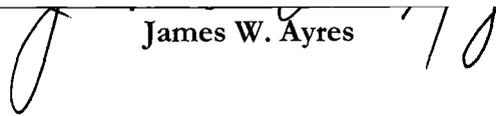


AN ABSTRACT OF THE THESIS OF

Carol Ann Keller for the degree of Doctor of Philosophy in Pharmacy presented on May 4, 2000. Title: Development and Testing of a Sustained Release Acetaminophen Tablet for the Treatment of Chronic Pain in Osteoarthritis Patients.

Redacted for privacy

Abstract approved:

 James W. Ayres

Acetaminophen has been safely used for analgesia for many years.

Literature suggests that a plasma acetaminophen level of $5\mu\text{g/ml}$ is necessary to maintain analgesic relief in humans. Current dosing regimens are inconvenient (every 4-6 hours) and do not maintain this minimum plasma level. Simulations were conducted to examine various doses and input rates for sustained release formulations of acetaminophen. Once parameters were selected from the simulations, sample formulations were prepared and tested using standard dissolution techniques. Investigations into dose/size relationships, hydroxypropylmethylcellulose (HPMC) percentage for erosion matrix tablets, compression force, tablet shape, tablet divisibility, and granulation methods were performed for non-disintegrating hydrophilic matrix tablets.

Tablets containing 5% and 7.5% HPMC were selected for pharmacokinetic study in 10 healthy human subjects. Tylenol Extra Strength and Tylenol Extended Relief tablets were administered as control formulations. Pharmacokinetic fitting of

the kinetic profiles of all four formulations were performed using Win Nonlin. The formulations were best described by a 1-compartment open model with first order input and first order elimination. The 5% HPMC sustained release acetaminophen formulation was selected for Phase II clinical trials.

Patients with osteoarthritis of the knee were recruited for a double blind crossover study of 5% HPMC sustained release acetaminophen formulations and immediate release acetaminophen. Patients received two tablets of study medication, four times a day for 4 weeks. After a seven day wash-out period patients were then crossed over to the other treatment. Patients were evaluated using a twelve question questionnaire and the time to walk 50 feet was measured. Thirty patients were enrolled in the study and seventeen patients completed the study. The sustained release formulations were statistically superior to the baseline treatments in reducing pain level, decreasing disability, and improving the duration of pain relief. Additional, larger scale studies are needed to confirm these findings.

**Development and Testing of a Sustained Release Acetaminophen Tablet for the
Treatment of Chronic Pain in Osteoarthritis Patients**

by

Carol Ann Keller

A THESIS

Submitted to

Oregon State University

**in partial fulfillment of
the requirements for the
degree of**

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**Presented May 4, 2000
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Doctor of Philosophy in Pharmacy thesis of Carol Ann Keller presented

on May 4, 2000

APPROVED:

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I understand that my thesis will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my thesis to any reader upon request.

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Carol Ann Keller, Author

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This thesis is dedicated to my grandmother, Monico Haywood, from whom I inherited the stubbornness and perseverance necessary to succeed.

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DEVELOPMENT AND TESTING OF A SUSTAINED RELEASE ACETAMINOPHEN TABLET FOR THE TREATMENT OF CHRONIC PAIN IN OSTEOARTHRITIS PATIENTS

INTRODUCTION

Osteoarthritis affects nearly 10 % of the population over age 60 and is second only to cardiovascular disease in causing severe chronic pain and disability. These patients suffer from increasing disability and chronic pain. Acetaminophen has been shown to be effective in relieving the pain caused by osteoarthritis, but the dosing interval is inconvenient (every 4-6 hours) and chronic use of high doses of acetaminophen are associated with hepatic toxicity. This research was designed to use both the pharmacodynamic properties and pharmacokinetic parameters of acetaminophen to design a sustained release dosage form of acetaminophen to relieve chronic pain in osteoarthritis and other chronic pain patients.

Chapter 1 describes the design and testing of several sustained release acetaminophen formulations. Formulations are hydrophilic matrix tablets made with hydroxypropylmethylcellulose (HPMC) and are tested using standard dissolution techniques. Investigations into tablet size, tablet shape, HPMC content, amount of drug, and tablet disintegration were performed. Two promising formulations were then selected for pharmacokinetic characterization in human subjects.

Chapter 2 describes the pharmacokinetic characterization of the 5% and 7.5% HPMC formulations of acetaminophen. Tylenol Extra Strength and Tylenol Extended Relief tablets were used as reference formulations. Each of the formulations was administered to ten healthy human subjects and saliva concentrations were measured. The saliva data was used to

characterize the pharmacokinetic parameters of each formulation. The 5% HPMC sustained release formulation was selected for testing in the target population.

Chapter 3 describes the double blind, placebo controlled crossover study conducted comparing four grams of immediate release acetaminophen per day to 2.6 grams of sustained release acetaminophen per day in patients with osteoarthritis of the knee. Patients with osteoarthritis were recruited from the Veterans Administration Outpatient clinic.

Performance of the products was tested by a twelve question questionnaire and a timed walking test. The sustained release acetaminophen formulations was compared to the immediate release formulation as well as to the baseline treatments to determine efficacy in these patients.

CHAPTER 1

FORMULATION OF A SUSTAINED RELEASE ACETAMINOPHEN

PRODUCT: FROM CONCEPT TO PRODUCTION

ABSTRACT

Acetaminophen has been safely used for analgesia for many years. Literature suggests that a plasma acetaminophen level of 5mg/L is necessary to maintain analgesic relief in humans. Current dosing regimens are inconvenient (every 4-6 hours). Simulations were conducted to examine various doses and input rates for sustained release formulation of acetaminophen. Once parameters were selected from the simulations, sample formulations were prepared and tested. Investigations into dose/size relationships, hydroxypropylmethylcellulose (HPMC) percentage for erosion matrix tablets, compression force, tablet shape, tablet divisibility, and granulation methods were performed for non-disintegrating hydrophilic matrix tablets. Dose/size ratios for tablets ranging from 500mg to 650mg were investigated and tablets with 650mg of acetaminophen were selected as being an acceptable size. Drug release from tablets was inversely related to increasing HPMC percentage. Compression force of 4,000-10,000 pounds did not affect drug release from tablets. Drug release from substantially different shaped tablets was related to surface area of the dosage form as suggested by the Noyes-Whitney equation. Drug release from tablet halves was not significantly different then from intact tablets. Two wet granulation methods and one slugging technique were investigated. Methods were evaluated for percent yield of granules of proper size, time/labor involvement, and ease of scale-up. A preliminary formulation that met the simulation goals was selected for further study.

INTRODUCTION

Acetaminophen has been safely used as an effective analgesic and anti-pyretic medication for many years. While effective, acetaminophen use in chronic pain has been limited by dose related toxicity and the short half-life of the drug. Current immediate release dosage forms must be administered every 4-6 hours to maintain analgesia. The goal of this research was to use new pharmacodynamic data in conjunction with existing pharmacokinetic data to develop sustained release acetaminophen tablets for use in chronic pain. This chapter describes development and in vitro testing of a sustained release acetaminophen formulation and provides insight into rational drug design based on pharmacokinetic parameters.

DESIRED CHARACTERISTICS IN A SUSTAINED RELEASE DOSAGE FORM

The first step in rational drug design is to identify the desired characteristics of the finished formulation. Goals should be set for the minimum plasma concentration of drug, dosing interval, overall daily dose, drug release characteristics, and formulation appearance and palatability. Considerations for this acetaminophen formulation include:

1. Published pharmacokinetic data suggests that a plasma acetaminophen level of 3mg/L must be maintained for anti-pyretic activity and a level of 5mg/L must be maintained for analgesic effect¹. The steady state minimum (C_{min}) plasma concentration goal for this formulation is 5mg/L.
2. The dosing interval should be once or twice daily for best patient compliance. Since this formula is being developed for chronic pain and is likely to become an ongoing medication, patient convenience is a significant factor in clinical treatment response.
3. The overall daily dose should be minimized. Current maximum daily dose recommendations for acetaminophen are 4 grams/day²⁻⁵. Recent studies have expressed concern that even 4gms/day is too much acetaminophen and can result in chronic hepatotoxicity. The desired sustained release acetaminophen formulation would therefore contain less than 4gms/day. The Food and Drug Administration is currently investigating new recommendations for the maximum overall daily dose of acetaminophen.

Preliminary results suggest a new overall daily dose recommendation of 2.6gm/day of acetaminophen for chronic use⁶⁻⁷. Goal overall daily dose for the new formulation should therefore fall at or below 2.6gm/day.

4. Drug release characteristics from the formulation are in large part a reflection of the type of dosage form selected. Zero-order release of the medication would be ideal, however true zero-order release is difficult to achieve. Zero order release provides the most constant plasma concentrations of medication and allows the formulator to minimize the overall dose needed. Osmotic pumps are currently the only true zero order release formulations on the market. Their manufacture requires complex technology and expensive equipment which are not generally available. Realizing this limitation, true zero-order release is not a feasible reality for this product.

Pseudo zero order release can often be obtained with coated beads inside a capsule. This approach is limited by the amount of volume occupied by the beads and the amount of dead-space found within the capsule. This approach is not feasible for an acetaminophen formulation with one capsule because of the high total dose that must be delivered.

Most sustained release formulations are a blend of first and zero order release characteristics. Compressed hydrophilic polymer tablets exhibit this type of release. They are a logical choice for formulators wishing to deliver large doses, as the compression minimizes any dead space in the formulation. Hydrophilic polymers, such as hydroxypropylmethylcellulose (HPMC), are readily available in a variety of

molecular weights and purities and require no special manufacturing equipment.

It was decided that this type of formulation would be best suited for a sustained release acetaminophen formulation.

5. Appearance and palatability are also important especially when dealing with chronically administered medications. The tablets must be of a size and shape conducive to swallowing with little or no perceivable taste. As acetaminophen is a bitter compound, coating of the finished product must be considered.

PHARMACOKINETIC SIMULATIONS

Once a general profile of the desired formulation is obtained, pharmacokinetic simulations may be performed to further identify desired release characteristics of the formulation. Table 1.1 is a summary of the some pharmacokinetic data found in the literature for acetaminophen.

Table 1.1: Summary of Pharmacokinetic Data for Acetaminophen

Parameter	Ref 1 ^{a,8}	Ref 2 ^{a,9}	Ref 3 ^{a,10}	Ref 4 ¹¹	Ref 5 ¹²
S	1.0	1.0	1.0	1.0	1.0
F	-----	-----	-----	0.88	-----
C _{max} (mg/L)	8.0	9.3	6.8	-----	-----
t _{max} (h)	0.5 - 1	0.7	0.9	-----	-----
t _{1/2} (h)	1.8	1.8	1.8	2.0	1.97
k _{el} (h ⁻¹)	0.385	0.376	0.39	0.346 ^b	0.351 ^b
k _a (h ⁻¹)	-----	3.25	2.20	-----	-----
Vd (L/kg)	-----	0.86	-----	0.95	0.89

- a. These references quote data for children of various ages. Several references state that the pharmacokinetic parameters do not significantly differ for children over 1 year and adults, once adjusted for weight.
- b. Calculated from the t_{1/2} using the formula $k_{el} = \ln 2 / t_{1/2}$.
Table 1.2 contains parameter values selected for pharmacokinetic simulations. They were selected as values which are representative of the literature values.

Table 1.2: Pharmacokinetic Values Selected for Simulations

Parameter	Selected Value
$t_{1/2}$ (h)	1.8
k_{el} (h^{-1})	0.385
k_a (h^{-1})	3.25
Vd (L/kg)	0.86
F	1.0
S	1.0

Several assumptions were made and some parameters were set based on the desired dosage form parameters discussed earlier. Simulations were performed using PSIPLOT assuming both zero order and first order release from the formulation.

This was done with the realization that actual release from the formulation would be not a single release mechanism but a combination of both. It is also understood that these simulations represent a starting point for the formulation and are not intended to predict exact performance of any formulation. Simulations were performed for a variety of single dose and multiple dose situations using the equations listed below.

Assumptions remaining constant throughout the simulation process are:

1. Maximum gastric transit time of any given tablet is 12 hours. After this time the tablets are assumed to have passed out of the gastrointestinal tract and contribute no further input into the system.
2. The average adult weight is assumed to be 70kg. This may not be an accurate representation of the average weight of Americans in the 1990's, but it has historical precedent as the ideal "Goodman and Gilman" person.¹²

3. The desired dosing interval (τ) is set at 12 hours. Once daily dosing was briefly investigated, however the dose needed per tablet proved to be prohibitive. Some simulations of currently available immediate release products were done for comparison purposes.

Equation A: Single Dose, First Order Input^{13,14}

$$C_p = \frac{(S)(F)(D)(k_a)}{(Vd)(wt)(k_a - k_{el})} * (e^{-k_{el}(t)} - e^{-k_a(t)})$$

Where

- C_p = the plasma acetaminophen level at any time t (mg/L)
- F = the fraction of the dose absorbed
- S = the salt form of the drug
- D = the dose given (mg)
- Vd = the apparent volume of distribution of the drug within the body (L/kg)
- wt = weight of patient (kg)
- k_{el} = the apparent elimination rate constant (h^{-1})
- k_a = the observed absorption rate constant (h^{-1})
- t = the time elapsed since administration (h)

Equation B: Single Dose, Zero Order Input^{13,14}

$$C_p = \frac{(S)(F)(D)}{(\tau)(Vd)(wt)} * (1 - e^{-k_{el}(t)})$$

K_0 is known as the zero-order input rate constant for this equation and is equal to the total dose of acetaminophen to be delivered divided by the selected value of τ . For example, the K_0 for 1500mg of acetaminophen dosed every 12 hours would be equal to 1500mg/12 hours = 125mg/hour.

Multiple dose plots were obtained by addition of the C_p contribution of each individual dose (superposition method).¹⁵ After 12 hours, input from a given dose

stopped and any remaining contribution from that dose was allowed to decay exponentially in the simulation.

Figure 1.1 is a comparison of a drug concentration vs. time curve from a simulated 1000mg immediate release dose to published plasma data¹⁶ for the same dose. Although not identical, the simulation has the same C_{max} (12.1mg/L) and t_{max} (1 hour) as the published data. Unfortunately, the published data are an average of 12 subjects and the standard deviation information for these values was not included in the publication. Both the simulated curve and the published curve fall below the target plasma concentration of 5mg/L at slightly over 3.5 hours following administration of the dose.

