presystemic hepatic biotransformation at doses >500 mg. To offset any significant losses in the amount of drug systemically available, a sustained release dosage form for acetaminophen should include an immediate release portion which, when combined with early drug release from the sustained release portion, will provide acetaminophen concentrations in excess of 10 µg/ml.

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APPENDICES

APPENDIX A. Determination of Microcapsule Wall Thickness[a]

Wall thickness, t, is given by

$$t = V_w/S$$

where V_w is volume of wall material recovered and S is the surface area of particles encapsulated.

$$V_w = W_w/p_w$$

where W_w is weight of wall material collected and p_w is density of wall material. The surface area, s, of a single spherical particle is given by

$$s = d_1^2$$

where d_1 is diameter of the particle. The number of particles per gram, N, is given by

$$N = 6/d_1^2 p$$

where p is the density of the encapsulated particle. Total surface area, S, of N particles in a unit weight is

$$S = (d_1^2)(6/d_1^3 p) = 6/d_1 p$$

Since the weight of particles encapsulated is $W-W_w$, where W is weight of microcapsules taken, then

$$S = (W-W_w)(6/d_1 p)$$

Therefore,

$$t = (W_w/W-W_w)(p/p_w)(d_1/6)$$

The wall thickness of 90% acetaminophen/ 10% ethylcellulose microcapsules is calculated as an

example. For these microcapsules,

$$p = 1.293 \text{ g/cm}^3 \text{ b}$$

$$p_w = 1.13 \text{ g/cm}^3 \text{ c}$$

$$d_1 \leq 75 \text{ µm}$$

In one gram of microcapsules, 0.9 g is acetaminophen and 0.1 g is ethylcellulose. Thus,

$$t = (0.1/1-0.1)(1.293/1.13)(75/6) = 1.59 \text{ µm}$$

In the case of microcapsules with several layers of coating materials, this calculation is repeated for each coating. For example, acetaminophen powder ($d \leq 75$ µm) was spray coated with a 10% inner coat of ethylcellulose, 10% center coat of Eudragit L30D (a polymethacryclic acid ester polymer), and 10% outer coat of ethylcellulose. For a 10% ethylcellulose inner coat, the inner coating thickness is 1.59 µm as calculated above. The diameter of the particle has been increased to $2(r_i+t)$ where r_i $(d_1/2)$ is the inner particle radius. Thus,

$$d_2 = 2((75/2)+1.59) = 78.18 \text{ µm}$$

Assuming that the density of the coated particle is not affected by the addition of a thin coat,

$$p = 1.293 \text{ g/cm}^3$$

$$p_w = 0.84 \text{ g/cm}^3 \text{ d}$$

and thus,

$$t_2 = (0.1/1-0.1)(1.293/0.84)(78.18/6) = 2.23 \text{ µm}$$

where t_2 is the thickness of the 10% center Eudragit

L30D coat. Now, the diameter of the double-coated particle is given by

$$d_3 = 2((78.18/2)+2.23) = 82.64\ \mu m$$

The outer coating thickness for a 10% ethylcellulose coat is then given by

$$t_3 = (0.1/1-0.1)(1.293/1.13)(82.64/6) = 1.75\ \mu m$$

Thus, the total coating thickness is calculated from the sum of the thickness of each coat:

$$t_{total} = \Sigma t_i$$

where i is the number of separate coats applied.

[a]Madan, P.L., Luzzi, L.A. and Price, J.C., Microencapsulation of a waxy solid: wall thickness and surface appearance studies. J. Pharm. Sci., 63 (1974) 280-284.

[b]Fels, G. Z. Krystallog. u. Mineralog., 32 (1900) 387-388.

[c]FMC Corp., Personal communication (1985).

[d]Rohm Pharma, Personal communication (1985).

Appendix B. Calculation of Maintenance Dose to Achieve the Desired Steady State Acetaminophen Concentration[a]

$$c_{ave} = FD/Vk\tau$$

where c_{ave} is average plasma concentration at steady state, F is the fraction of the dose absorbed, V is the volume of distribution, k is the elimination rate constant, and τ is the dosing interval. For acetaminophen, average reported pharmacokinetic parameters[b] are

$V = 0.9$ l/kg

$k = 0.277$

$F = 0.90$ for doses ≥ 1.0 g[c]

For an acetaminophen oral dosage form, a 12 hour dosing interval, and steady state plasma acetaminophen concentration of 15 µg/ml, the predicted dose would be

$$D = c_{ave}Vk\tau/F = (15)(0.9)(0.277)(12)/0.9 = 49.9 \text{ mg/kg}$$

which for a 70 kg individual would amount to 3.49 g.

[a]Winter, M.E. Basic Clinical Pharmacokinetics, Applied Therapeutics, Inc., San Francisco, 1980, pp. 39-58.

[b]Forrest, J.A.H., Clements, J.A. and Prescott, L.F., Clinical pharmacokinetics of paracetamol. Clin. Pharmacokin., 7 (1982) 93-107.

[C]Rawlins, M.D., Henderson, D.B. and Hijab, A.R., Pharmacokinetics of paracetamol (acetaminophen) after intravenous and oral administration. Europ. J. Clin. Pharmacol., 11 (1977) 283-286.

APPENDIX C. Calculation of Mean Residence Time (MRT)[a]

The drug concentration-time curve following a single dose can be regarded as a statistical distribution curve. The zero and first moments for the curve are given by

$$AUC = \int_0^\infty C\ dt$$

$$MRT = \int_0^\infty tC\ dt / \int_0^\infty C\ dt$$

where $\int_0^\infty tC\ dt$ is referred to as the area under the first moment curve (AUMC). There is a convenient relationship between statistical moments and the Laplace-transformed equation[b] which allows pharmacokinetic parameters to be connected with the moments. Yamoaka has reported the moments of the concentration-time curves following oral administration of a drug for several pharmacokinetic models. For the one compartment model with first-order input, MRT is given by

$$MRT = 1/k_a + 1/k_{el}$$

where k_a is the apparent first-order absorption rate constant and k_{el} is the apparent first-order elimination rate constant. For the two compartment model with first-order input, MRT is given by

$$MRT = 1/k_a + (k_{12}+k_{21})/k_{el}k_{21}$$

where k_{12} and k_{21} are first-order rate constants for intercompartmental transfer of drug between the control and peripheral compartments and k_a and k_{el} are as

defined above. MRT values given in Chapter III were calculated using the estimates of k_a, k_{el}, k_{12}, and k_{21} obtained from AUTOAN2. For example, pharmacokinetic parameters for Subject 2, 325 mg dose, are given in Table III.2a (k_a = 14.401 hr^{-1}, k_{12} = 0.527 hr^{-1}, k_{21} = 0.566, k_{el} = 0.415 hr^{-1}). MRT is calculated using the previous equation for a two compartment model:

$$MRT = 1/14.401 + (.527+.566)/(.415)(.566) = 4.720 \text{ hr}$$

MRT can also be determined without specifying a compartmental model, provided that linear pharmacokinetics can be assumed. AUC and AUMC are calculated using the linear or log mean trapezoidal equations, or a combination of both[c]. The linear trapezoidal equations for AUC and AUMC are given by

$$AUC = [(C_n+C_{n-1})/2][t_n+t_{n-1}] + C_z/\lambda_z$$

$$AUMC = [(t_nC_n+t_{n-1}C_{n-1})/2][t_n-t_{n-1}] + t_zC_z/\lambda_z + C_z/(\lambda_z)^2$$

where C_z represents the value for the concentration at the last data point, t_z, and λ_z is the slope of the terminal portion of the concentration-time curve. Thus,

$$MRT = AUC/AUMC$$

[a]Yamoaka, K., Nakagawa, T. and Uno, T., Statistical moments in pharmacokinetics. J. Pharmacokin. Biopharm., 6 (1978) 547-558.

[b]Yamoaka, K. and Nakagawa, T., An application of numerical Laplace transformation to chromatographic peak analysis. J. Chromatog., 92 (1974) 213-222.

[c]Riegelman, S. and Collier, P., The application of statistical moment theory to the evaluation of *in vivo* dissolution time and absorption time. J. Pharmacokin. Biopharm., 8 (1980) 509-534.