Figure 1.1: Comparison of Plasma Data to Simulated Data for 1000mg of Immediate Release Acetaminophen

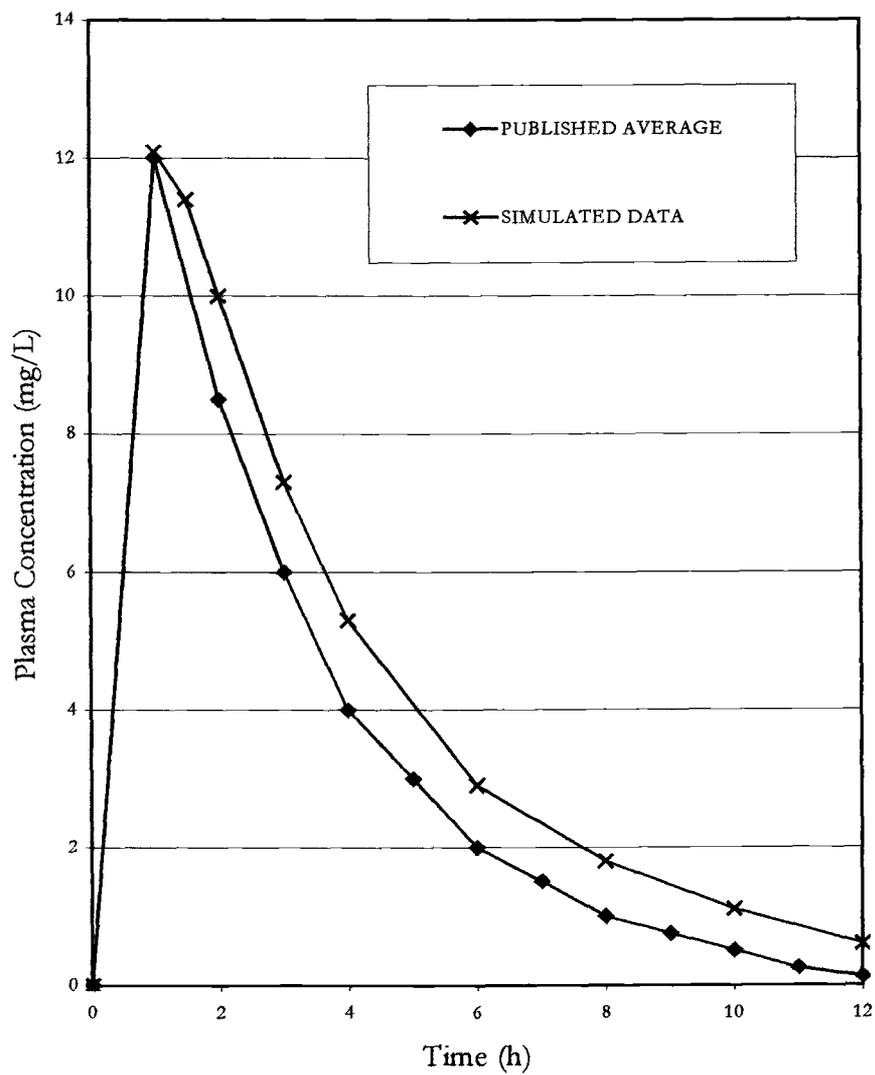
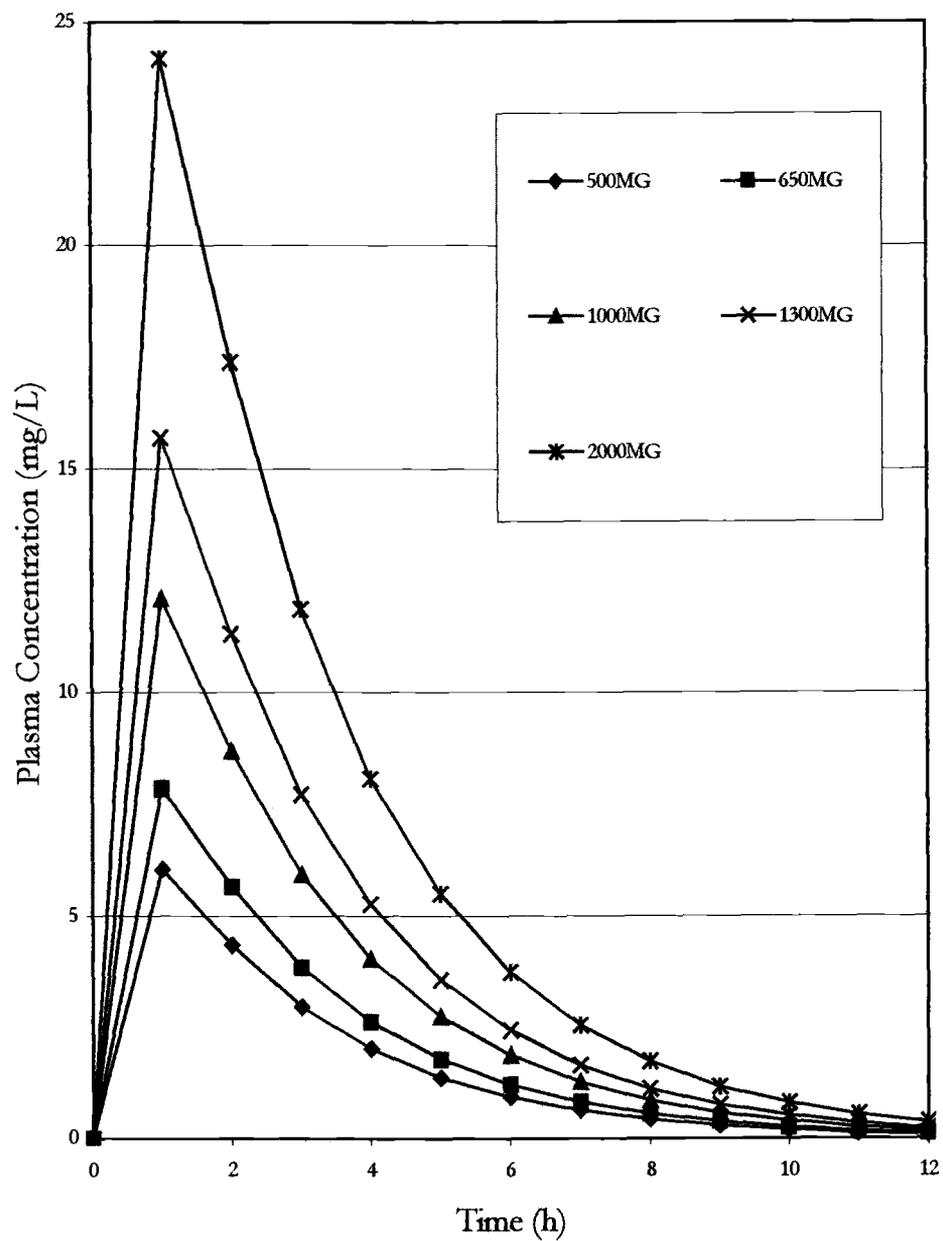


Figure 1.2 is a graph of several simulated immediate release curves that differ only in the overall dose delivered. All other pharmacokinetic parameters were kept constant. The 500mg dose barely reaches above the target plasma concentration of 5mg/L, and even drug concentrations from the 2000mg dose falls below 5mg/L soon after 5 hours. Keep in mind that these simulations are single doses only and that multiple dosing of the formulations will result in higher (but not necessarily effective) steady state plasma concentrations of drug. The currently available over the counter products recommend 650-1000mg every 4-6 hours.

Figure 1.2: Simulations of Single Dose, Immediate Release Acetaminophen at Different Overall Dosages



Figures 1.3A-D show simulations for the recommended multiple dosage regimens. The simulation for 650mg every 6 hours (Figure 1.3A) represents the lowest recommended dosing regimen. Upon multiple dosing, the plasma drug concentration is above the target level for only 40% of the dosing interval. The remaining 60% of the time there is a potential for recurring pain. The product is sub-therapeutic for 3.6 hours during each dosing interval or a total of 14.4 hours per day. By increasing the dosing frequency to 650mg every 4 hours (Figure 1.3B) the product performs slightly better but still falls below the target plasma concentration for 37% of the dosing interval. The product is sub-therapeutic 1.5 hours out of each dosing interval or 8.8 hours a day. It also has the inconvenience of requiring the patient to take the product 6 times a day! As the dose is increased to 1000mg every 6 hours (Figure 1.3C) the performance is about the same as the 650mg dose every 4 hours. The 1000mg every 6 hours dose has the advantage of being slightly more convenient for the patient because it only needs to be taken 4 times a day rather than 6 times a day. However, it still falls below the target plasma concentration for 37% of the dosing interval, and therefore still has the potential for recurring pain during this time. That's 2.2 hours per dose or 8.8 hours per day. The 1000mg every 4 hours regimen (Figure 1.3D) is the only dosing regimen to maintain the target plasma concentration for the entire dosing interval. Unfortunately it must be taken all day and night, and at 6 grams of acetaminophen per day, it has exceeded the maximum recommended daily dose of acetaminophen²⁻⁵ and may cause hepatotoxicity.

Figure 1.3A: Simulated Plasma Concentrations for 650mg of Acetaminophen Every 6 Hours

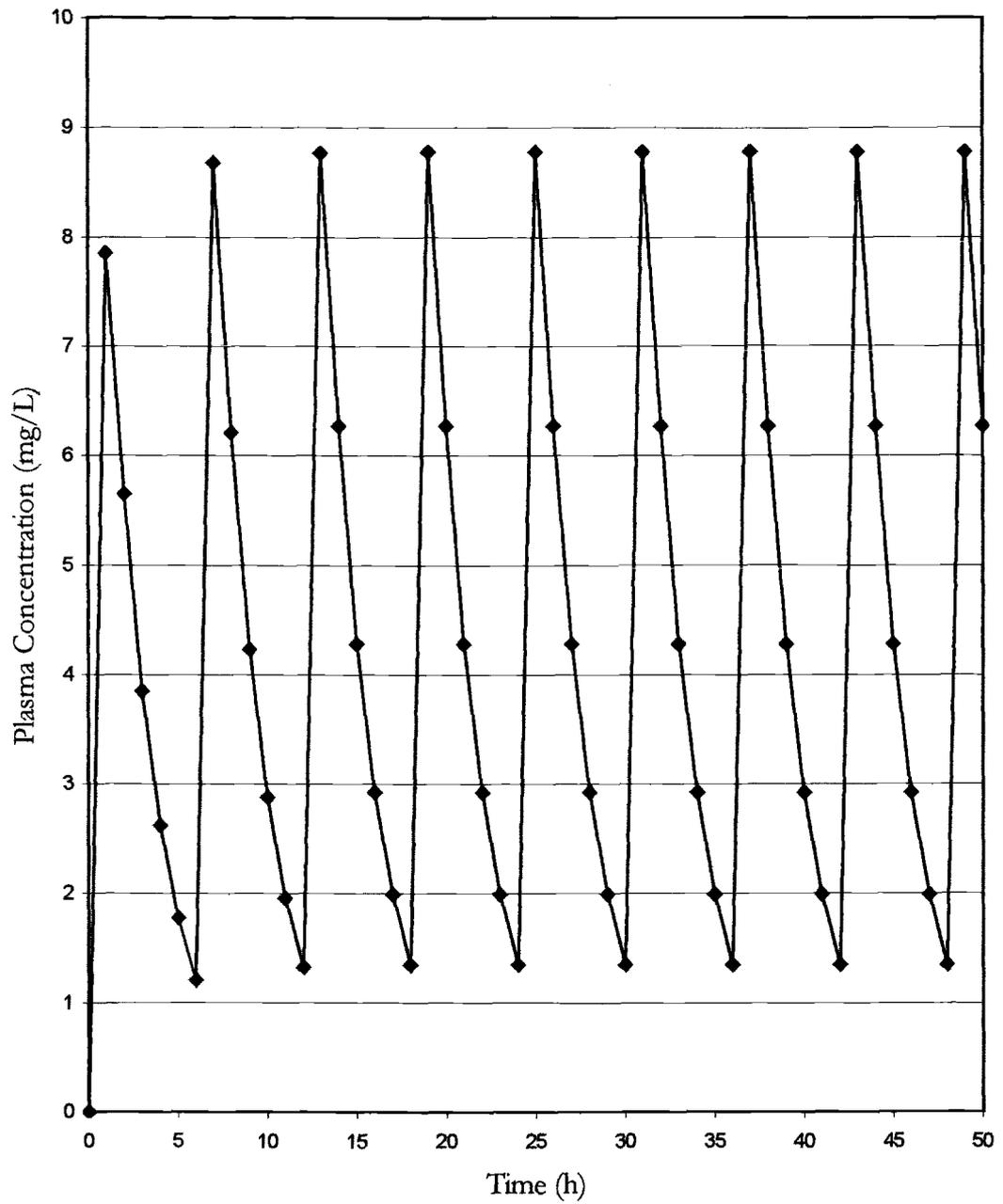


Figure 1.3B: Simulated Plasma Concentrations for 650mg of Acetaminophen Every 4 Hours

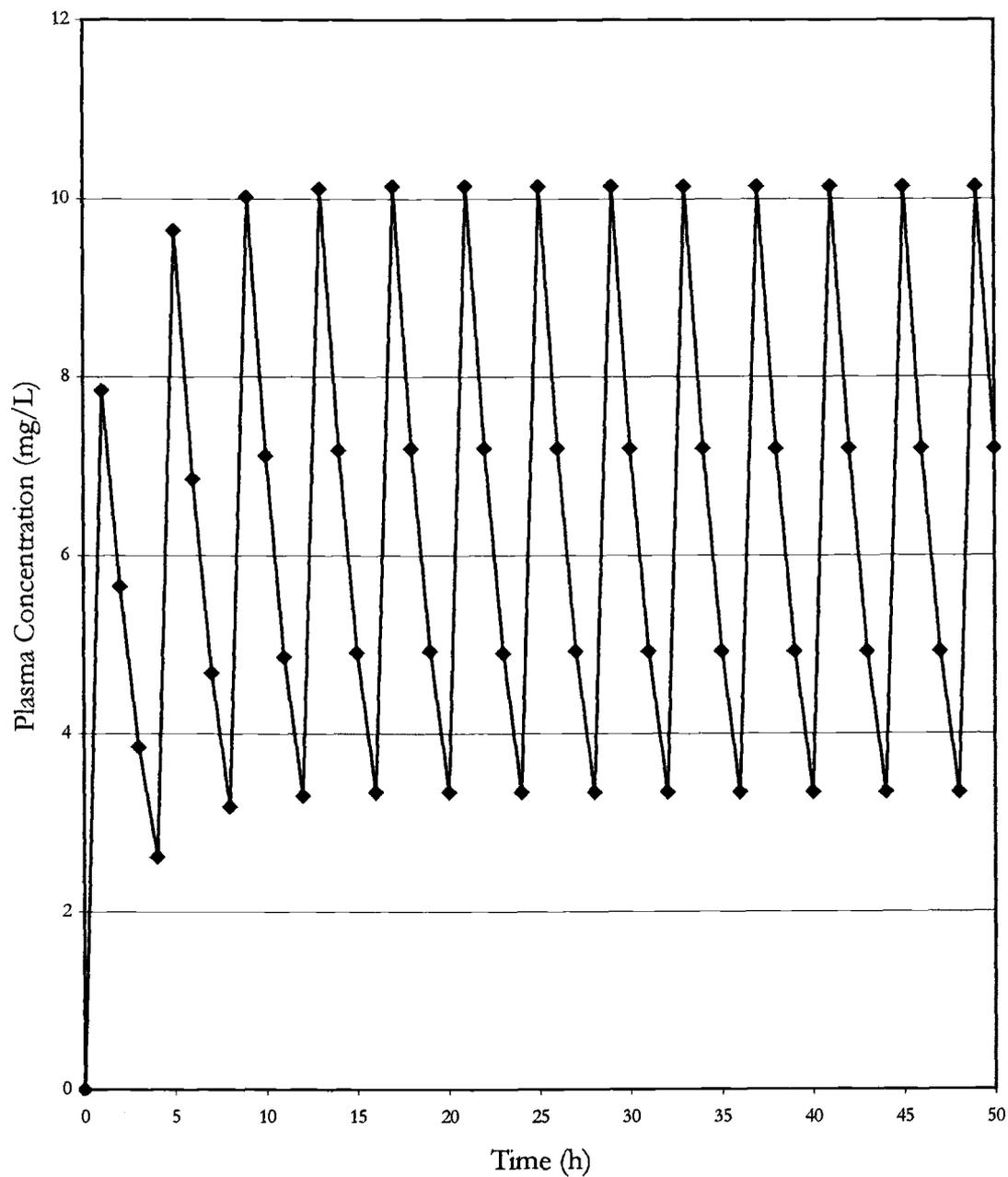


Figure 1.3C: Simulated Plasma Concentrations for 1000mg of Acetaminophen Every 6 Hours

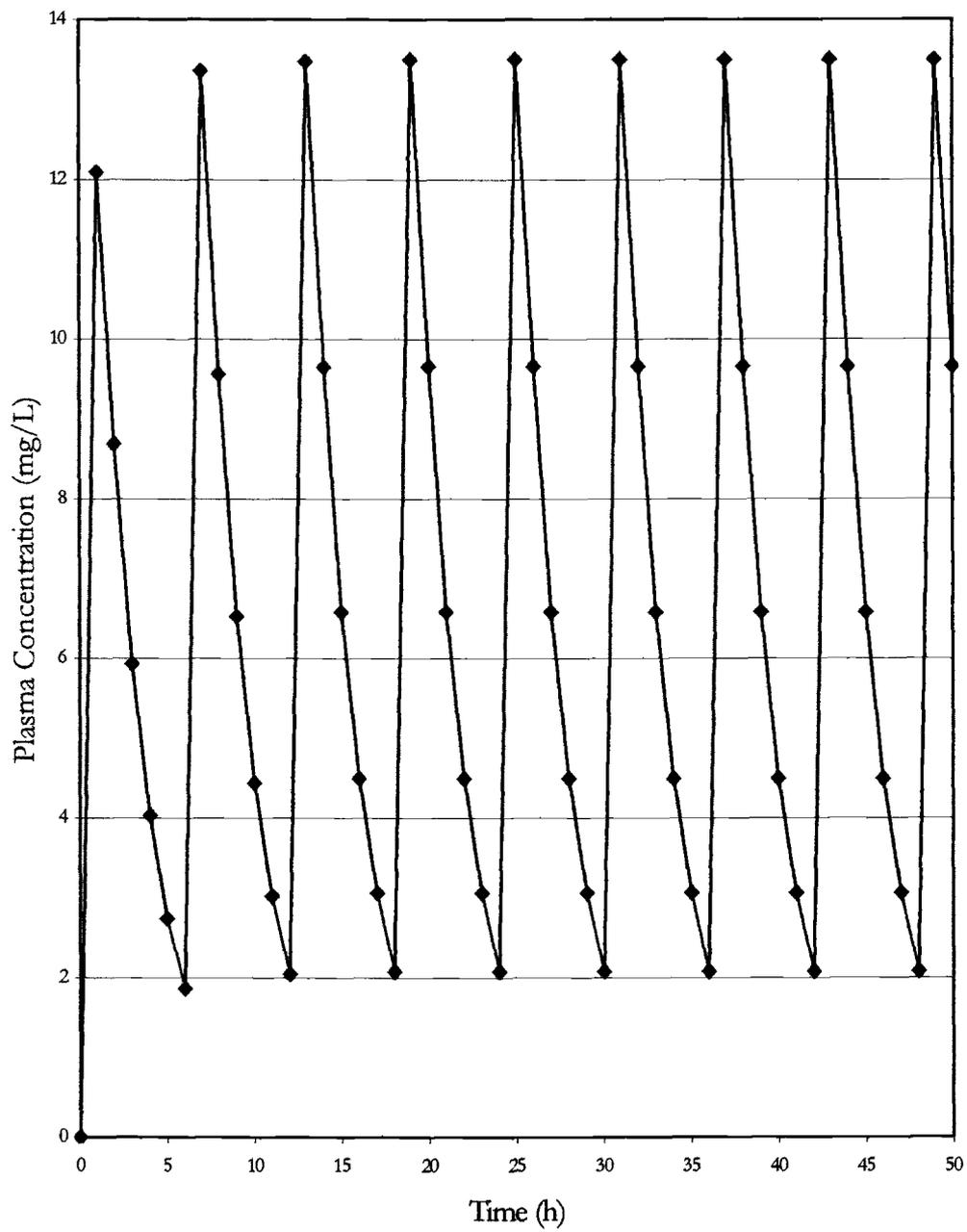
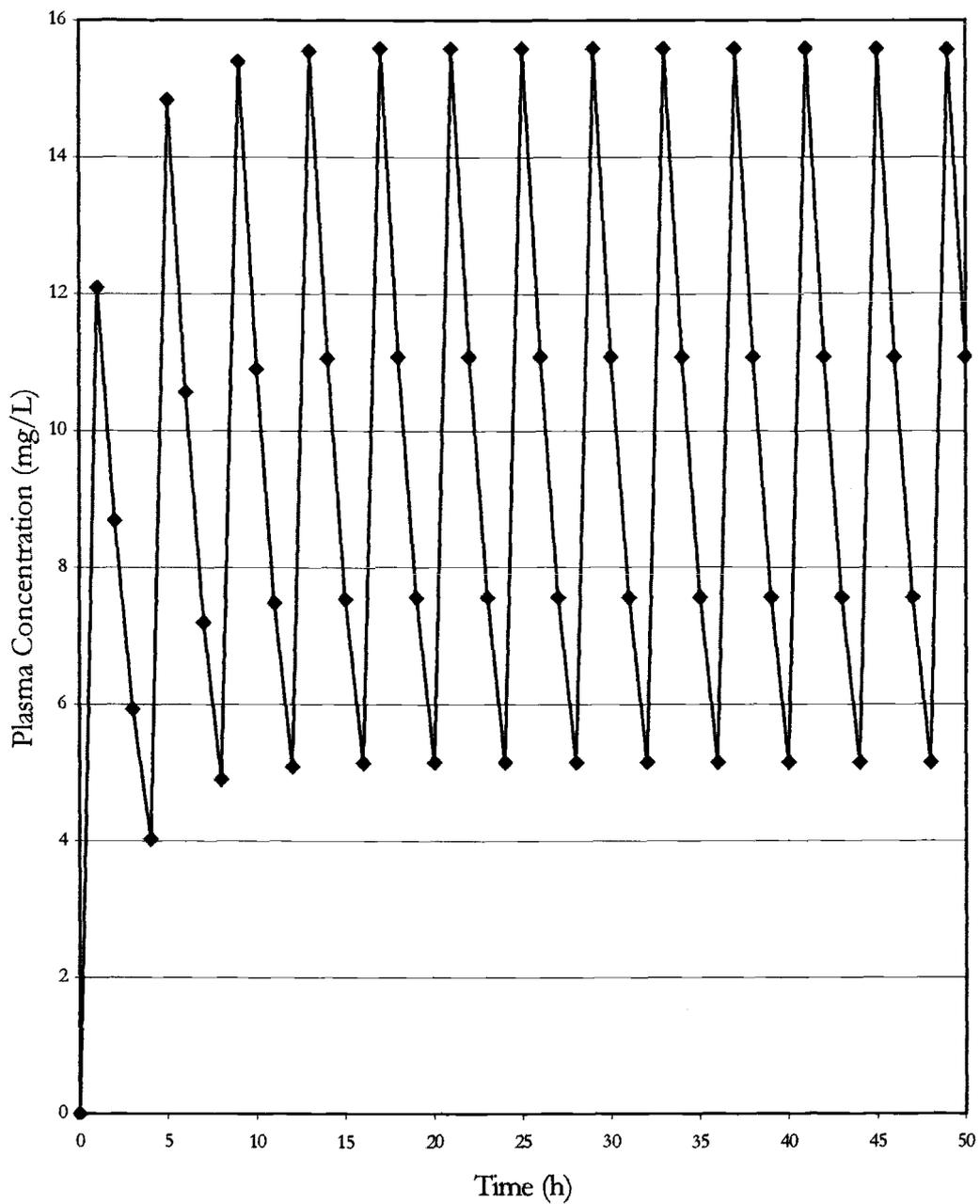


Figure 1.3D: Simulated Plasma Concentrations For 1000mg of Acetaminophen Every 4 Hours



All of the above simulations assume that the dosing regimen is followed exactly and around the clock. In real life, patients rarely get up during the night to take medication. A more realistic simulation of patient use is shown in Figures 1.4A-B. These simulations display expected plasma concentrations when the patients take 650mg or 1000mg every 4 hours while awake. During the "night" the plasma concentrations decline to near zero. While this may be acceptable for acute pain, chronic pain suffers awake with little or no pain relief at a time when patients often notice the pain most.

Figure 1.4A: Simulated Plasma Concentrations for 650mg of Acetaminophen every 4 Hours While Awake

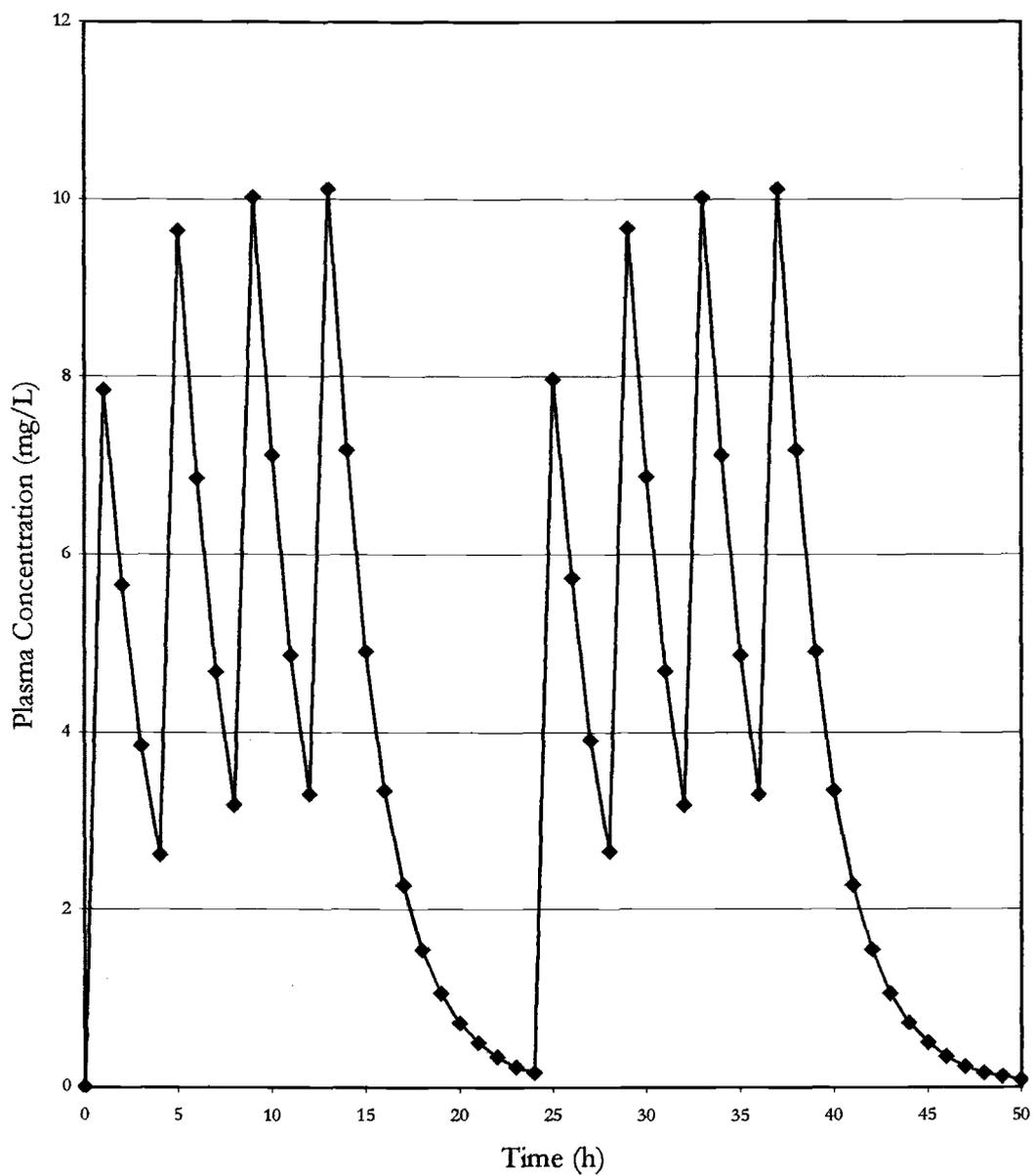
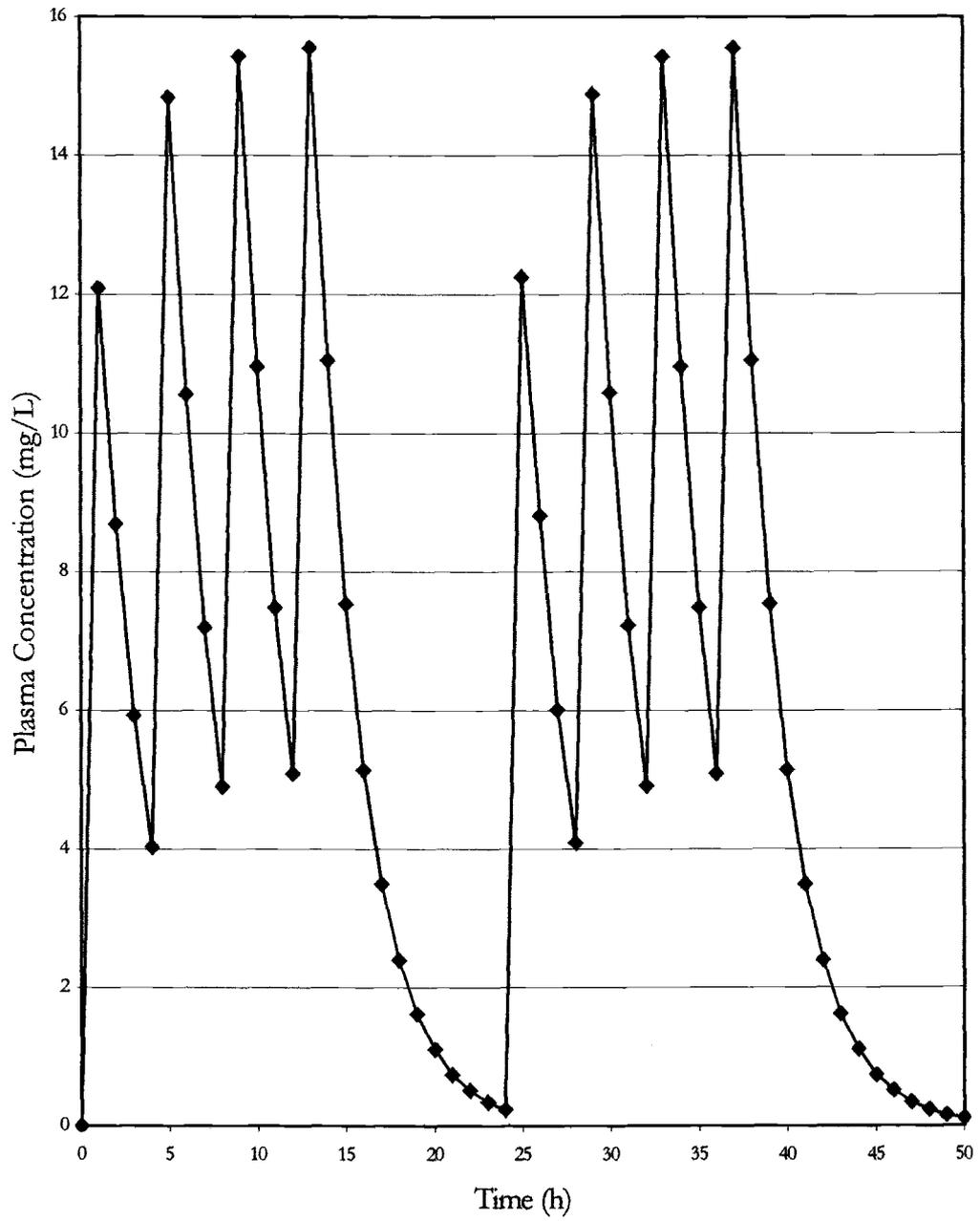


Figure 1.4B: Simulated Plasma Concentrations for 1000mg of Acetaminophen Every 4 Hours While Awake



The ideal sustained release formulation would provide a constant level of drug for the entire dosing interval, thus avoiding the potential for breakthrough pain between doses or the loss of efficacy during the night. As mentioned before, true zero-order release formulations might provide this type of release. Using the same pharmacokinetic parameters as were used in the immediate release simulations, several zero-order release simulations were performed. There are no published data for this type of acetaminophen formulation, so the accuracy of the simulations cannot be compared to published data.