APPENDIX D. Saliva Concentration-Time Curves for Individual Subjects

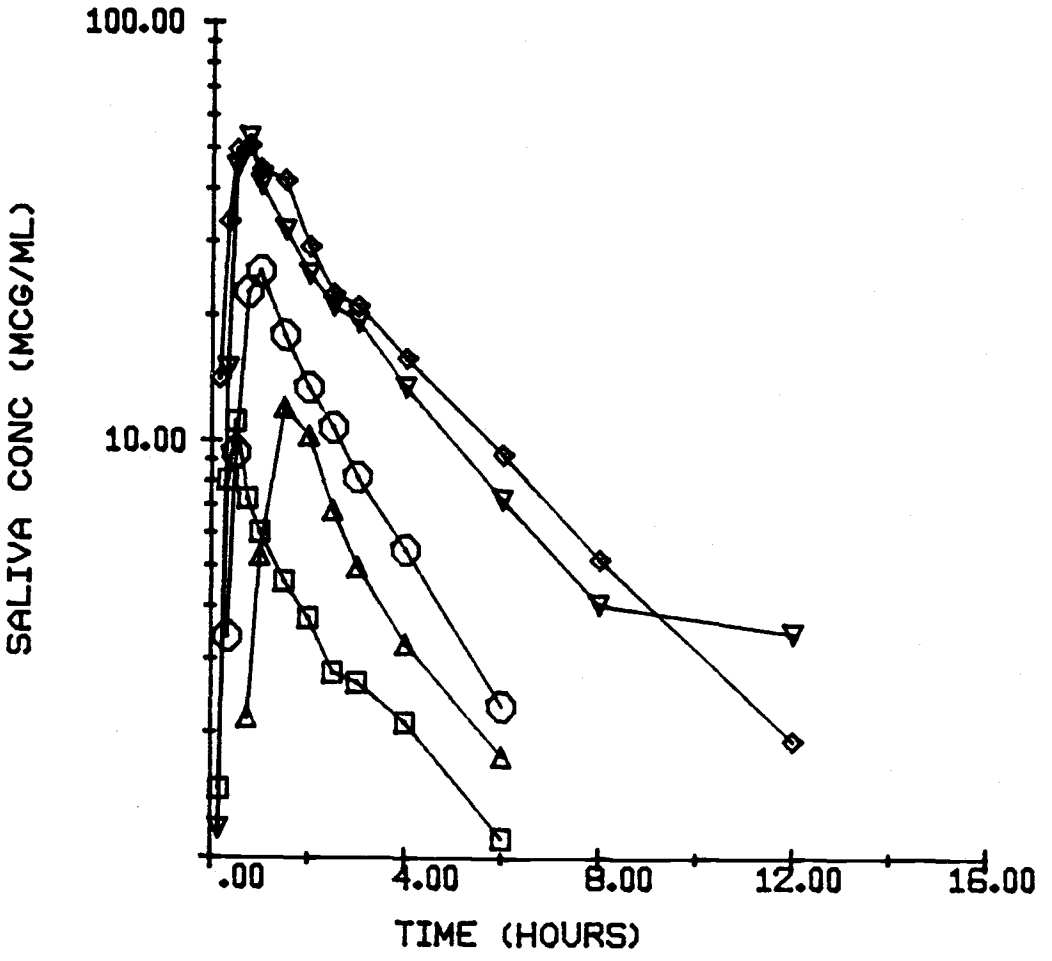

Figure D.1 Saliva acetaminophen concentrations in Subject 1 following administration of commercial acetaminophen tablets. Key: (□) 325 mg tablet; (△) 500 mg tablet; (◯) two 500 mg tablets (1000 mg dose); (▽) three 500 mg tablets (1500 mg dose); (◇) four 500 mg tablets (2000 mg dose).

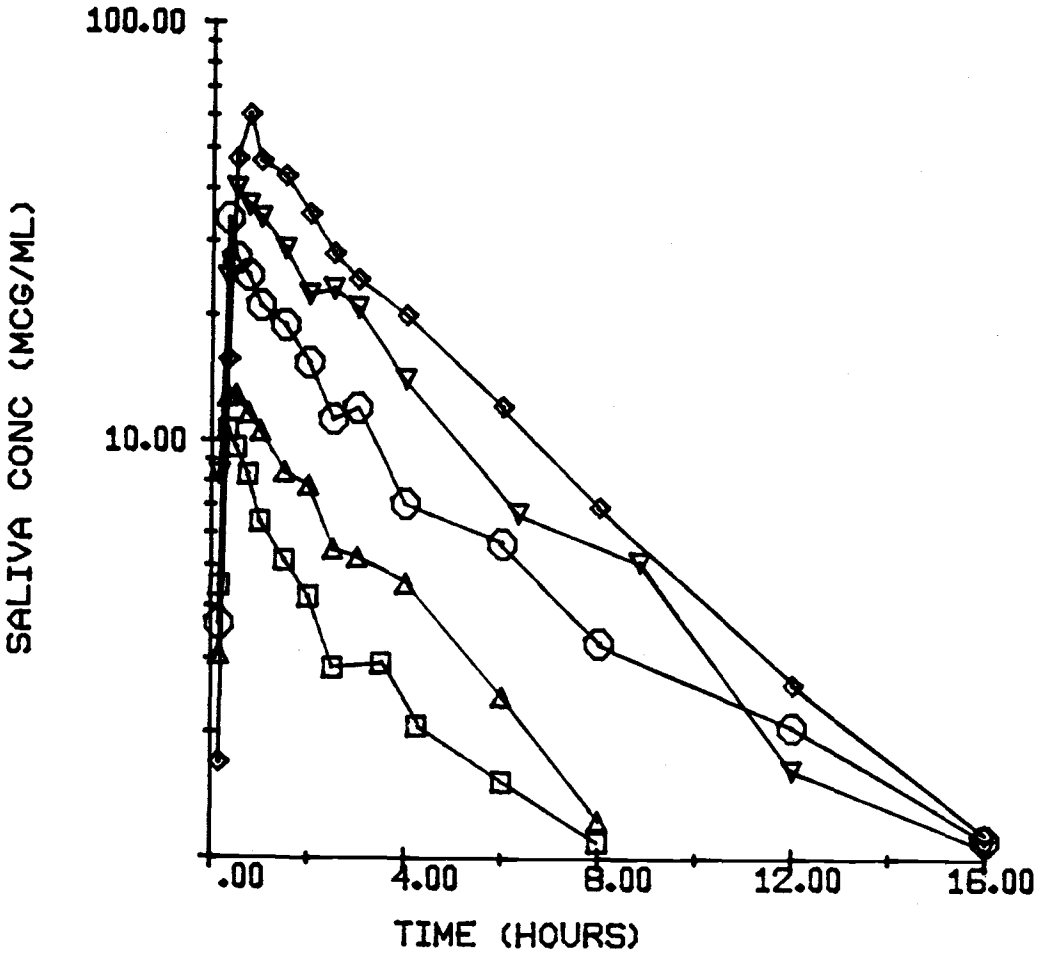

Figure D.2 Saliva acetaminophen concentrations in Subject 2 following administration of commercial acetaminophen tablets. Key: (□) 325 mg tablet; (△) 500 mg tablet; (○) two 500 mg tablets (1000 mg dose); (▽) three 500 mg tablets (1500 mg dose); (◇) four 500 mg tablets (2000 mg dose).

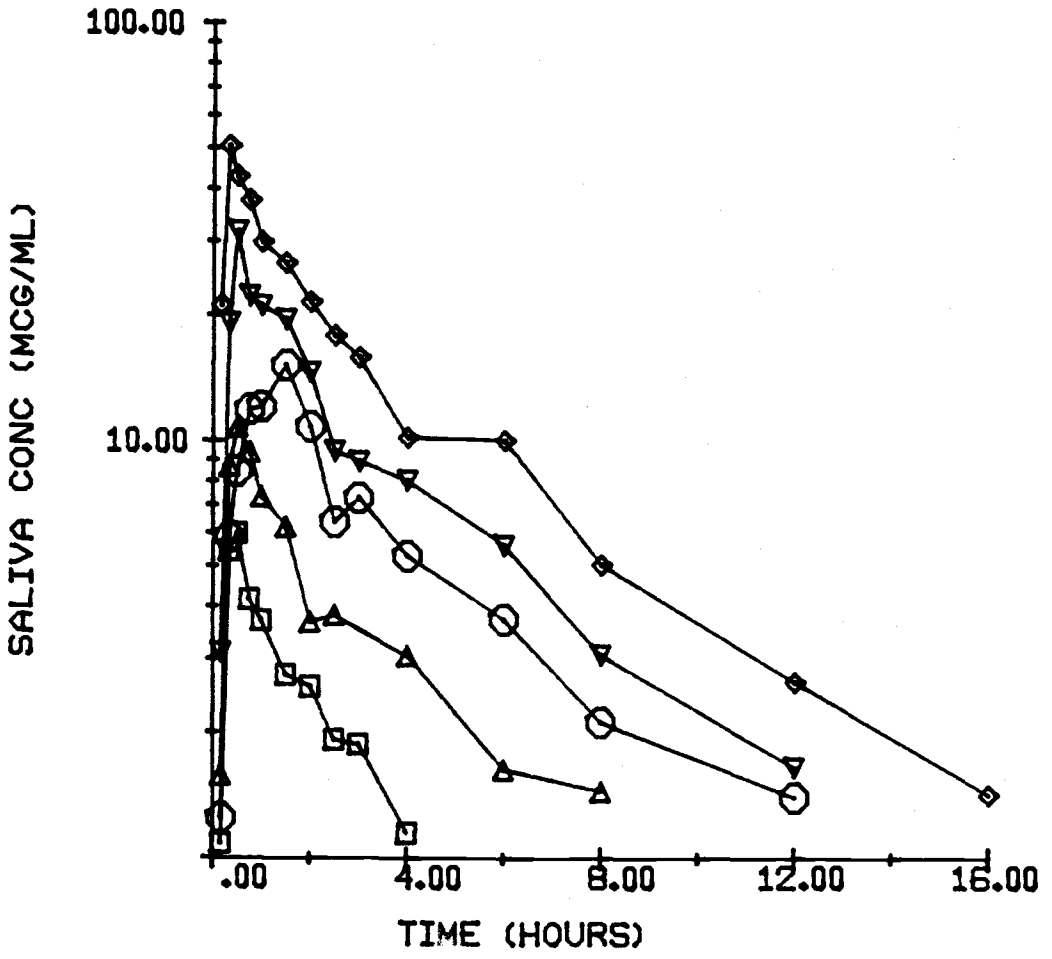

Figure D.3 Saliva acetaminophen concentrations in Subject 3 following administration of commercial acetaminophen tablets. Key: (□) 325 mg tablet; (△) 500 mg tablet; (⬡) two 500 mg tablets (1000 mg dose); (▽) three 500 mg tablets (1500 mg dose); (◇) four 500 mg tablets (2000 mg dose).