Figure 1.5 shows a single dose of 5 different zero-order products. All variables in the simulations are the same, only K_0 changes. Recall that K_0 is the zero order input constant and is equal to the total dose/dosing interval. In this figure, two of the formulations reach the target plasma concentration. Both the 2000 mg dose ($K_0 = 166.6\text{mg/hr}$) and the 1300mg dose ($K_0 = 108.3\text{mg/hr}$) reach or exceed 5mg/L. The 2000mg dose has the advantage of reaching the target about 5.5 hours sooner than the 1300mg dose. The 1300mg dose has the advantage of allowing compliance with the new maximum daily dose recommendations of 2.6 grams per day. Neither product would be acceptable for acute pain because of the lag time (2.5 hours for the 2000mg dose and 8 hours for the 1300mg dose) before reaching the desired target plasma concentration.

Figure 1.5: Simulated Plasma Concentrations for Single Dose, Zero-Order Acetaminophen Formulations With Different K_0 Values

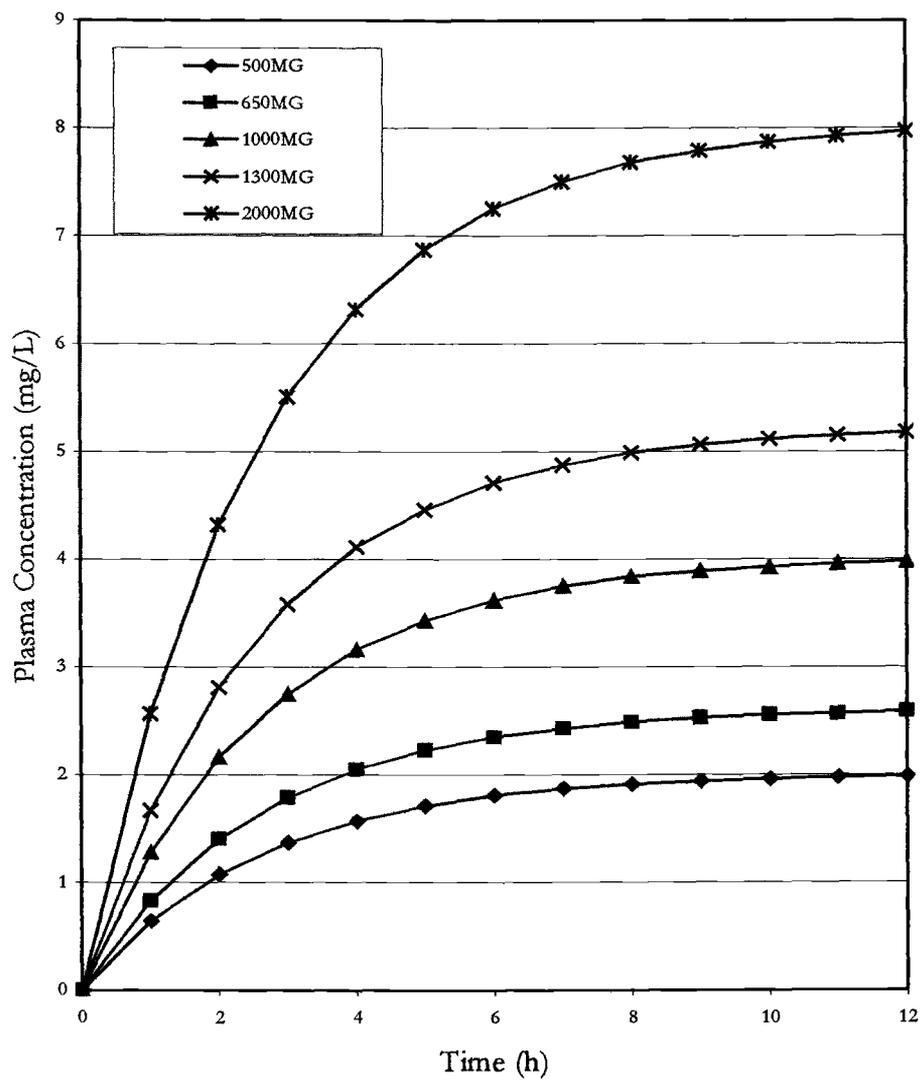
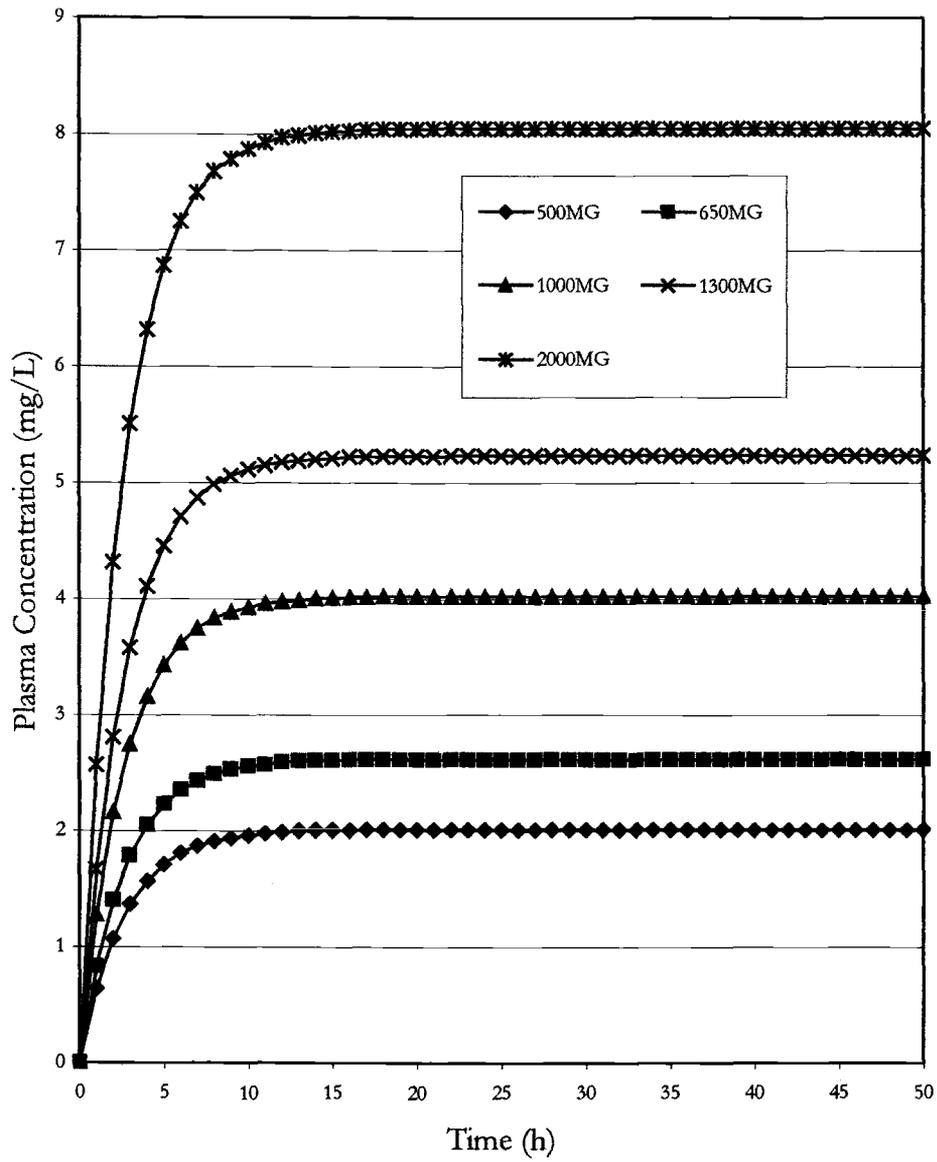
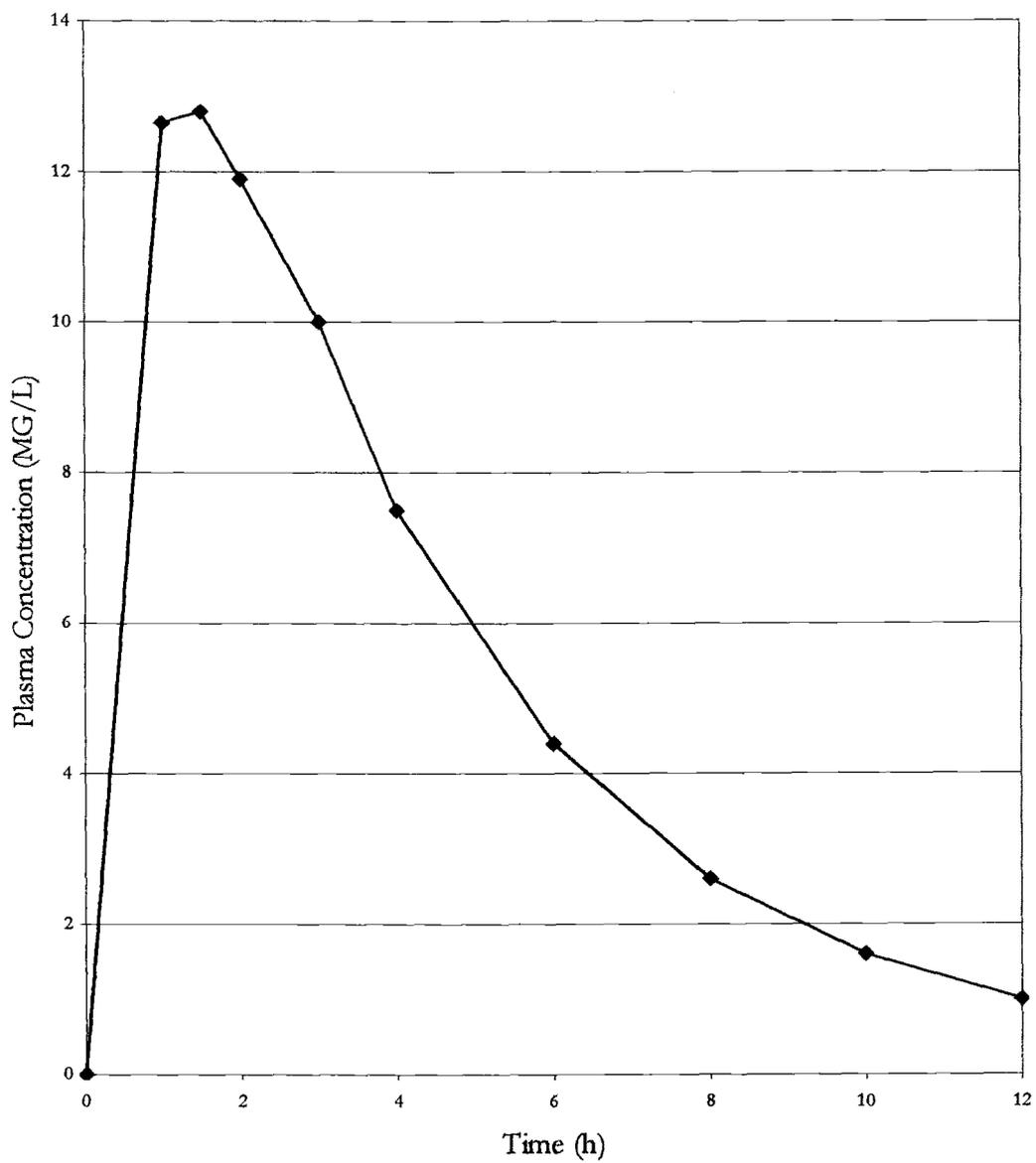


Figure 1.6 depicts plasma simulations for the zero order formulations when dosed every 12 hours. With chronic use and consistent dosing, the 1300mg every 12 hour product maintains a plasma steady state concentration of just slightly above the target plasma concentration. It also provides a constant plasma concentration throughout the day and night, potentially providing relief in the morning as well as when the patient is awake.

Figure 1.6: Simulated Plasma Concentrations for Multiple Dose (q 12h), Zero-Order Acetaminophen Formulations With Different K_0 Values



During the simulation process, a new commercial product was released onto the market. Named Tylenol Extended Relief, the product contains 650mg of acetaminophen in each tablet. One half of that dose (325mg) is a traditional immediate release formulation. The second half of the dose (325mg) is present in a hydrophilic matrix for extended release. The two halves are compressed together to form a bi-layered caplet. The recommended dose is 1300mg every 8 hours. Figure 1.7 is from published plasma data for the product¹⁶. The data represent an average of twelve patients. The product rapidly reaches the target plasma concentration in about 0.5 hours, but after 5.5 hours, it falls below the target.

Figure 1.7: Published Serum Data for Tylenol Extended Relief Product

To better compare this product to the immediate release product previously studied, Figures 1.8 through 1.10 were prepared. Figure 1.8 compares the published data for 1300mg of Tylenol Extended Relief (2 x 650mg tablets) to published data for 1000mg of Tylenol Extra Strength (2 x 500mg tablets). Both curves represent an average of twelve patients. Patients fasted 8 hours prior to each dose. As expected, the Tylenol Extended Relief (which contains a larger dose) has a slightly broader and slightly higher peak. The hydrophilic matrix portion of the tablet slows release just enough to cause slight broadening and delaying of the C_{max} . Reported values for the average area under the curve (AUC) are 64.3 for the Extended Relief product and 49.5 for the Extra Strength product. Again, this agrees with what is expected given the difference in dose. Pharmacokinetic theory dictates that the increase in AUC should be proportional to the increase in dose for drugs that follow linear pharmacokinetics. In this case the ratio of the AUC for the Extended Relief product to the Extra Strength product is $64.3/49.5 = 1.29$. The ratio of the dose for the Extended Relief product to the dose of the Extra Strength product is $1300\text{mg}/1000\text{mg} = 1.3$. This confirms that linear pharmacokinetics are at play in this situation.

Figure 1.8: Comparison of Published Serum Data for 1300mg of Tylenol Extended Relief and 1000mg of Tylenol Extra Strength

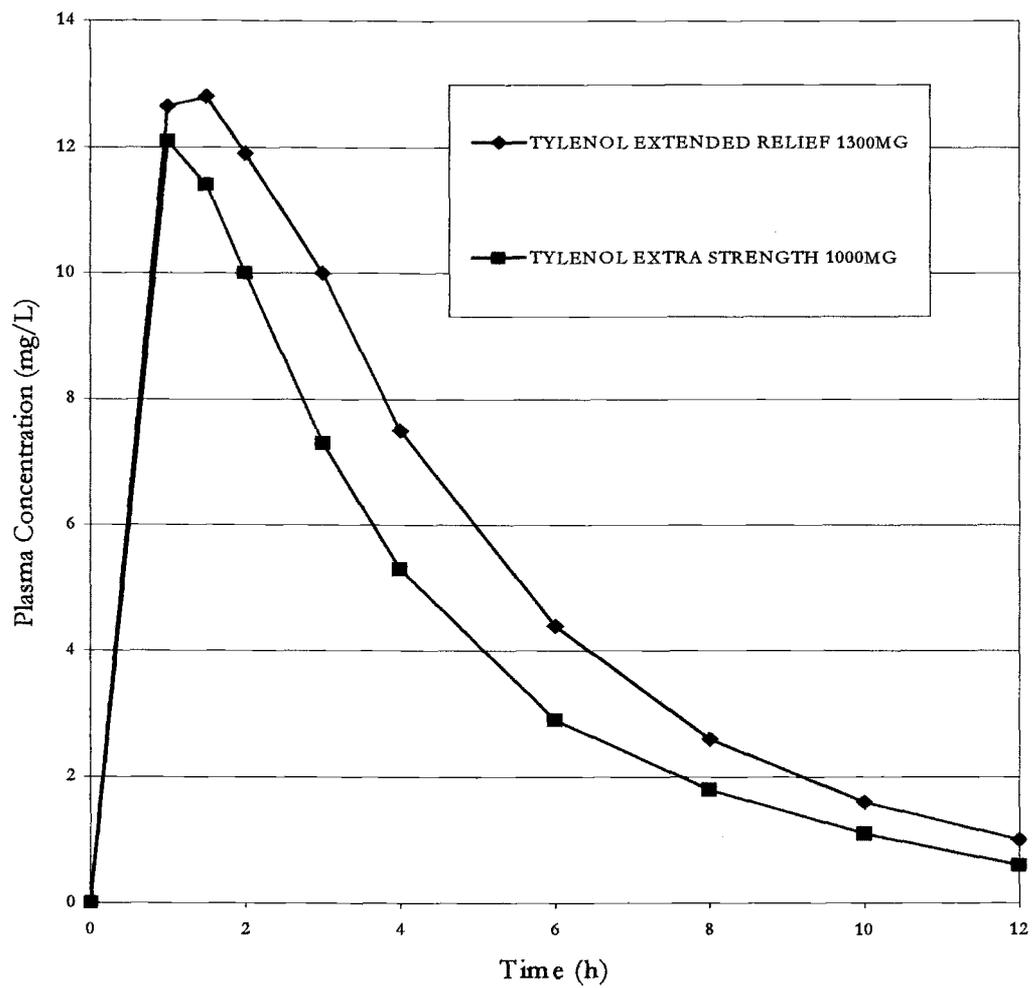


Figure 1.9: Comparison of Published Serum Data for 1300mg of Tylenol Extended Relief to Tylenol Extra Strength After Scaling to 1300mg