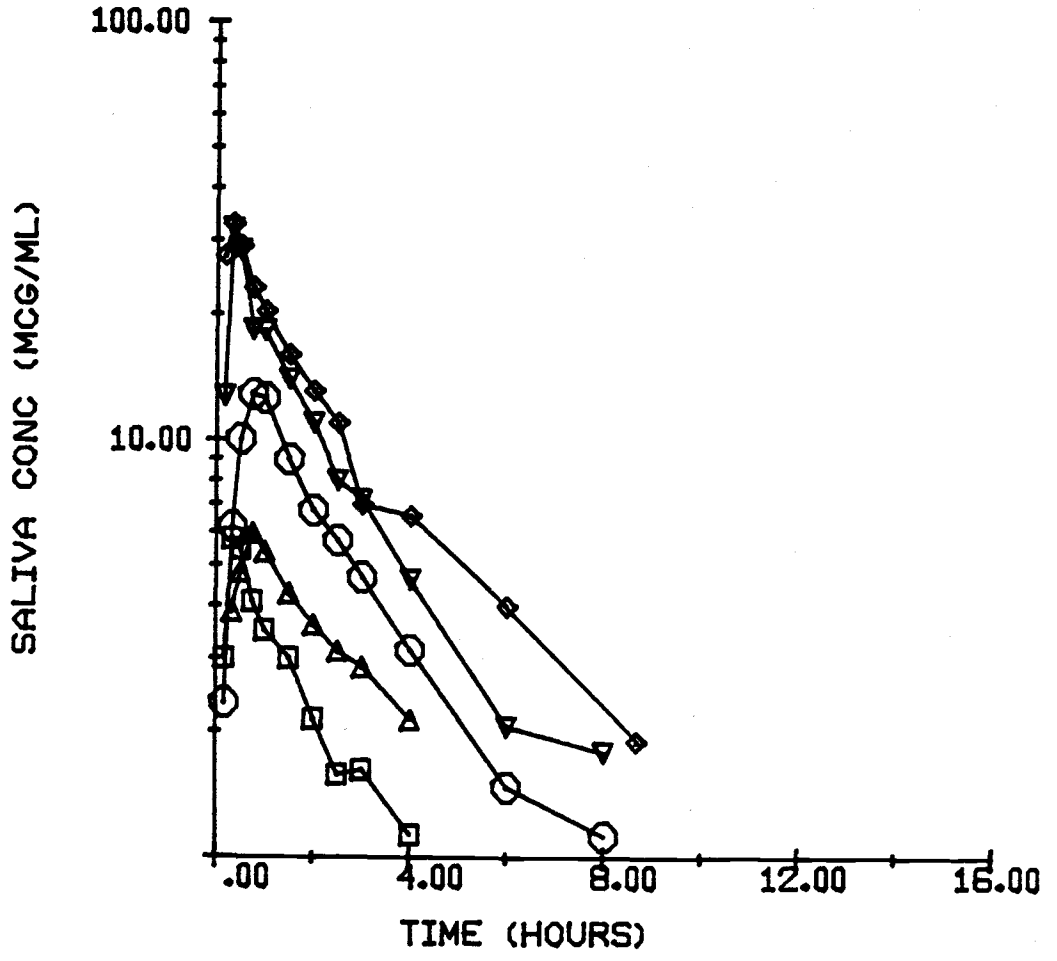

Figure D.4 Saliva acetaminophen concentrations in Subject 4 following administration of commercial acetaminophen tablets. Key: (▢) 325 mg tablet; (△) 500 mg tablet; (⬡) two 500 mg tablets (1000 mg dose); (▽) three 500 mg tablets (1500 mg dose); (◇) four 500 mg tablets (2000 mg dose).

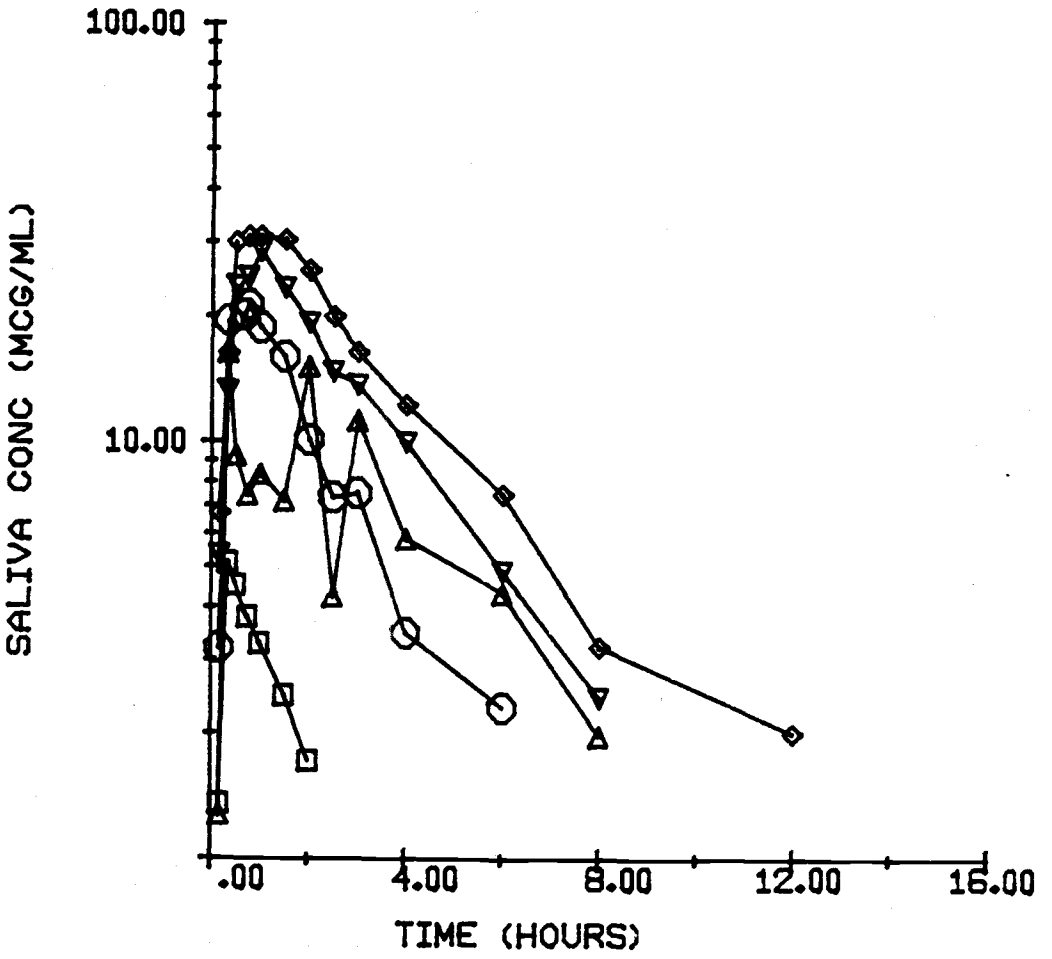

Figure D.5 Saliva acetaminophen concentrations in Subject 5 following administration of commercial acetaminophen tablets. Key: (□) 325 mg tablet; (△) 500 mg tablet; (⬡) two 500 mg tablets (1000 mg dose); (▽) three 500 mg tablets (1500 mg dose); (◇) four 500 mg tablets (2000 mg dose).

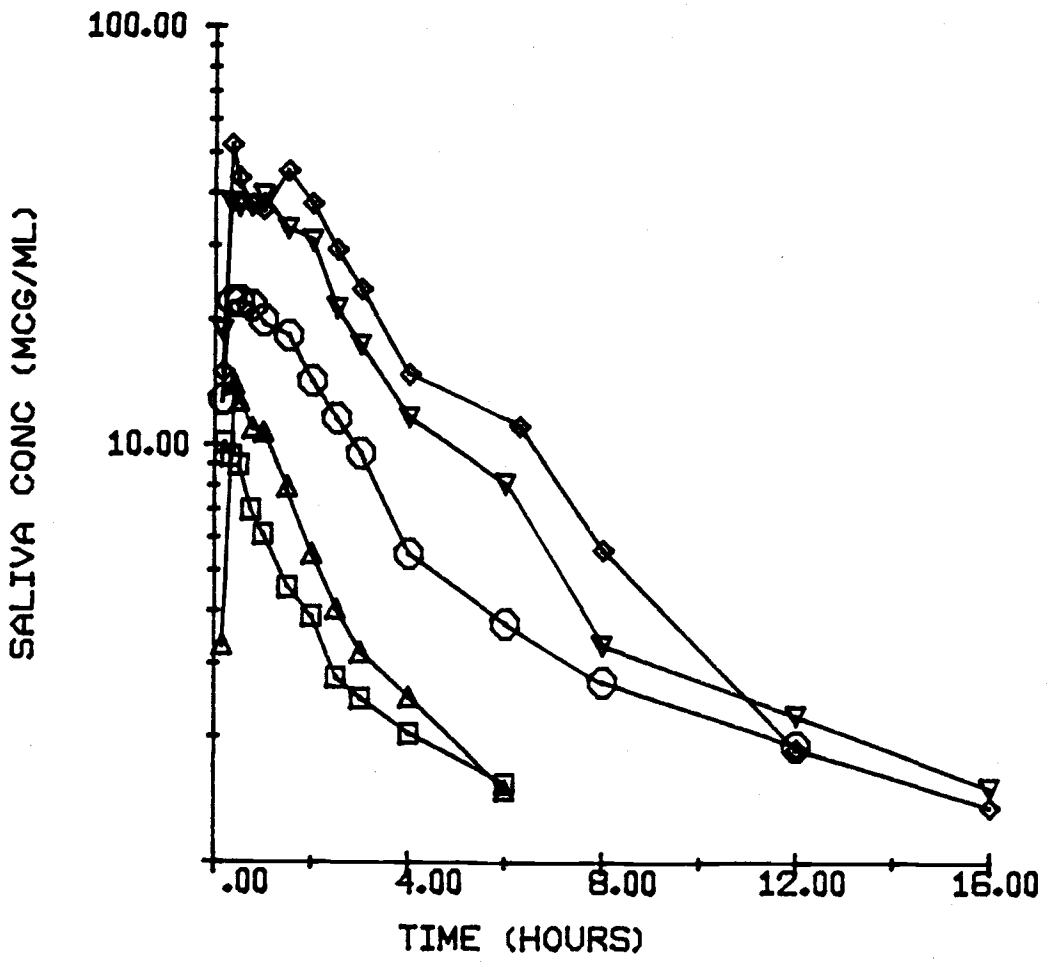

Figure D.6 Saliva acetaminophen concentrations in Subject 6 following administration of commercial acetaminophen tablets. Key: (□) 325 mg tablet; (△) 500 mg tablet; (○) two 500 mg tablets (1000 mg dose); (▽) three 500 mg tablets (1500 mg dose); (◇) four 500 mg tablets (2000 mg dose).

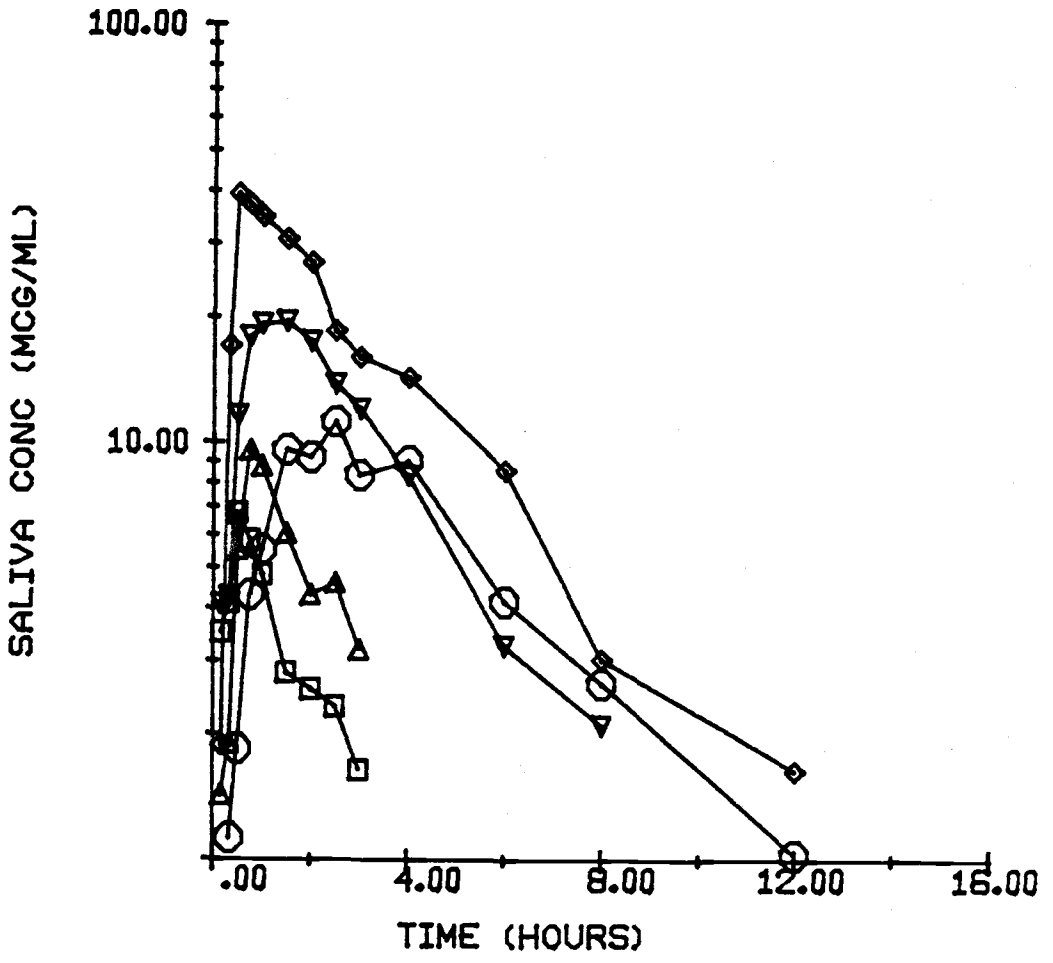

Figure D.7 Saliva acetaminophen concentrations in Subject 7 following administration of commercial acetaminophen tablets. Key: (□) 325 mg tablet; (△) 500 mg tablet; (○) two 500 mg tablets (1000 mg dose); (▽) three 500 mg tablets (1500 mg dose); (◇) four 500 mg tablets (2000 mg dose).

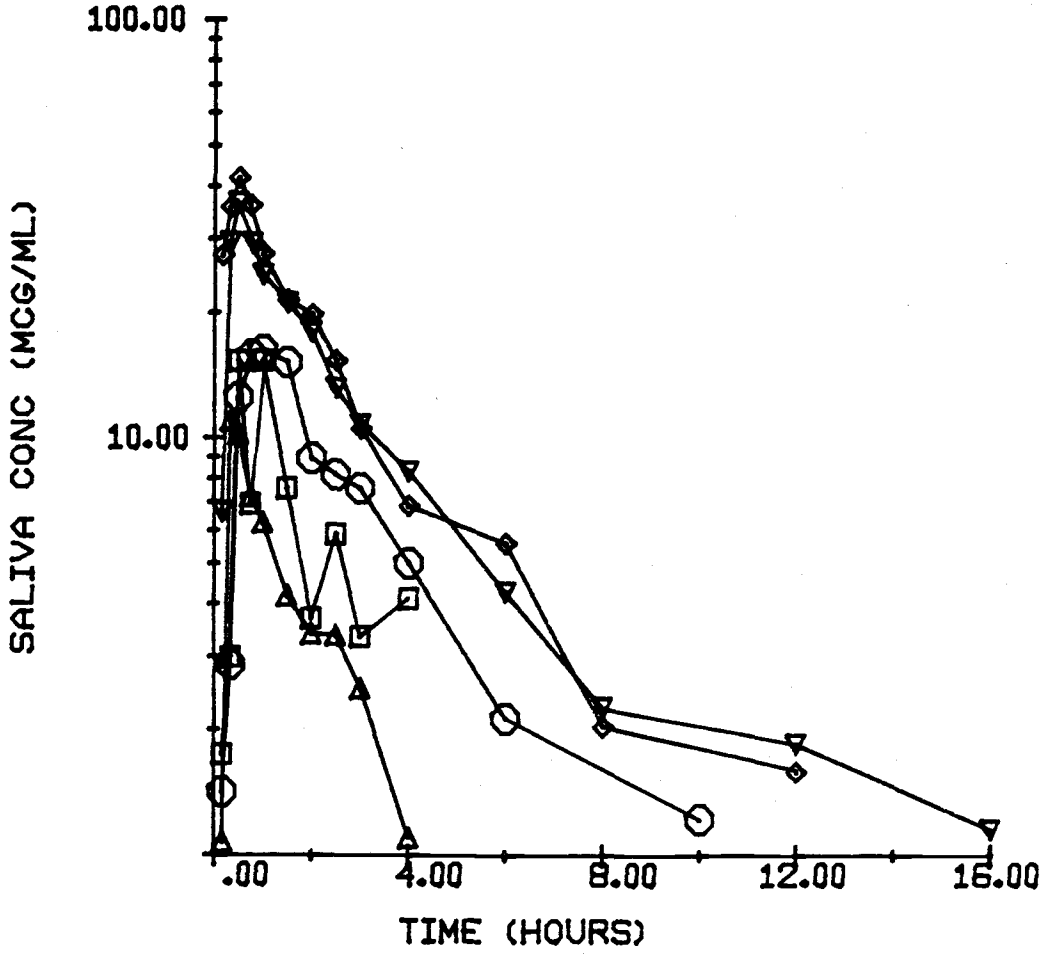

Figure D.8 Saliva acetaminophen concentrations in Subject 8 following administration of commercial acetaminophen tablets. Key: (▢) 325 mg tablet; (△) 500 mg tablet; (◯) two 500 mg tablets (1000 mg dose); (▽) three 500 mg tablets (1500 mg dose); (◇) four 500 mg tablets (2000 mg dose).

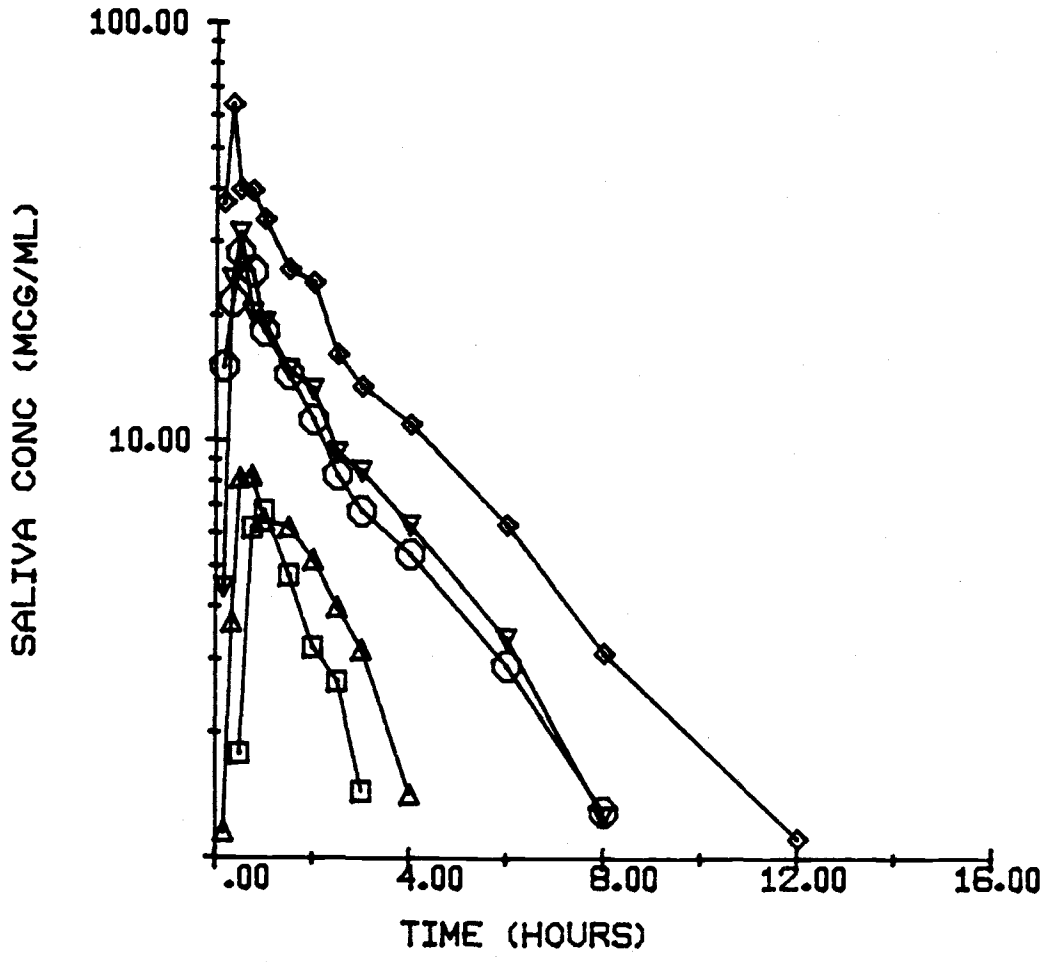

Figure D.9 Saliva acetaminophen concentrations in Subject 9 following administration of commercial acetaminophen tablets. Key: (□) 325 mg tablet; (△) 500 mg tablet; (⬡) two 500 mg tablets (1000 mg dose); (▽) three 500 mg tablets (1500 mg dose); (◇) four 500 mg tablets (2000 mg dose).