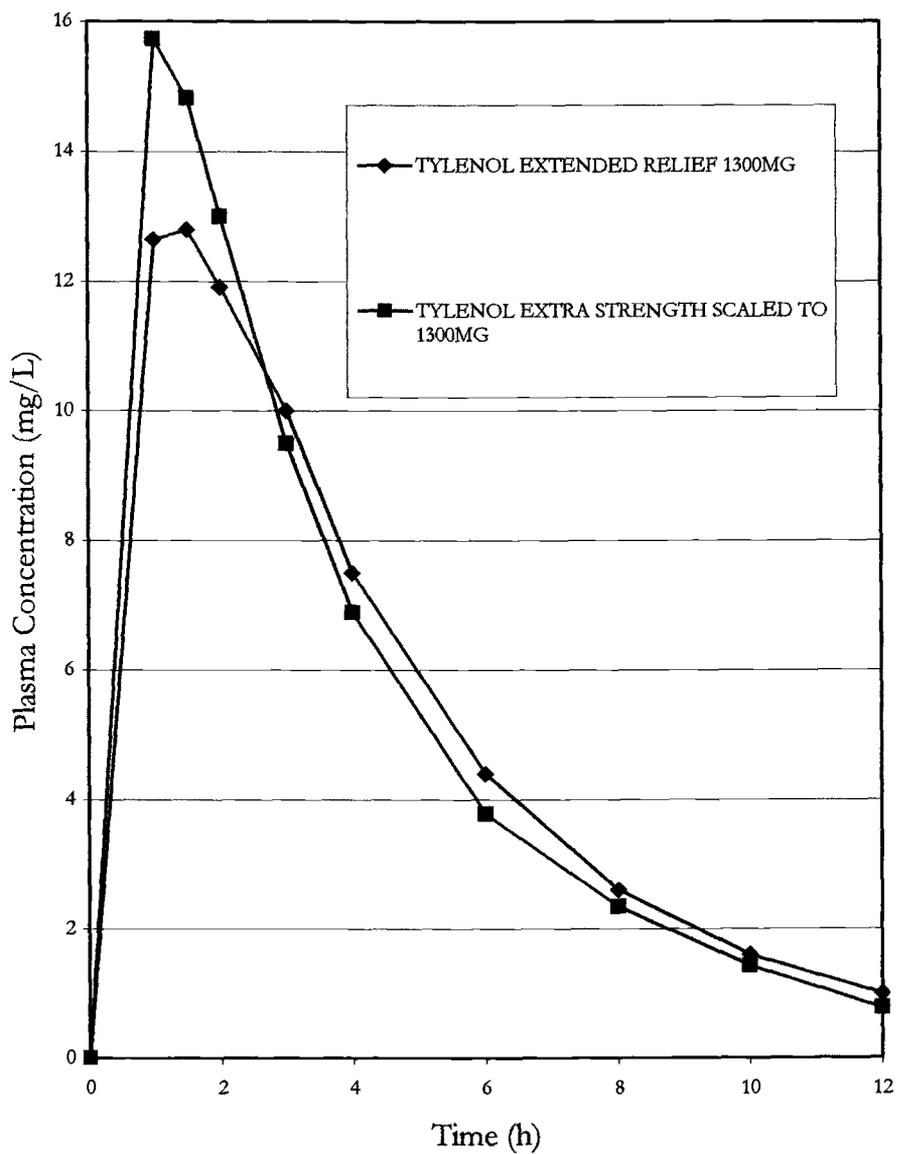
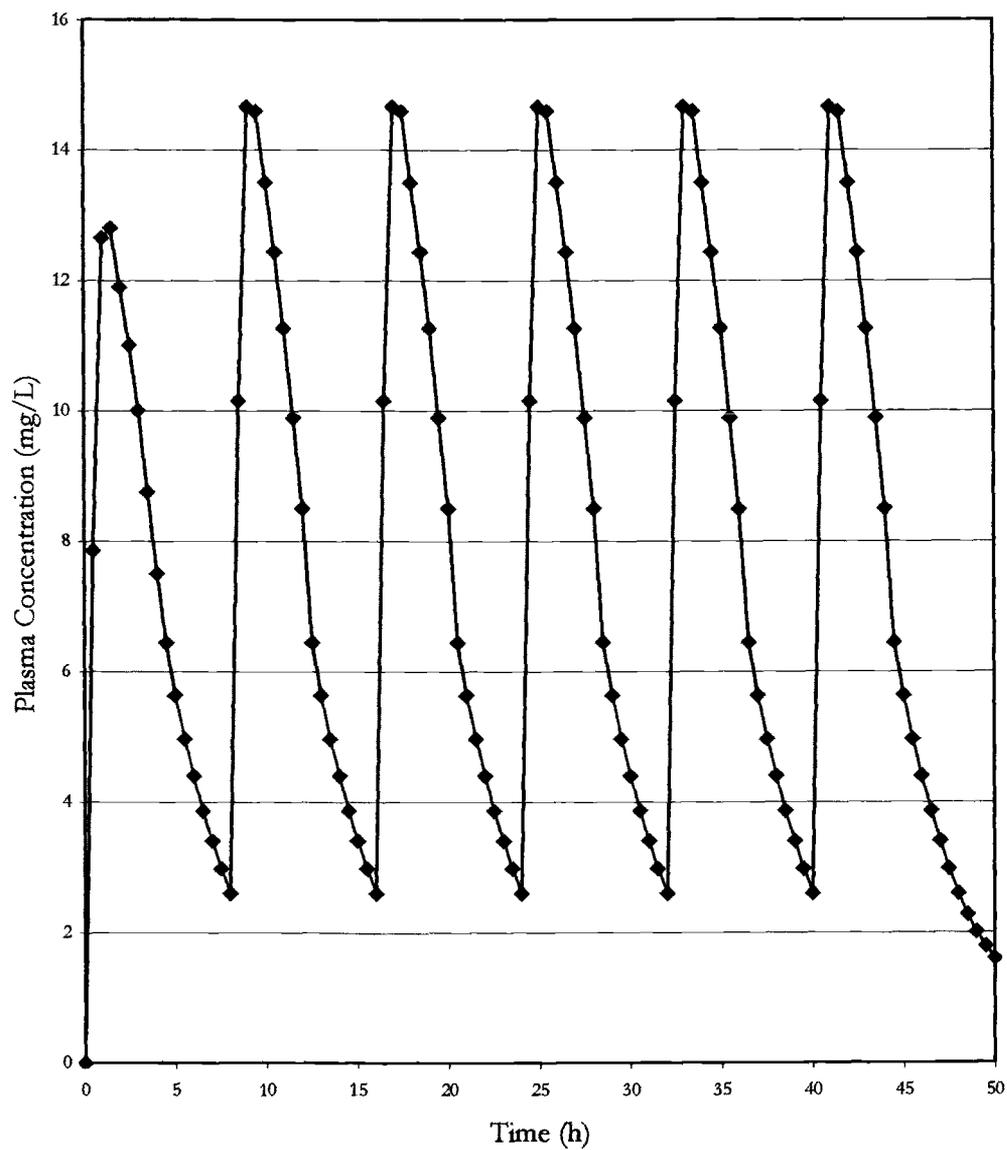


Figure 1.10: Simulated Plasma Concentrations for 1300mg of Tylenol Extended Relief Every 8 Hours



Since both products follow linear pharmacokinetics, it is reasonable to scale the 1000mg curve up to a 1300mg curve by multiplying all plasma values by 1.3. The comparison of the resulting curve to the 1300mg Tylenol Extended Relief curve can be seen in Figure 1.9.

Although the Tylenol Extra Strength has a higher C_{max} (16mg/L as compared to 13mg/L for Tylenol Extended Relief) the elimination portions of the curves are essentially identical. This suggests that once adjusted for the difference in dose, the formulations release drug nearly identically. The hydrophilic portion of the Tylenol Extended Relief tablets does not substantially alter the release characteristics of the tablet. The difference in performance of the two products is a result of the difference in dose.

Figure 1.10 is a simulation of 1300mg of the Tylenol Extended Relief product dosed every 8 hours as directed by the manufacturer. For 24% of the dosing interval (almost 2 hours per dose or 6 hours per day) the curve falls below the target plasma concentration in spite of the larger dose administered.

It is interesting to note that the manufacturers elected to call the product "Extended Relief" rather than use a term such as sustained or controlled release. The Food and Drug Administration describes the term "Extended" as referring to dosage forms that increase the dosing interval less than 2 times the dosing interval of the immediate release product¹⁷. It goes on to describe the terms "Sustained" or "Controlled" as referring to dosage forms that extend the release of the drug greater than or equal to 2 times the dosing interval of the immediate release product. Since

the Tylenol Extended Relief product extends the dosing interval for only 2 hours (4-6 hours to every 8 hours), it is referred to as extended release and not sustained or controlled release. If successful, the target product of this research would extend the dosing interval from 4-6 hours to 12 hours, thus earning the title "sustained or controlled" release.

TABLET FORMULATION AND TESTING

Tablet Ingredients:

All chemicals used in the production of tablets were National Formulary (NF)/United States Pharmacopeia (USP) grade. They include acetaminophen NF/USP (Spectrum Chemical Mfg. Corp., Gardena, CA) Lot JE321, polyvinylpyrrolidone K-30 NF/USP (Spectrum Chemical Mfg. Corp., Gardena, CA) Lot KD186, Magnesium Stearate NF/USP (Spectrum Chemical Mfg. Corp., Gardena, CA) Lot KC502, and Methocel K100M PREM CR brand of hydroxypropylmethylcellulose (Dow Chemical Co., Midland, MI) Lot MM92101105K. Dry ingredients were sifted together and then compressed into tablets.

Tablet Compression:

Tablets were compressed in a Carver press using a caplet shaped punch and die. The requisite amount of powder was weighed, loaded into the carver press, then tablets were compressed at 5,000 lbs for 30 seconds. After removal, each tablet was again weighed and a post-compression weight was recorded.

Dissolution Parameters:

All dissolution testing used the USP Paddle method. Tablets were exposed to a 2 hour simulated gastric fluid pre-treatment followed by 22 hours exposure to simulated intestinal fluid. Temperature was maintained at 37 degrees C and paddles rotated at 60 rpm. Samples were collected with replacement at 20 min, 40 min, 1 h, 1 h 20 min, 1 h 40 min, and 2 h. After changeover to intestinal fluid, additional samples

were taken at 3 h, 4 h, 6 h, 9 h, 12 h, and 24 h. Changeover was accomplished by filtering each flask using vacuum filtration and returning collected tablets to the new flask. Sample containers were covered in foil to protect the drug from UV degradation and stored in the refrigerator until UV analysis. Simulated gastric fluid and simulated intestinal fluid were prepared using the following recipes:

Simulated Enzyme-Free Gastric Fluid (4 L)

Distilled, deionized water	3.5L
NaCl	8g
HCl acid	28ml

adjust pH to 1.4 + or - 0.1

qs with distilled, deionized water 4.0L

Simulated Enzyme-Free Intestinal Fluid (4 L)

0.2N NaOH (2g/250ml)	760ml
K ₂ HPO ₃	27.2g
Distilled, deionized water	3.5L

adjust pH to 7.4 + or - 0.1

qs with distilled, deionized water 4.0L

Note: It is important to adjust the pH of the intestinal fluid when it has a total volume of 3.5L as it often requires significant adjustment to bring it into the correct pH range.

UV Analysis:

Proper dilution of the samples was determined using a Beer's Law calculation.

Beer's Law:

$$A = (\epsilon)(c)(l) \quad \text{where } A = \text{absorbance}$$

$$\epsilon = \text{molar absorptivity}$$

$$c = \text{molar concentration}$$

$$l = \text{path length}$$

For best results the maximum absorbance should be less than or equal to 1. The path length is a constant 1 cm, and the molar absorptivity of acetaminophen is listed in the Merck Index¹⁸ as 13,800 L/mol* cm.

The desired dilution concentration can therefore be calculated as:

$$A = (\epsilon)(c)(l)$$

$$1 = (13,800 \text{ L/mol} * \text{cm})(c)(1 \text{ cm})$$

rearranging to obtain

$$c = 0.000072464 \text{ mol/L} = 11\text{mg/L acetaminophen}$$

Analyzed samples should therefore be diluted to a concentration of less than or equal to 11mg/L.

Most dissolutions involve 650mg acetaminophen in 900 ml of dissolution fluid, or lower concentrations. If completely dissolved, the resulting concentration is 0.7222mg/ml or 722mg/L. For the samples to be in the correct concentration range for analysis they should be diluted 1:100. Samples were diluted 1:100 with distilled, deionized water and analyzed on a Hewlett Packard 8452A Diode Array variable wavelength UV-VIS spectrophotometer set at 244nm.

Sample absorbance values are compared to absorbance values produced by acetaminophen standards of 1mg/L, 2mg/L, 4mg/L, 6mg/L, 8mg/L, and 10mg/L also made in distilled, deionized water.

Data Analysis:

All data were analyzed using the PSI-PLOT spreadsheet and graphics program.

Investigations into Dose/Tablet Size:

Based on previous work in this laboratory a formulation containing 25% hydroxypropylmethylcellulose was chosen as a starting formulation. The dose/size relationship of the tablets was not known at this time. The percentage of magnesium stearate, polyvinylpyrrolidone, and HPMC was kept constant throughout the formulation, and the total dose of acetaminophen was varied from 500mg to 650mg per tablet.

Four tablets of each formulation were made. The formulas and sizes are shown below.