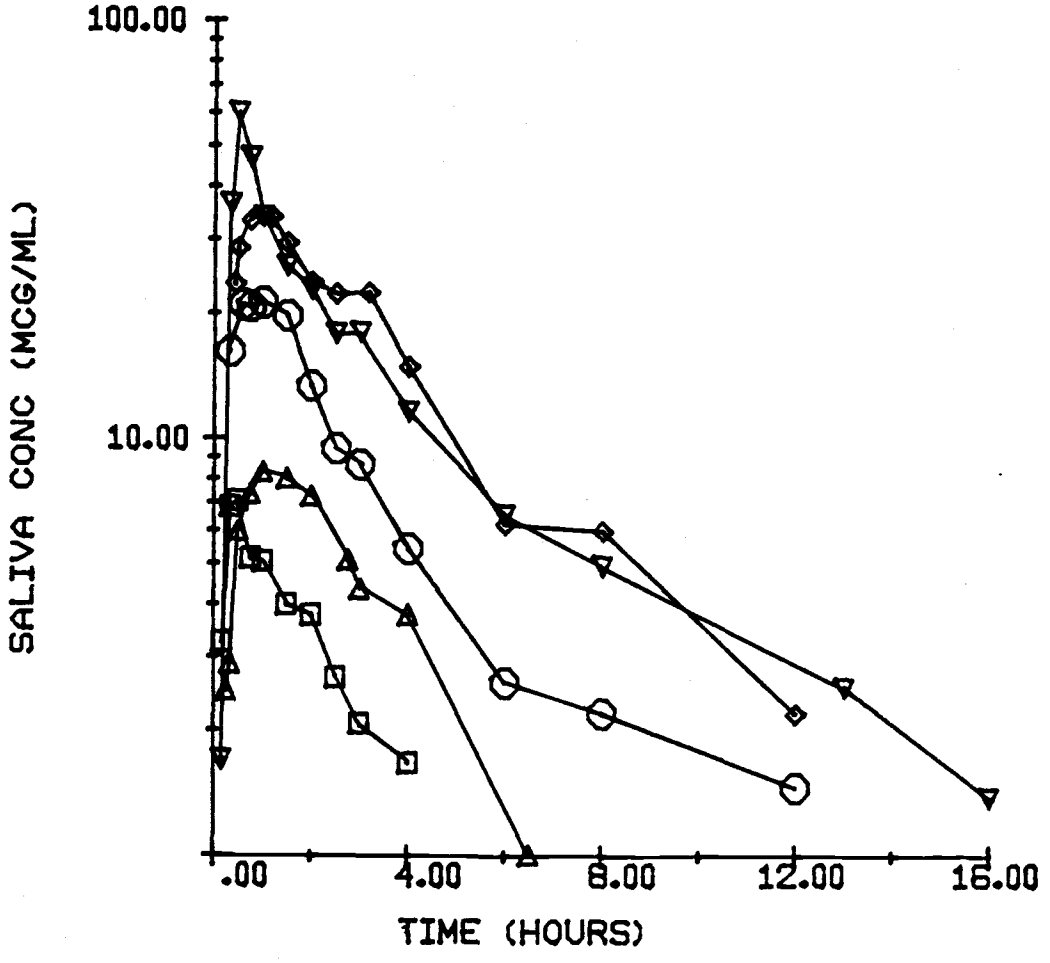

Figure D.10 Saliva acetaminophen concentrations in Subject 10 following administration of commercial acetaminophen tablets. Key: (□) 325 mg tablet; (△) 500 mg tablet; (○) two 500 mg tablets (1000 mg dose); (▽) three 500 mg tablets (1500 mg dose); (◇) four 500 mg tablets (2000 mg dose).

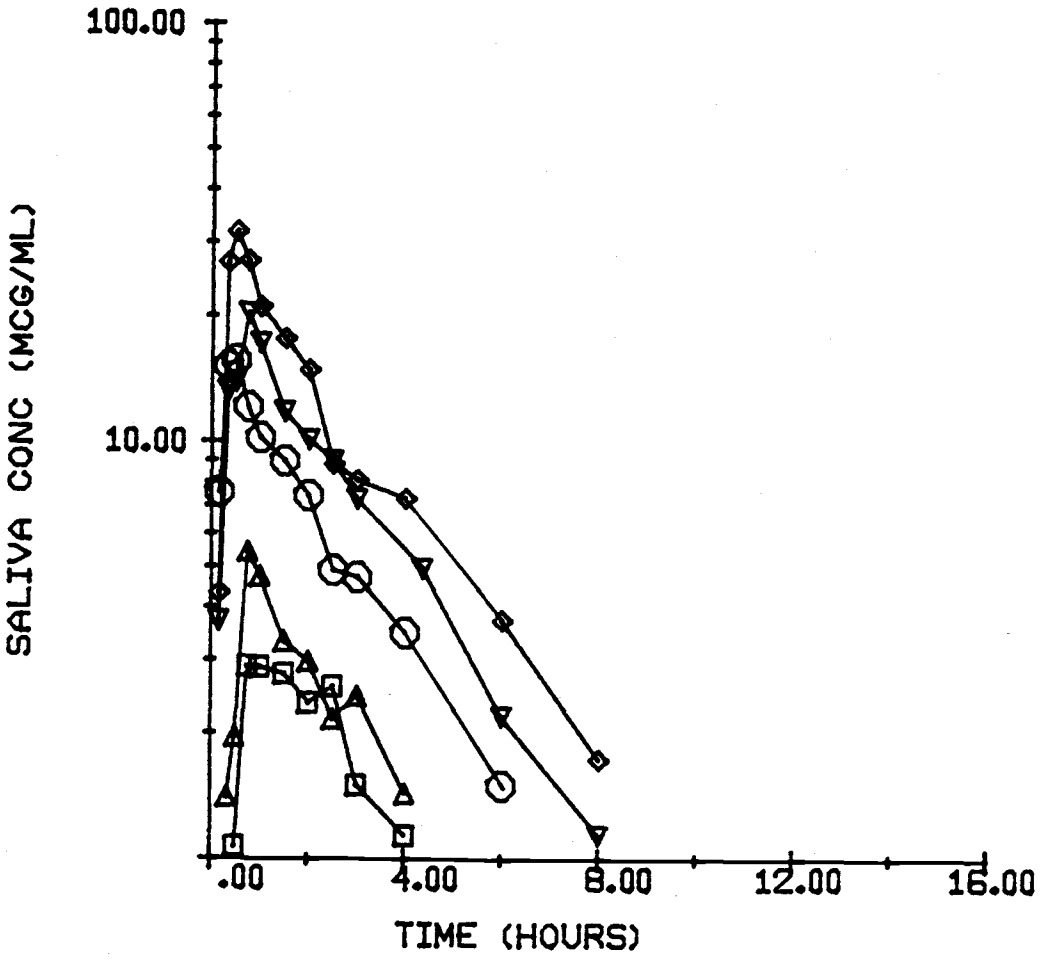

Figure D.11 Saliva acetaminophen concentrations in Subject 11 following administration of commercial acetaminophen tablets. Key: (□) 325 mg tablet; (△) 500 mg tablet; (○) two 500 mg tablets (1000 mg dose); (▽) three 500 mg tablets (1500 mg dose); (◇) four 500 mg tablets (2000 mg dose).