Table 1.3: Dose/Size Formulation Relationships

	Formula A	Formula B	Formula C	Formula D
HPMC (25%)	181.0mg	199.0mg	217.0mg	236.0mg
Mg Str (1%)	7.2mg	7.9mg	8.7mg	9.4mg
PVP (5%)	36.0mg	40.0mg	43.0mg	47.0mg
APAP (69%)	500.0mg	550.0mg	600.0mg	650.0mg
Tab wt.	724.2mg	796.9mg	868.7mg	942.4mg
Length	19.0mm	19.0mm	19.0mm	19.0mm
Height	3.0mm	4.0mm	5.0mm	6.0mm

Table 1.4: Pre and Post Compression Weights of the Tablets

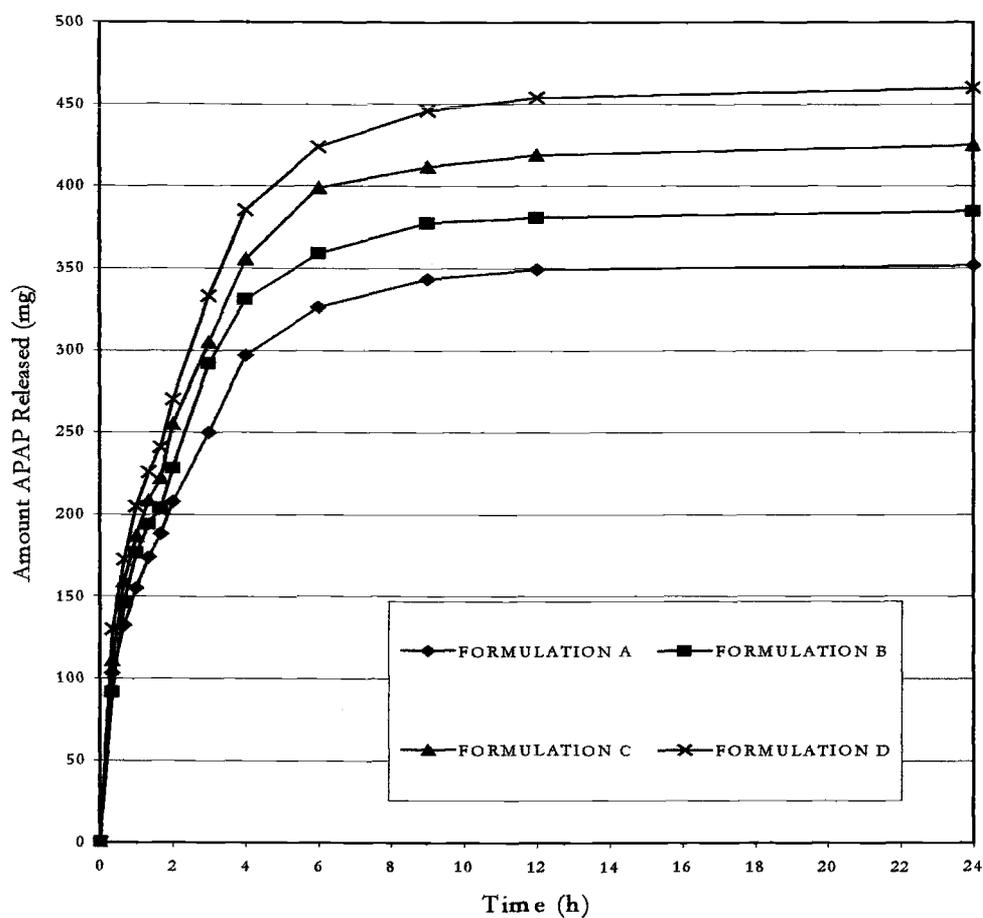
Formulation	Tablet	Precompression wt. (mg)	Postcompression wt. (mg)
A	1	725	717
	2	724	718
	3	724	719
	4	725	724
B	1	798	797
	2	797	796
	3	798	796
	4	797	795
C	1	869	867
	2	868	865
	3	870	865
	4	870	869
D	1	944	941
	2	942	942
	3	942	942
	4	943	940

Dissolution was performed on two tablets of each formulation. Results were compared with two Tylenol Extra Strength tablets (500mg per tablet) and two Tylenol Extended Relief tablets (650mg per tablet). Figure 1.11 shows dissolution results for the formulations. The size of all of the tablets is acceptable in terms of swallowability, but it is noted that all of the sustained release formulations only released about 70% of the total drug in 24 hours. All tablets of the commercial

product released 100% of the total dose by the 20 minute sample for the immediate release product and before the 1 hours sample for the extended relief product.

Incomplete release from the new formulations is probably due to too much HPMC in the formulation. Other potential causes include too much compaction force and a HPMC product with too high of a molecular weight. It is obvious that further investigation into the proper HPMC quantity were needed.

Figure 1.11: Dissolution Profiles for Four Acetaminophen Formulations Containing 25% HPMC



Investigations into HPMC Polymer Concentration:

Results of the previous investigation suggest that 25% HPMC prevented complete release of drug from the formulation. Formulations were prepared containing 2.5%, 5%, 7.5%, 10%, 12.5%, and 15% HPMC. The amount of drug per tablet was fixed at 650mg and the relative amounts of PVP and magnesium stearate were maintained at 5% and 1%, respectively. Four tablets of each formulation were made using the Carver press and pre and post compression weights of each tablet were recorded. Dissolution was performed on two tablets of each formulation. Two tablets of Tylenol Extra Strength and two tablets of Tylenol ER were also analyzed for comparison. The data are as listed in Tables 1.5 and 1.6.

Table 1.5: Recipes for Acetaminophen Formulations Differing by HPMC Concentration

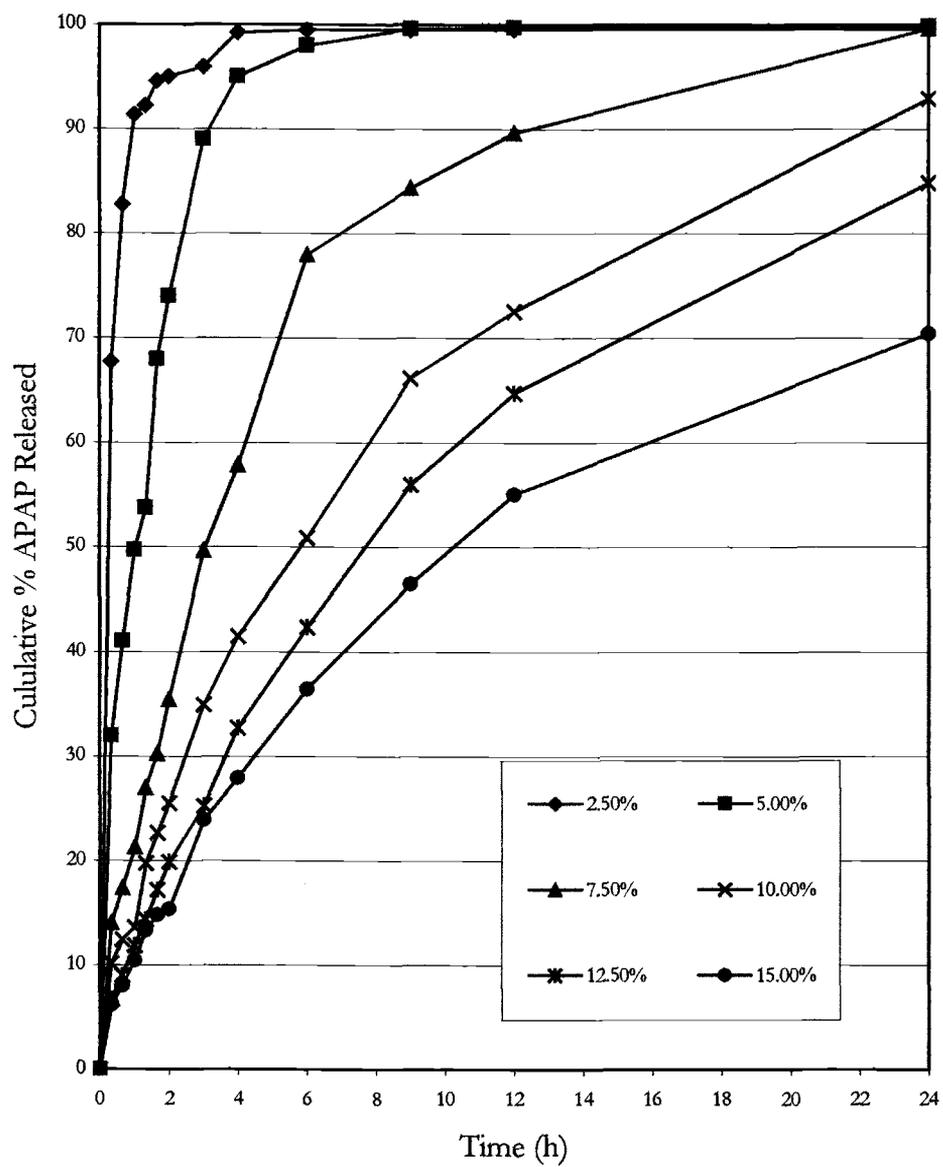
% HPMC	APAP (mg)	PVP (mg)	HPMC (mg)	Mg Str (mg)	Total tab wt.
2.5%	650	35.5	17.8	7.1	710.4
5.0%	650	36.5	36.5	7.3	730.3
7.5%	650	37.6	56.4	7.5	751.5
10.0%	650	38.5	77.4	7.7	773.6
12.5%	650	49.8	99.7	7.9	809.5
15.5%	650	41.1	123.4	8.2	822.7

Table 1.6: Pre and Post Compression Weights for Tablets Differing in HPMC Concentration

%HPMC	Tablet #	Precompression wt. (mg)	Postcompression wt. (mg)
2.5%	1	714	702-capped
	2	714	711
	3	715	711
	4	714	708
5.0%	1	735	729
	2	734	729
	3	734	712-capped
	4	733	725
7.5%	1	754	751
	2	753	752
	3	755	747
	4	755	749
10.0%	1	775	770
	2	778	771
	3	778	768
	4	775	772
12.5%	1	814	808
	2	815	811
	3	815	807
	4	815	812
15.0%	1	822	819
	2	823	820
	3	822	819
	4	822	818

Figure 1.12 shows the effect of HPMC amount on the release of acetaminophen from tablets. The goal is complete but controlled release of the drug over a 12 hour period. The formulation that most closely fulfills those requirements is the 7.5% formulation. It provided about 90% drug release at 12 hours and shows well controlled release throughout the time period. The 2.5 and 5% formulations provide complete release by 3.5 and 8 hours respectively. The 10, 12.5 and 15% formulations do not completely release the acetaminophen even after 24 hours. The 7.5% HPMC formulation was therefore selected for further testing.

Figure 1.12: Effect of Polymer Concentration on Dissolution of Acetaminophen Sustained Release Formulations



Effect of Compression Force on Acetaminophen Release:

Once a formulation had been selected, the effects of compression force on release of drug from the tablet were investigated. Sufficient powder was mixed of the 7.5% HPMC formulation to make 20 tablets. Three tablets each were produced using 30 seconds of compression at 4,000, 5,000, 6,000, 7,000, 8,000, and 10,000 pounds of pressure. Dissolution testing was performed on 2 tablets of each.

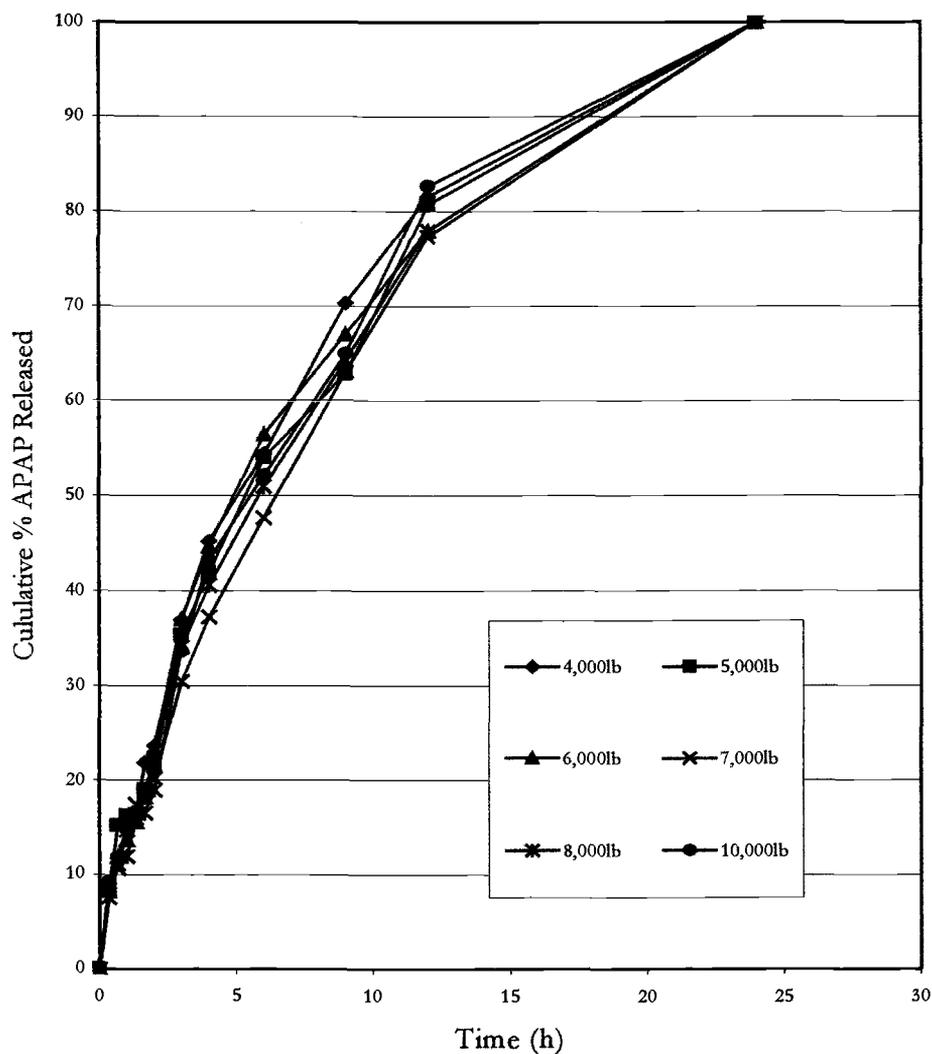
Table 1.7: Pre and Post Compression Weights for Tablets Differing by Compressions Force.

Compression force (lbs)	Tablet #	Precompression wt. (mg)	Postcompression wt. (mg)
4,000	1	754	750
	2	755	753
	3	754	749
5,000	1	754	752
	2	753	751
	3	755	752
6,000	1	753	749
	2	754	751
	3	754	752
7,000	1	755	754
	2	754	753
	3	754	752
8,000	1	753	749
	2	753	750
	3	754	750
10,000	1	753	750
	2	754	751
	3	755	753

As shown in Figure 1.13, dissolution profiles from the tablets were virtually superimposable. The results teach that compression force does not significantly

affect drug dissolution between 4,000 and 10,000 pounds force. These results are consistent with findings of others using HPMC matrix tablets¹⁹.

Figure 1.13: Effect of Compression Force on the Dissolution of Acetaminophen Sustained Release Formulations



Investigations into Tablet Shape:

The overall rate of drug dissolution from a non-disintegrating dosage form can often be described by the Noyes-Whitney Equation²⁰.

$$\frac{dc}{dt} = \frac{(D)(A)(K)}{h} (C_s - C)$$

- where dc/dt = rate of drug dissolution
 D = diffusion rate constant
 A = surface area of the particle or dosage forms
 K = oil/water partition coefficient
 h = thickness of the stagnant layer
 C_s = concentration of drug in the stagnant layer
 C = concentration of drug in the bulk solvent

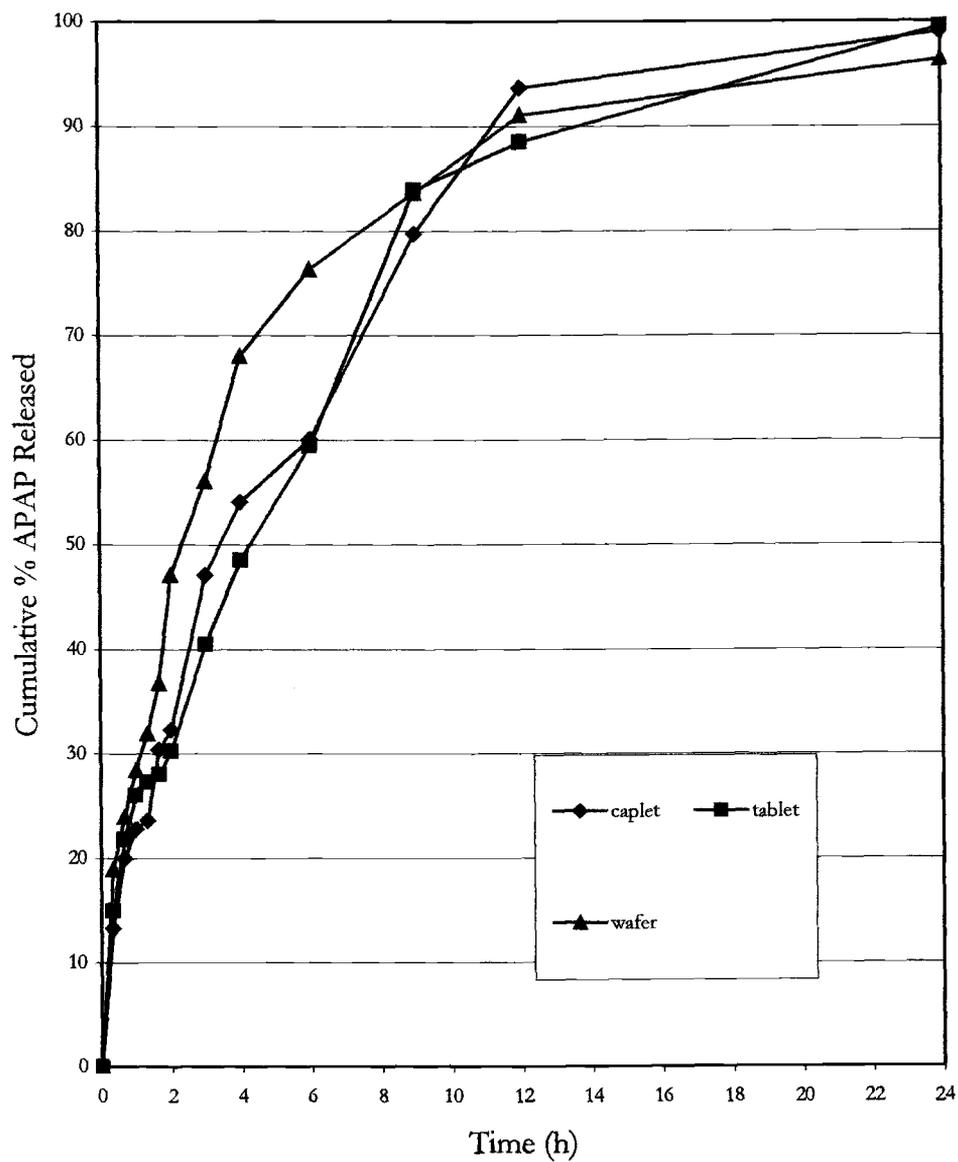
Of interest to this research is the effect of the shape of the tablet on A , and therefore on dc/dt . Tablets of the 7.5% HPMC formulation were compressed in three differing shapes to investigate these effects. Several tablets were made in the caplet shape that has been used up to this point, several wafers were made using a slugging die with large tablet faces, and finally, several conventionally shaped round tablets were produced. Dissolution testing was performed on two tablets of each shape. Samples were taken with replacement and analyzed using UV spectrophotometry as previously described. Table 1.8 shows the relative size and surface areas of the three tablets.