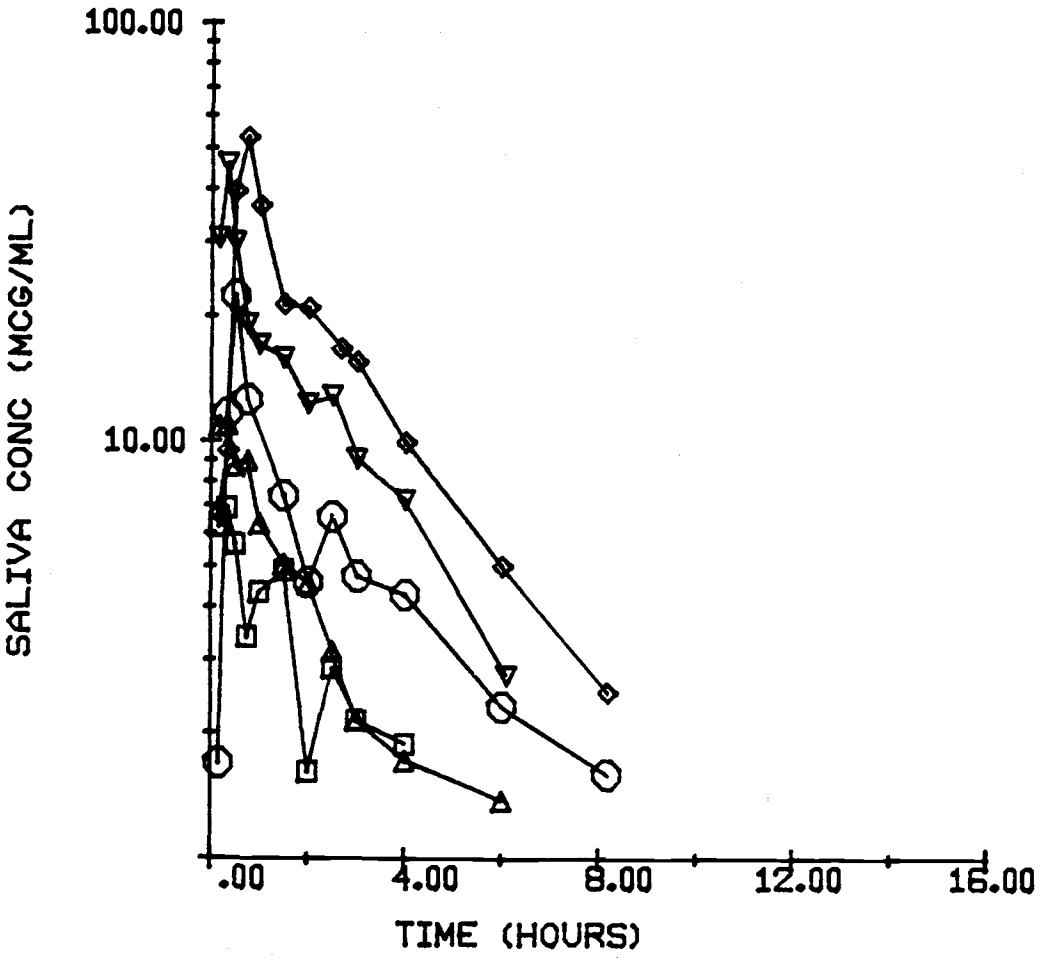

Figure D.12 Saliva acetaminophen concentrations in Subject 12 following administration of commercial acetaminophen tablets. Key: (□) 325 mg tablet; (△) 500 mg tablet; (○) two 500 mg tablets (1000 mg dose); (▽) three 500 mg tablets (1500 mg dose); (◇) four 500 mg tablets (2000 mg dose).

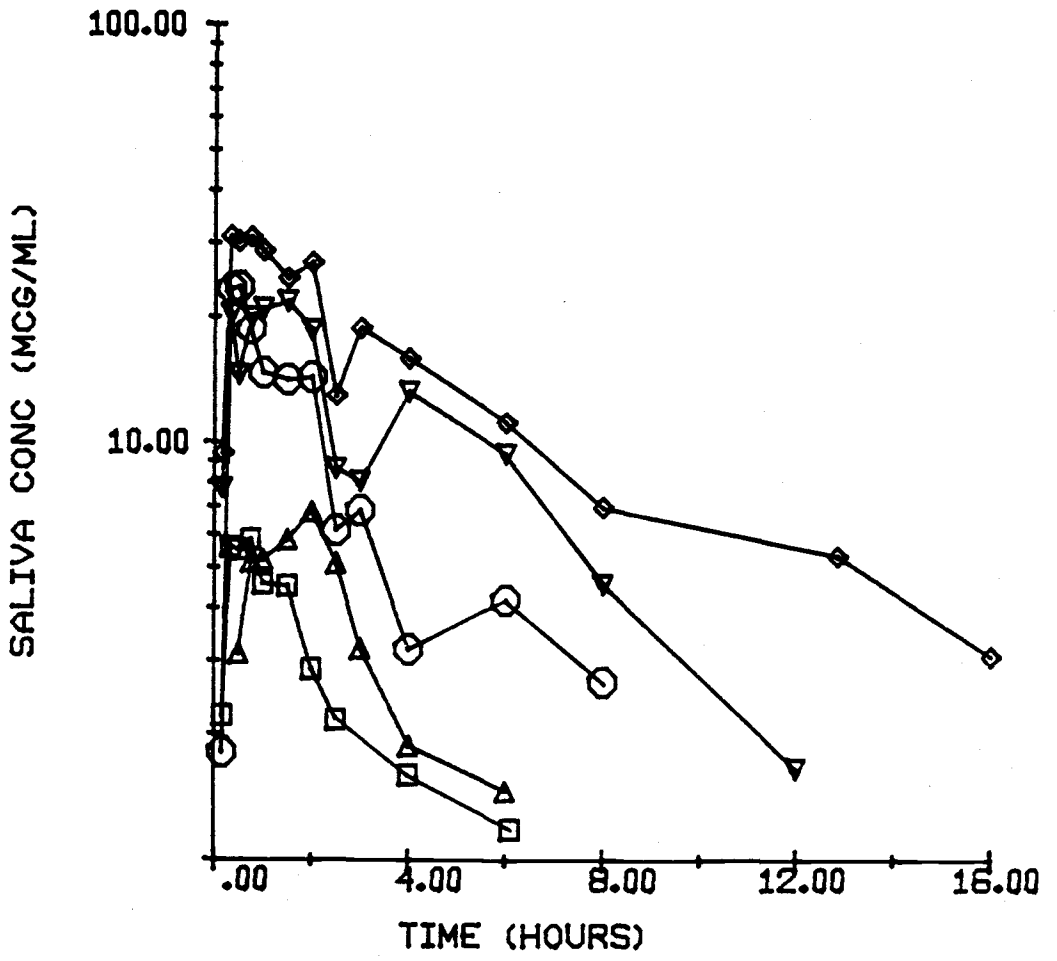

Figure D.13 Saliva acetaminophen concentrations in Subject 13 following administration of commercial acetaminophen tablets. Key: (□) 325 mg tablet; (△) 500 mg tablet; (○) two 500 mg tablets (1000 mg dose); (▽) three 500 mg tablets (1500 mg dose); (◇) four 500 mg tablets (2000 mg dose).

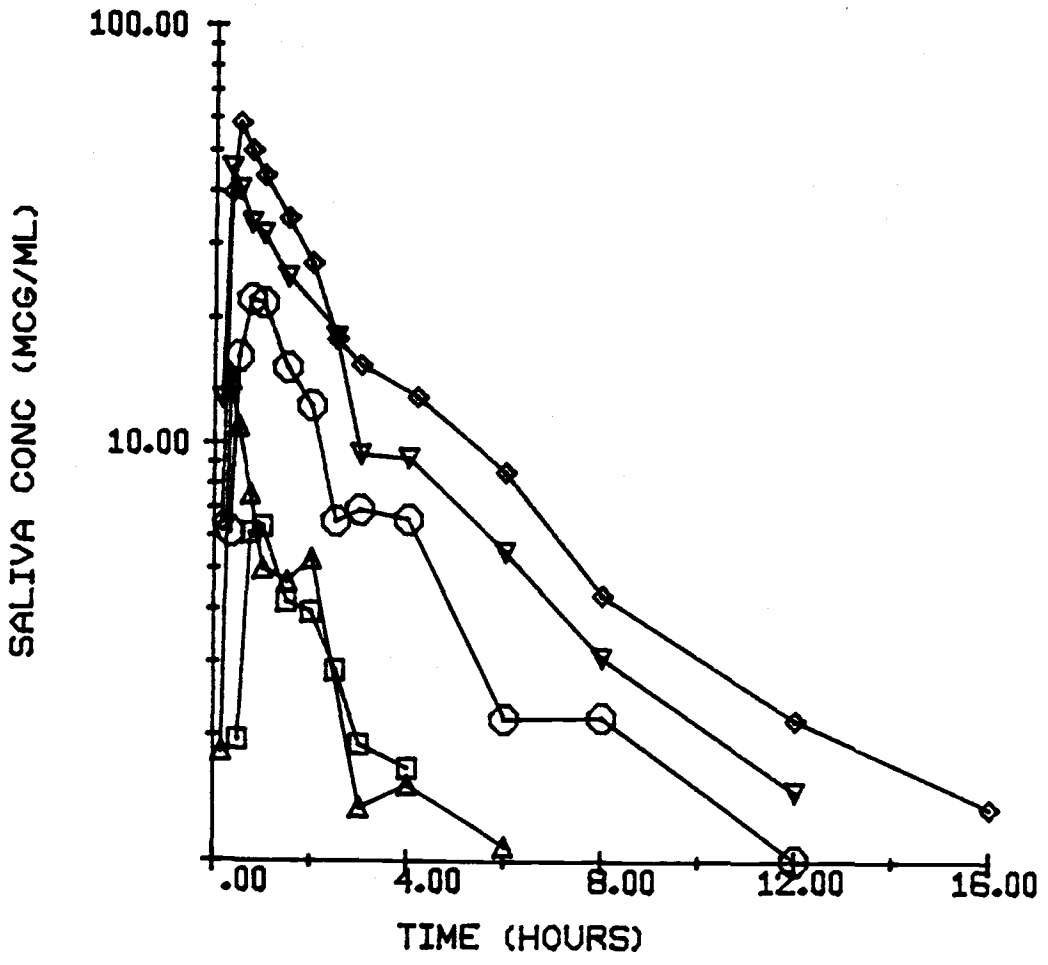

Figure D.14 Saliva acetaminophen concentrations in Subject 14 following administration of commercial acetaminophen tablets. Key: (□) 325 mg tablet; (△) 500 mg tablet; (○) two 500 mg tablets (1000 mg dose); (▽) three 500 mg tablets (1500 mg dose); (◇) four 500 mg tablets (2000 mg dose).

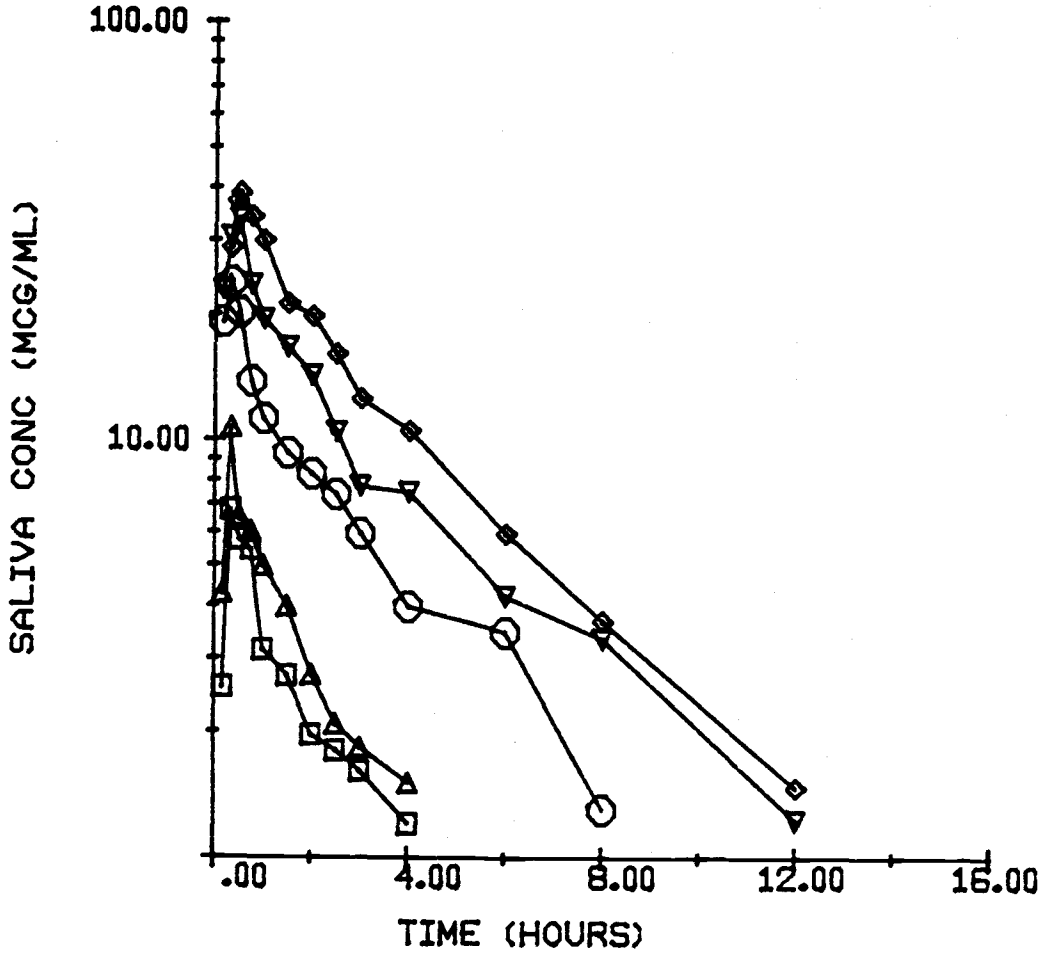

Figure D.15 Saliva acetaminophen concentrations in Subject 15 following administration of commercial acetaminophen tablets. Key: (□) 325 mg tablet; (△) 500 mg tablet; (⬡) two 500 mg tablets (1000 mg dose); (▽) three 500 mg tablets (1500 mg dose); (◇) four 500 mg tablets (2000 mg dose).

APPENDIX E. Saliva Concentration-Time Data for Individual Subjects

Table E.1 Saliva Acetaminophen Concentrations (µg/ml) Following Oral Administration of 325 mg Acetaminophen Tablet

Time, hr	Subject No. 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0.167	1.463	4.489	1.085	3.002	1.354	---	3.519	1.747	---	3.263	---	6.246	2.218	---	2.562
0.200	---	---	---	---	---	10.13	---	---	---	---	---	---	---	---	---
0.333	8.046	10.64	5.460	5.792	5.124	9.399	4.125	2.999	---	6.875	---	6.905	5.619	---	6.819
0.500	11.13	9.633	6.008	5.470	4.524	8.957	6.770	15.33	1.787	7.103	1.070	5.664	5.527	1.957	5.769
0.750	7.259	8.288	4.170	4.112	3.804	6.994	5.838	6.960	6.193	5.179	2.901	3.401	5.841	6.104	5.451
1.000	6.029	6.396	3.719	3.504	---	6.119	4.831	15.40	6.786	5.089	2.890	4.356	4.585	6.324	3.149
1.083	---	---	---	---	3.290	---	---	---	---	---	---	---	---	---	---
1.500	4.597	5.171	2.754	3.006	2.471	4.561	2.812	7.578	4.764	4.013	2.785	4.910	4.528	4.184	2.730
2.000	3.763	4.232	2.582	2.147	1.716	3.889	2.566	3.701	3.207	3.788	2.371	1.616	2.866	3.955	1.967
2.500	2.788	2.863	1.925	1.581	---	2.780	2.330	5.892	2.658	2.685	2.597	2.870	2.168	2.867	1.802
3.000	2.638	---	1.876	1.622	---	2.478	1.644	3.352	1.447	2.084	1.504	2.149	---	1.905	1.611
3.500	---	2.939	---	---	---	---	---	---	---	---	---	---	---	---	---
4.000	2.118	---	1.148	1.133	---	2.039	---	4.131	---	1.678	1.141	1.885	1.600	1.669	1.204
4.250	---	2.080	---	---	---	---	---	---	---	---	---	---	---	---	---
6.000	1.115	1.531	---	---	---	1.547	---	---	---	---	---	---	---	---	---
6.100	---	---	---	---	---	---	---	---	---	---	---	---	1.187	---	---
8.000	---	1.097	---	---	---	---	---	---	---	---	---	---	---	---	---

Table E.2 Saliva Acetaminophen Concentrations (µg/ml) Following Oral Administration of 500 mg Acetaminophen Tablet

Time, hr	Subject No.														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0.167	---	3.078	1.577	---	1.268	3.313	1.427	1.075	1.154	---	---	10.84	---	1.830	4.293
0.250	---	---	---	---	---	---	---	---	---	2.497	---	---	---	---	---
0.333	---	12.81	8.681	3.878	16.34	---	1.898	11.02	3.686	2.895	1.406	10.92	---	14.21	10.73
0.400	---	---	---	---	---	13.96	---	---	---	---	---	---	---	---	---
0.500	---	12.89	10.78	4.828	9.236	12.71	5.531	10.21	8.149	6.006	1.966	8.672	3.122	10.99	6.572
0.750	2.170	11.65	9.402	5.989	7.436	---	9.593	7.255	8.251	7.368	5.466	8.962	5.175	7.561	6.046
0.767	---	---	---	---	---	10.97	---	---	---	---	---	---	---	---	---
1.000	5.299	10.56	7.339	5.388	8.346	10.72	8.771	6.288	6.404	8.323	4.768	6.322	---	5.010	4.998
1.083	---	---	---	---	---	---	---	---	---	---	---	---	5.223	---	---
1.500	12.02	8.425	6.214	4.294	7.200	7.930	6.056	4.197	6.206	8.033	3.338	5.055	5.843	4.676	4.000
2.000	10.28	7.826	3.690	3.614	15.15	5.483	4.320	3.404	5.178	7.273	2.985	4.551	6.824	5.289	2.747
2.500	6.825	5.505	3.827	3.124	4.246	4.048	4.618	3.379	3.998	---	2.171	3.137	5.135	---	2.091
2.750	---	---	---	---	---	---	---	---	---	5.120	---	---	---	---	---
3.000	4.984	5.267	---	2.861	11.24	3.196	3.201	2.526	3.171	4.376	2.472	2.145	3.219	1.345	1.836
4.000	3.265	4.563	3.066	2.141	5.844	2.495	0.979	1.103	1.423	3.802	1.439	1.717	1.882	1.525	1.512
6.000	1.756	2.454	1.634	---	4.329	1.491	---	---	---	---	---	1.381	1.468	1.088	---
6.500	---	---	---	---	---	---	---	---	---	1.009	---	---	---	---	---
8.000	---	1.235	1.448	---	1.973	---	---	---	---	---	---	---	---	---	---

Table E.3 Saliva Acetaminophen Concentrations (µg/ml) Following Oral Administration of Two 500 mg Acetaminophen Tablets (1000 mg dose)

Time, hr	Subject No. 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0.167	---	3.644	1.245	2.344	3.201	12.82	---	1.419	15.07	---	7.557	1.689	1.809	---	19.15
0.333	3.388	34.01	5.874	6.188	19.49	22.04	1.123	2.872	21.64	16.16	15.19	11.63	23.35	6.128	23.78
0.500	9.347	27.31	8.449	10.06	---	22.04	1.842	12.55	28.12	---	15.67	22.29	23.59	16.19	20.19
0.583	---	---	---	---	---	---	---	---	---	20.93	---	---	---	---	---
0.667	---	---	---	---	20.14	---	---	---	---	---	---	---	---	---	---
0.750	22.69	24.88	11.91	12.89	21.25	21.50	4.306	---	25.43	20.77	12.14	12.56	18.72	22.16	13.82
0.767	---	---	---	---	---	---	---	15.83	---	---	---	---	---	---	---
1.000	25.38	21.10	12.11	12.63	18.78	19.85	5.521	16.24	18.32	21.18	10.23	---	14.71	21.75	11.26
1.500	17.90	19.01	15.22	8.999	15.99	---	9.577	---	14.43	19.70	8.991	7.373	14.17	15.22	9.297
1.517	---	---	---	---	---	18.26	---	---	---	---	---	---	---	---	---
1.567	---	---	---	---	---	---	---	15.21	---	---	---	---	---	---	---
2.000	13.42	15.43	10.83	6.775	10.10	14.22	9.177	8.951	11.22	13.36	7.422	4.580	14.35	12.32	8.289
2.500	10.76	11.29	6.385	5.736	7.339	11.57	11.18	8.167	8.263	9.439	4.992	6.562	6.160	6.503	7.390
3.000	8.168	12.01	7.296	4.687	7.516	9.538	8.339	7.586	6.770	8.644	4.734	4.735	6.882	6.940	5.954
4.000	5.468	7.088	5.303	3.147	3.486	5.478	9.005	5.028	5.347	5.441	3.499	4.285	3.204	6.570	3.988
6.000	2.315	5.686	3.745	1.478	2.312	3.736	4.157	---	2.902	2.606	1.507	2.320	4.202	2.202	3.473
6.100	---	---	---	---	---	---	---	2.136	---	---	---	---	---	---	---
8.000	---	3.294	2.125	1.125	---	2.709	2.649	---	1.293	2.198	---	---	2.678	2.216	1.303
8.170	---	---	---	---	---	---	---	---	---	---	---	1.595	---	---	---
10.00	---	---	---	---	---	---	---	1.222	---	1.459	---	---	---	1.008	---
12.00	---	2.074	1.401	---	---	1.906	1.029	---	---	---	---	---	---	---	---
16.00	---	1.114	---	---	---	---	---	---	---	---	---	---	---	---	---