Table 1.8: Size and Surface Area of Tablets Differing in Shape.

Shape	Length	Width	Height	Est. Surface Area
Tablet	14mm	14mm	5mm	528mm ²
Caplet	19mm	11mm	5mm	589mm ²
Wafer	20mm	20mm	3mm	817mm ²

Figure 1.14 shows the comparative dissolution profiles of drug from the three different dosage form shapes. The caplet and conventional tablet shape showed very little difference in the dissolution rate. This is expected since they have very similar surface areas. However, the wafer shape showed significantly faster release between 4 and 9 hours. This is not unexpected as the wafer has a much larger surface area. By the 12 hour dissolution sample, the release profiles from the three shapes have rejoined each other. Release of acetaminophen is essentially complete from all three shapes by the 12 hour dissolution sample.

Figure 1.14: Effect of Tablet Shape on the Dissolution of Acetaminophen Sustained Release Formulations

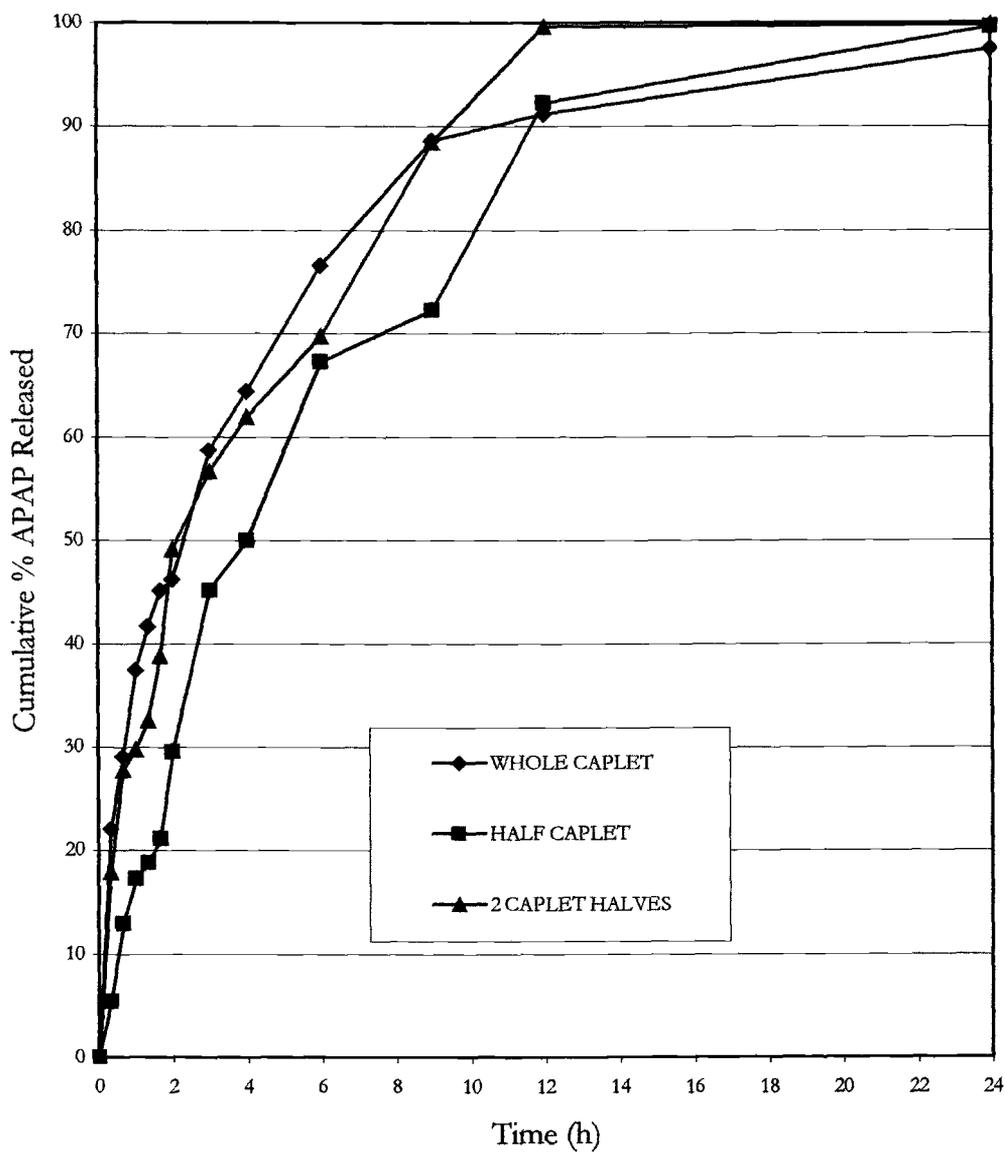


Investigations into Dosage Form Division:

Related to the above investigations, it is common in the realm of clinical pharmacy for a patient to divide tablets if they feel that the tablets are too difficult to swallow or if a smaller dose is desired. Dissolution was performed on 7.5% HPMC tablets. Two flasks contained whole tablets, two flasks contained 2 tablets that had been divided in half, and two flasks contained only 1/2 tablet each. Samples were taken with replacement and analyzed using UV spectrophotometry as previously described.

Figure 1.15 shows the dissolution profiles of each type of division. The figure is scaled to percent of total drug release to adjust for the difference in dose between the flasks that contained whole tablets and those that contained only half tablets. There is no significant difference in the release of the whole tablets, the divided tablets, or the half tablets once the profiles are scaled for dose. This suggests that the tablets could be divided in half without significant effect on the overall release of acetaminophen from the tablets.

Figure 1.15: Effect of Dosage Form Division on the Dissolution of Acetaminophen Sustained Release Formulations



Clinically, this would allow dosage reductions to be made in the elderly or in children without sacrificing the controlled release character of the product.

Investigations into Granulation methods:

The final area of these investigations into tablet formulation involved granulation methods. Acetaminophen is a very fluffy powder that does not flow well, and the formulation needed to be granulated to increase flowability. Three different granulation techniques were investigated.

Slugging Method

The 7.5% formulation powder was loaded into a slugging die and compressed with 10,000 pounds for 30 seconds. The slugging die was 20mm in diameter and produced round wafers. The resulting wafers were mechanically broken into granules and sieved. Granules that passed through a 14 mesh sieve but were retained on a 20 mesh sieve were used. The granules were weighed and compressed into caplets using the Carver press.

Wet Granulation Method

The APAP, HPMC, and PVP were mixed with 1 ml water per tablet. The resulting paste was forced through a 10 mesh screen to form granules and allowed to dry overnight at room temperature. The particles were further mechanically broken and sieved. Those granules that passed through a 14 mesh sieve but were retained on a 20 mesh sieve were used. Magnesium Stearate 1% was added to the granules prior to compression. The granules were weighed and compressed into caplets using the Carver press.

Extrusion Method

PVP was weighed and dissolved in 1 ml water per tablet. The APAP and the HPMC were weighed and dry mixed in a separate beaker. The PVP solution was slowly added to the APAP/HPMC powder to form a stiff paste. The paste was loaded into a 60 ml plastic syringe and "noodles" of the formulation were extruded onto plastic wrap. The noodles were allowed to dry at room temperature overnight. After drying, the noodles were mechanically broken into granules and sieved for size. Granules that passed through a 14 mesh sieve, but were retained on a 20 mesh sieve were used. Magnesium stearate 1% was added to the granules prior to compression. The granules were weighed and compressed into caplets using the Carver press.

Dissolution was performed on two tablets from each formulation and the profiles were compared to profiles previously obtained for the caplets made from powder. Comparative profiles are shown in Figure 1.16. Several subjective measures were also used to evaluate the granulations methods. Those measures included percent yield of granules in the 14-20 mesh range, preparation time, and expected ease of scale up. Investigator's preference was also a factor in the selection of the final method.

Figure 1.16: Effect of Granulation Method on the Dissolution of Acetaminophen Sustained Release Formulations

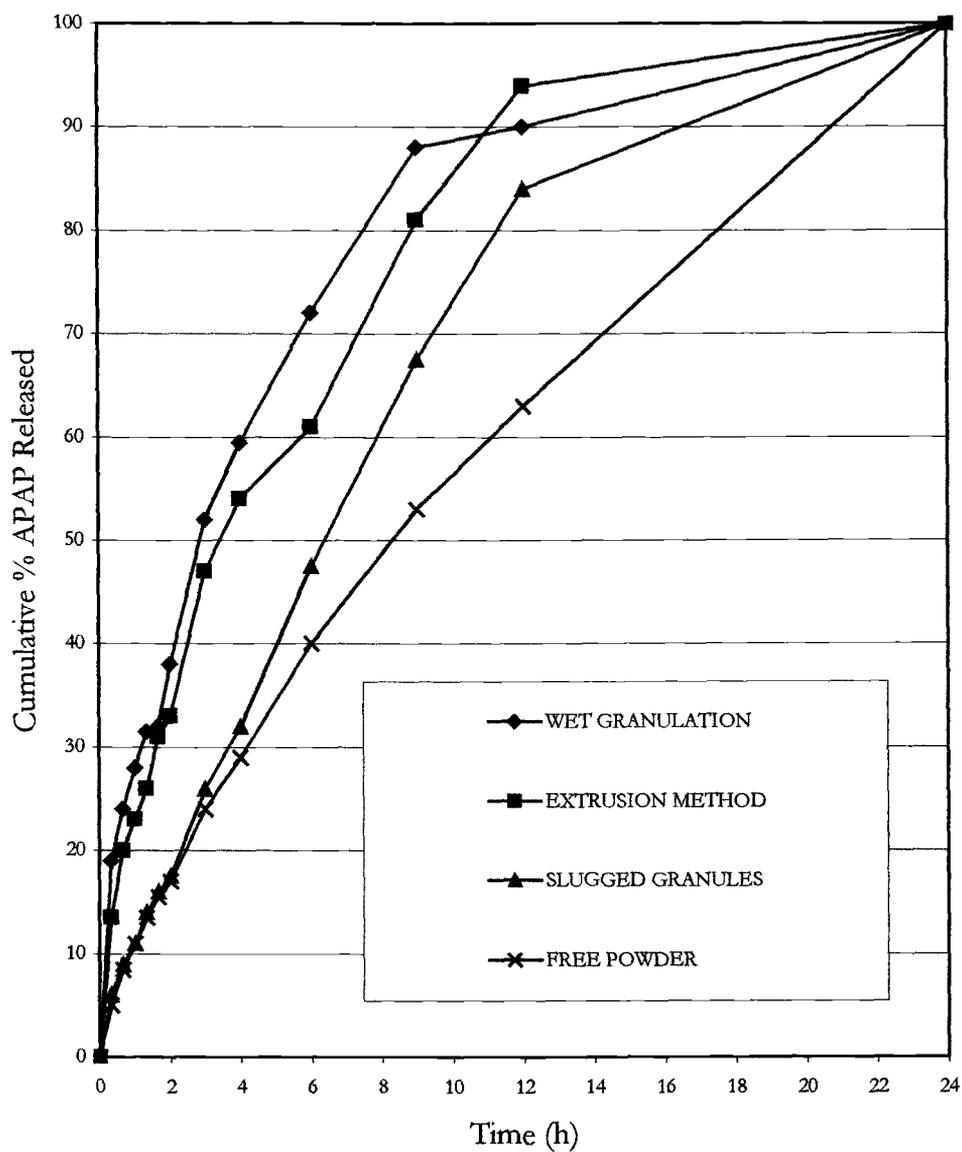


Table 1.9: Percent Yield of Granules in the 14-20 Mesh Range for Three Granulation Methods.

Method	Total Wt (g)	Wt of 14-20 mesh particles (g)	% particle yield
Slugging	7.515	4.014	53.4
Wet Granulation	7.516	2.654	35.3
Extrusion	7.515	4.681	62.3

Table 1.10: Time of Granule Preparation for Three Granulation Methods.

Method	Making granules	Drying time	Sizing granules	Total time
Slugging	6 hours	None	3 hours	9 hours
Wet Granulation	2 hours	24 hours	5 hours	7 hours
Extrusion	2 hours	24 hours	3 hours	5 hours

Ease of scale up was calculated as follows. Each method was rated 1, 2, or, 3 for both time of preparation and percent granules in the correct size. A rating of 1 was given to the fastest method and the method with the highest yield of granules in the correct size. Likewise a rating of 3 was given to the most time consuming method and the method with the lowest yield of granules in the correct size. The two numbers were multiplied together to yield a subjective scale-up parameter.

Table 1.11: Ease of Scale Up for Three Granulation Methods.

Method	Yield Rating	Time Rating	Scale-up parameter
Slugging	2	3	6
Wet Granulation	3	2	6
Extrusion	1	1	1

The slugging method produces a drug dissolution profile which was most similar to previous results from the direct compaction of the powder mixture. The traditional wet granulation method product was the most dissimilar. The extrusion method was selected for future granulations because of its expected ease of scale-up and relatively desirable drug dissolution profile. The slugging method was not used because of its long preparation time. The wet granulation method was not used both because of its dissimilarity to the desired release profile and due to the poor yield of properly sized granules from the batch. During the mechanical breaking down of the granules, particles did not neatly break into smaller granules. The granules were very hard and had a tendency to pulverize into powder yielding particles too small to use. It should also be noted that some attempts were made to dry the wet granulations in the vacuum oven rather than at room temperature. The vacuum introduces air into the formulation and does not produce granules but rather a fluffy mass that greatly resembles cooked meringue.