Table E.4 Saliva Acetaminophen Concentrations (µg/ml) Following Oral Administration of Three 500 mg Acetaminophen Tablets (1500 mg dose)

Time, hr	Subject No. 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0.167	1.169	8.315	3.107	12.74	5.323	18.70	4.095	6.646	4.441	1.691	3.714	30.56	7.755	12.78	22.80
0.333	14.86	24.55	19.14	32.03	13.22	37.78	4.251	29.44	24.34	36.34	13.25	45.87	20.34	45.44	30.52
0.500	44.89	40.10	31.69	28.49	23.54	37.11	11.59	36.60	31.36	60.04	13.95	29.87	14.53	40.50	33.73
0.750	52.85	36.61	22.17	18.39	24.70	37.18	17.95	---	20.17	46.94	20.34	19.14	19.92	33.67	23.53
0.783	---	---	---	---	---	---	---	29.25	---	---	---	---	---	---	---
1.000	40.88	34.22	21.06	18.31	28.59	39.42	19.24	24.65	19.19	33.94	17.26	17.05	20.93	31.77	19.48
1.500	31.86	28.92	19.56	14.00	23.32	32.80	19.49	21.10	14.80	25.92	11.80	15.83	21.77	25.07	16.70
2.000	25.08	22.50	14.64	10.98	19.25	30.70	17.47	18.01	13.28	22.77	10.11	12.29	18.60	---	14.28
2.500	21.05	23.19	9.439	7.972	14.69	21.23	13.81	13.17	9.339	17.87	8.988	12.83	8.648	18.04	10.42
3.000	19.22	20.89	8.923	7.180	13.67	17.36	12.01	10.78	8.432	18.04	7.283	9.037	8.062	9.433	7.740
4.000	13.42	14.10	8.024	4.629	9.942	11.61	8.303	8.313	6.254	11.60	---	7.209	13.24	9.222	7.488
4.350	---	---	---	---	---	---	---	---	---	---	4.967	---	---	---	---
6.000	7.212	---	5.621	2.064	4.881	8.057	3.261	4.284	3.367	6.559	2.206	---	9.403	5.508	4.224
6.100	---	---	---	---	---	---	---	---	---	---	---	2.751	---	---	---
6.333	---	6.734	---	---	---	---	---	---	---	---	---	---	---	---	---
8.000	4.045	---	3.073	1.789	2.438	3.310	2.101	2.266	1.253	4.945	1.143	---	4.574	3.083	3.345
8.833	---	5.147	---	---	---	---	---	---	---	---	---	---	---	---	---
12.00	3.458	1.633	1.654	---	---	2.250	---	1.856	---	---	---	---	1.658	1.471	1.230
13.00	---	---	---	---	---	---	---	---	---	2.540	---	---	---	---	---
16.00	---	1.064	---	---	---	1.505	---	1.154	---	1.381	---	---	---	---	---

Table E.5 Saliva Acetaminophen Concentrations (µg/ml) Following Oral Administration of Four 500 mg Acetaminophen Tablets (2000 mg dose)

Time, hr	Subject No. 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0.167	14.12	1.699	21.13	27.61	6.728	14.95	1.882	27.43	37.24	---	4.338	6.682	9.445	6.501	---
0.333	33.44	15.70	50.73	32.89	16.35	52.17	17.11	35.83	63.83	23.51	26.93	9.489	31.19	39.88	28.80
0.417	---	---	---	---	---	---	---	---	---	---	---	---	---	---	37.29
0.500	49.61	47.34	42.96	29.08	30.00	43.44	39.40	42.08	40.03	28.64	31.87	39.56	30.31	58.53	38.92
0.750	50.73	60.30	37.63	23.17	31.00	---	37.07	36.08	39.71	33.34	27.17	53.21	31.10	50.24	34.18
0.767	---	---	---	---	---	37.53	---	---	---	---	---	---	---	---	---
1.000	44.50	46.76	29.93	20.37	30.98	36.50	34.73	27.65	33.92	---	21.12	---	28.82	43.80	29.97
1.083	---	---	---	---	---	---	---	---	---	---	---	36.59	---	---	---
1.167	---	---	---	---	---	---	---	---	---	33.94	---	---	---	---	---
1.500	41.99	43.16	26.71	16.03	30.42	45.21	30.70	21.43	25.73	29.44	17.71	21.33	24.79	34.68	21.20
2.000	29.18	35.02	21.55	13.12	25.70	37.77	27.01	19.81	23.94	23.72	14.91	20.89	26.98	27.12	19.79
2.500	22.51	28.22	17.92	10.98	19.98	29.36	18.57	15.38	16.14	22.29	8.846	---	13.01	17.90	16.06
2.670	---	---	---	---	---	---	---	---	---	---	---	16.67	---	---	---
3.000	21.04	24.44	15.87	6.999	16.40	23.66	16.05	10.54	13.52	---	8.103	15.51	18.88	15.51	12.55
3.170	---	---	---	---	---	---	---	---	---	22.48	---	---	---	---	---
4.000	15.80	20.13	10.20	6.569	12.26	14.75	14.36	6.885	10.96	14.90	7.326	9.934	15.96	---	10.52
4.170	---	---	---	---	---	---	---	---	---	---	---	---	---	13.01	---
6.000	9.285	12.18	10.06	4.011	7.486	---	8.583	5.613	6.307	6.236	3.761	5.029	11.22	8.591	5.963
6.270	---	---	---	---	---	11.09	---	---	---	---	---	---	---	---	---
8.000	5.202	6.980	5.060	---	3.234	5.603	3.036	2.040	3.110	6.008	1.744	---	7.017	4.353	3.693
8.170	---	---	---	---	---	---	---	---	---	---	---	2.515	---	---	---
8.670	---	---	---	1.906	---	---	---	---	---	---	---	---	---	---	---
12.00	1.918	2.632	2.652	---	2.008	1.875	1.642	1.592	1.114	2.199	---	---	---	2.195	1.474
12.83	---	---	---	---	---	---	---	---	---	---	---	---	5.368	---	---
16.00	---	1.155	1.425	---	---	---	---	---	---	---	---	---	---	1.348	---
16.70	---	---	---	---	---	1.355	---	---	---	---	---	---	3.097	---	---

APPENDIX F. One and Two Compartment Open Models with First-Order Input[a,b]

One compartment model:

$$C = k_a FD/[V(k_a - k_{el})](e^{-k_{el}t} - e^{-k_a t})$$

One compartment model with lag time (t_l):

$$C = k_a FD/[V(k_a - k_{el})][e^{-k_{el}(t-t_l)} - e^{-k_a(t-t_l)}]$$

where k_a is the apparent first-order absorption rate constant, F is the fraction of the dose, D, that is absorbed, V is the apparent volume of distribution, and k_{el} is the apparent first-order elimination rate constant. AUTOAN2 provides estimates of k_{el}, k_a, C_0 and t_l.

$$AUC = FD/Vk_{el}$$

$$t_{\frac{1}{2}} = 0.693/k_{el}$$

where FD/V is C_0.

Two compartment model:

$$C = [k_a FD(k_{21} - \alpha)/V_1(k_a - \alpha)(\beta - \alpha)][e^{-\alpha t}] + [k_a FD(k_{21} - \beta)/V_1(k_a - \beta)(\alpha - \beta)][e^{-\beta t}] + [k_a FD(k_{21} - k_a)/V_1(\alpha - k_a)(\beta - k_a)][e^{-k_a t}]$$

Two compartment model with lag time (t_l):

$$C = [k_a FD(k_{21} - \alpha)/V_1(k_a - \alpha)(\beta - \alpha)][e^{-\alpha(t-t_l)}] + [k_a FD(k_{21} - \beta)/V_1(k_a - \beta)(\alpha - \beta)][e^{-\beta(t-t_l)}] + [k_a FD(k_{21} - k_a)/V_1(\alpha - k_a)(\beta - k_a)][e^{-k_a(t-t_l)}]$$

where k_a, k_{el}, F and D are as defined above, k_{12} and k_{21} are first-order rate constants for intercompartmental

transfer of drug between the central and peripheral compartments, V_1 is the volume of the central compartment, α is the distribution rate constant, and ß is the elimination rate constant. AUTOAN2 provides estimates of k_{12}, k_{el}, k_{21}, k_a, C_0, and t_1.

$$AUC = FD/V_1k_{el}$$

$$\alpha = 1/2[(k_{12}+k_{21}+k_{el}) + ((k_{12}+k_{21}+k_{el})^2-4k_{21}k_{el})^{\frac{1}{2}}]$$

$$ß = 1/2[(k_{12}+k_{21}+k_{el}) - ((k_{12}+k_{21}+k_{el})^2-4k_{21}k_{el})^{\frac{1}{2}}]$$

$$t_{\frac{1}{2}} = 0.693/ß$$

where FD/V_1 is C_0.

[a]Gibaldi, M. and Perrier, D., Pharmacokinetics, 2nd Edn, Marcell Dekker, Inc., New York, 1982.

[b]Wagner, J.G., Fundamentals of Clinical Pharmacokinetics, Drug Intelligence Publications, Inc., Hamilton, 1975.