CONCLUSIONS

From investigations described in this chapter, two formulations were selected for further testing. The 5% HPMC formulation released 100% of the 650mg dose of acetaminophen by the 9 hour dissolution sample. This has complete release in the 12 hour dosing interval but does not provide controlled release of drug over 12 hours. The 7.5% HPMC formulation provides controlled release over the entire 12 hour dosing interval. However, only 90% of the dose is released in the 12 hour interval. It is expected that future testing in healthy human subjects will show one formulation to behave better *in vivo* than the other. Any further speculation at this point would be inappropriate.

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CHAPTER 2:
FORMULATION OF A SUSTAINED RELEASE
ACETAMINOPHEN PRODUCT: DETERMINATION OF
BIOPHARMACEUTIC AND PHARMACOKINETIC PROPERTIES

ABSTRACT

Pharmacokinetic studies were conducted in 10 healthy human subjects who were given four acetaminophen formulations. The four formulations included two commercially available products (Tylenol Extra Strength® tablets and Tylenol Extended Relief® tablets) as reference formulations and two sustained release acetaminophen formulations containing 5% or 7.5% hydroxypropylmethylcellulose (HPMC). Subjects ranged in age from 22-54 years of age. Three males and seven females participated in the study. Trial format was a single dose, four way crossover trial with 6 day washout periods between doses. Subjects provided 10 saliva samples during each 24 hours dosing period. Acetaminophen concentrations were measured using HPLC analysis.

Kinetic profiles were generated for each formulation in each subject using WinNonlin® kinetic simulation software. Tylenol Extra Strength® data were compared to hand calculations and to literature values to validate the fitting process. Both Tylenol Extra Strength® and Tylenol Extended Relief® tablets were fitted to 1 and 2 compartment open models with first order input and first order elimination, by weighing the data points equally or by $1/y$. Both products were best described by a 1-compartment open model with equally weighted data points, first order input, and first order elimination.

Each new sustained release acetaminophen product was fitted with four kinetics models. Each fitting assumed equally weighted data points and first

order elimination of the drug. Profiles were fitted to 1 and 2 compartment models with first order input and 1 and 2 compartment models with zero-order input from 0 to T_{max_data} hours. T_{max_data} was defined as the time associated with the highest measured acetaminophen concentration for that subject. Both the 5% and the 7.5% HPMC formulations were best described by a 1-compartment open model with equally weighted data points, first order input, and first order elimination.

The 5% HPMC sustained release acetaminophen formulation was selected for further study based on five target formulation criteria. Target selection criteria included acceptable tablet size, shape and palatability, estimated steady state plasma concentration of 5mg/L, convenient dosing interval, total daily dose, and sustained release character.

INTRODUCTION

Based on the formulation data in Chapter 1, two sustained release acetaminophen formulations were selected for study in human subjects. The formulations containing 5% or 7.5% hydroxypropylmethylcellulose (HPMC) showed most promising *in vitro* dissolution profiles. The dissolution profile of the 5% formulation showed complete release of the drug in the target 12 hour period, but the overly rapid release is complete in about 7 hours. The dissolution profile of the 7.5% formulation showed slow continuous release over a 12 hour period but incomplete drug release of only ninety percent. Each formulation shows one of the two desired characteristics during *in vitro* testing. The *in vivo* performance of the two formulations is unknown. Despite the best formulation efforts, no model exists that accurately predicts *in vivo* behavior of a HPMC matrix tablet formulation from *in vitro* data for acetaminophen or any other drug. So, once all known *in vitro* data have been collected, *in vivo* trials must be performed to develop the final *in vitro/in vivo* correlation that can be used to refine the product formulation and to select a formulation for further study.

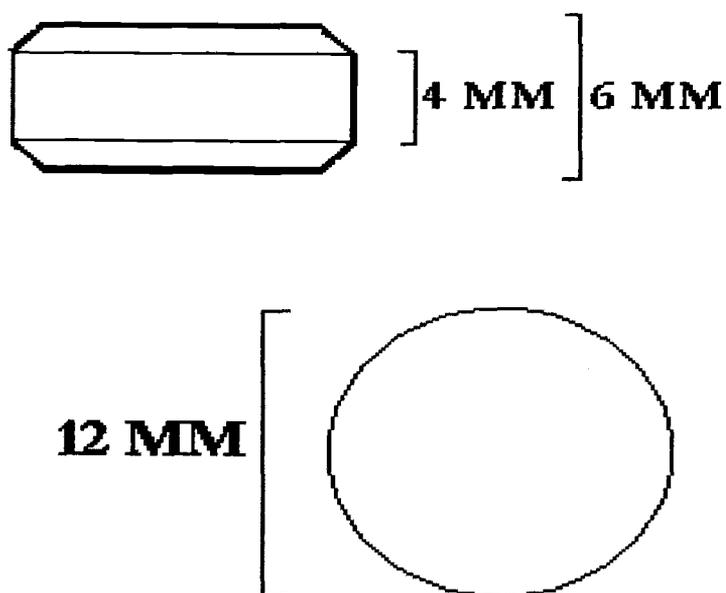
TABLET PREPARATION AND TESTING

Tylenol Extra Strength® and Tylenol Extended Relief® tablets were purchased at a local retail outlet and were dispensed without alteration as baseline or reference formulations. Sustained release acetaminophen tablets with 5% or 7.5% HPMC were made using the formulation techniques described in Chapter 1 with minor scale-up modifications.

Sufficient materials were prepared to make 50 tablets of each sustained release formulation. As previously described, the polyvinylpyrrolidone K-30 NF/USP (PVP, Spectrum Chemical Mfg. Corp., Gardena, CA, Lot KD186) was mixed with 1ml of distilled, de-ionized water per tablet (50mls) until completely hydrated. The HPMC (Methocel® K100M PREM CR, Dow Chemical Co., Midland, MI, Lot MM92101105K) and acetaminophen NF/USP (Spectrum Chemical Mfg. Corp., Gardena, CA, Lot JE321) were dry mixed in a separate container. The PVP solution was then added to the HPMC/acetaminophen mixture and mixed to form a stiff paste. The mixture was loaded into 60ml luer lock syringes and extruded into thin noodles onto a surface covered with plastic wrap and allowed to dry at room temperature for a minimum of twenty-four hours. The extruded noodles were mechanically broken and sieved to size. Granules that passed through a 14 mesh screen but were retained on a 60 mesh screen were used for tableting. One percent (w/w) magnesium stearate NF/USP (Spectrum Chemical Mfg. Corp., Gardena, CA, Lot KC502) was added to the granules and mixed thoroughly to coat all granules.

The granules were loaded into a single punch tableting machine (Chemical and Pharmaceutical Industry Co., New York, NY, Model TPK-12) for compression. Resulting tablets displayed convex sides and were 14mm in diameter with a 4mm belly band (See Figure 2.1). The tablets had a target fill weight of 730mg or 750mg for the 5% and the 7.5% tablets respectively. In contrast to previously produced tablets, tablets made in the tableting machine were round not caplet shaped. As previously shown, the shape does not significantly effect the release of acetaminophen from the tablets.

Figure 2.1: Size and Shape of Tablets from Single Punch Tableting Machine.



Tablet Testing:

1. Tablet Hardness

Tablet hardness was measured for each manufactured lot of sustained release acetaminophen tablets. To test the hardness, a tablet is placed between two anvils on a Strong-Cobb tester. The plunger of the tester is pumped to add increasing amounts of hydraulic pressure. Once the tablet fractures, the force reading is obtained from the hydraulic gauge. The force reading is converted into kilograms by dividing the reading by a conversion factor of 1.6. Acceptable values must be 4 kilograms or greater¹.

2. Tablet Friability:

Tablet friability was also measured for each manufactured lot of sustained release acetaminophen tablets. Tablet friability is measured by placing a pre-weighed tablet sample (5 tablets) inside a Roche Friabilator. The friabilator is then operated for a set number of revolutions. During operation, the friabilator rotates at 25 rpm and drops the tablet sample 6 inches with each revolution. After 100 revolutions, the sample is removed, dusted, and re-weighed. Tablet friability (f) is calculated using the following formula¹.

$$f = 100 \times (1 - (W_o/W))$$

Where f = tablet friability
W_o = original weight of the tablet sample
W = weight of the tablet sample after 100 revolutions in the friabilator

Acceptable values of f should be less than one. Tablet lots that exhibit capping during friability testing should be discarded regardless of the calculated f value.

3. Tablet Weight Variation:

Weight variation of the tablets was tested using a USP weight variation test. During this test, 20 tablets are weighed individually, an average weight calculated, and the individual weights are compared to the average. Tablets have met acceptable weight variation if no more than 2 tablets are outside of the percentage limit and no tablets differ by more than 2 times the percentage limit. The percentage limit depends on the average weight of the tablet. In this case, the average weight of the tablets is greater than 324mg, therefore the maximum percentage difference allowed is 5% (see Table 2.1)¹.

Table 2.1: Weight Variation Tolerances for Uncoated Tablets¹.

Average Weight of Tablets (mg)	Maximum Percentage Difference Allowed
130 or less	10
130-324	7.5
More than 324	5

4. Tablet Dissolution:

Dissolution testing was performed on 6 tablets of each lot. USP dissolution paddle method II was used as previously described in Chapter 1. Dissolution was considered to be equivalent to previous tests if the percentage of drug released from the tablet at time t was within 5% of previously measured value at all sample times.

5. Tablet Test Results:

Forty-seven usable tablets were obtained from compression of the acetaminophen 5% HPMC granules and were designated Lot #4. Average weight of 5% tablets was 729 ± 0.3 mg. Tablet hardness was measured to be 5.75kg and the friability was measured to be 0.36%. All tests were within acceptable parameters. Dissolution tests yielded results that were consistent with previous findings.

Forty-one usable tablets were obtained from compression of the acetaminophen 7.5% HPMC granules and were designated Lot #5. Four tablets were lost due to capping of the tablets. Average weight of 7.5% tablets was 750 ± 0.15 mg. Tablet hardness was measured to be 7.45kg and the friability was measured to be 0.12%. All tests were within acceptable parameters. Dissolution tests yielded results that were consistent with previous findings.

SUBJECT RECRUITMENT AND CLINICAL TRIALS

Permission was obtained from the Oregon State University Protection of Human Subjects Committee to conduct limited trials of the new acetaminophen formulations in healthy human subjects. A copy of the application may be found in Appendix 2A. For comparison, Tylenol Extra Strength® and Tylenol Extended Relief® tablets were also administered to human subjects. The study was a four way crossover test of four formulations of acetaminophen. Subjects were not blinded to the formulation identity. The study involved 1 trial day per week for 4 weeks separated by 6 days without acetaminophen as a washout period.

Volunteers for in vivo trials of the different acetaminophen formulations were drawn primarily from Oregon State University students and staff. After informed consent was obtained, each individual was supplied with a dose (two tablets) of a single formulation of acetaminophen. The tablets were either Tylenol Extra Strength®, Tylenol Extended Relief®, sustained release acetaminophen 5% HPMC, or sustained release acetaminophen 7.5% HPMC. Subjects were asked to fast overnight prior to taking the provided formulation, to avoid any acetaminophen containing preparations for 7 days prior to the first trial day and during all washout periods, and to continue to fast 2 hours after the dose was taken to standardize gastric emptying of the tablets.

During the trial, 12 saliva samples were collected from each subject for each formulation. For each saliva sample, subjects were asked to refrain from eating or

drinking for 5 minutes prior to the sample, to chew a 1 inch square of Parafilm® for 1 minute to stimulate salivation, and to collect a sample in the marked tubes provided.

A baseline sample was taken just prior to administration of the dose. Additional samples were taken 30 mins., 1 hr, 1.5 hr, 2.0 hr, 3.0 hr, 4.0 hr, 5.0 hr, 6.0 hr, 9.0 hr, 12.0 hr, and 24 hours after the dose was given for a total of 12 samples. Samples were collected in 4ml plastic sample tubes and frozen at 4°C soon after collection.

Saliva Analysis:

Each saliva sample was frozen for 24 hours, thawed for 2 hours, and centrifuged at 14,000 rpm for 20 minutes to remove proteinaceous material from the sample. The supernatant was decanted and refrozen for at least 24 hours. The samples were thawed and centrifuged a second time to remove additional protein before analysis. Samples were analyzed using High Pressure Liquid Chromatography (HPLC).

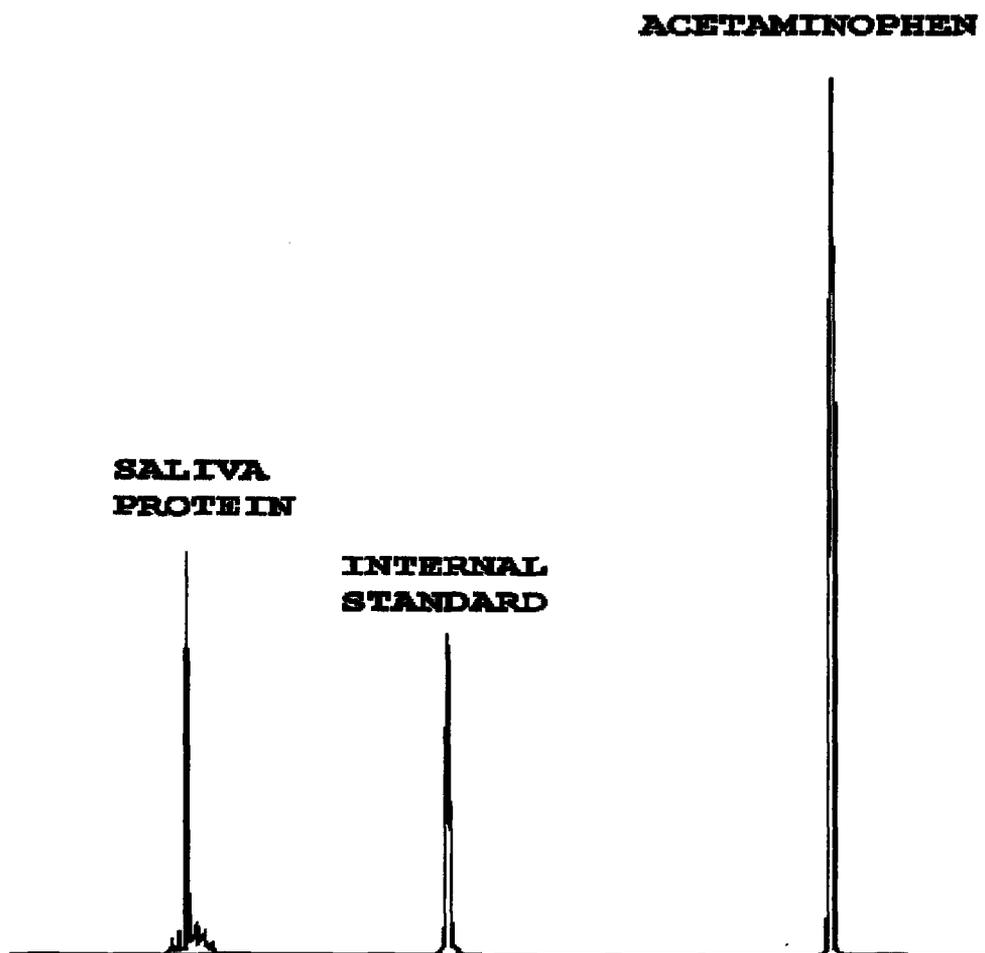
Standard solutions of acetaminophen were prepared at concentrations of 0.6, 1.0, 2.0, 4.0, 6.0, 8.0, 10.0, and 16.0 µg/ml in distilled, deionized water. For each sample 150 µl of either the sample supernatant or acetaminophen standard was added to a 350 µl micro-centrifuge tube. A 150 µl aliquot of 7-β-hydroxyethyl-theophylline 40 µg/ml was added to each sample tube as an internal standard and the sample vortexed for 30 seconds to ensure complete mixing.

Samples were injected onto the HPLC system using an automatic sampler (WISP 712; Waters Assoc.). The injection volume was set at 20 µl. Separation of

components was obtained using a C18-Reverse Phase Column. The mobile phase of 30% methanol/70% distilled de-ionized water was de-gassed and delivered at 0.8ml/min (M-6000A Solvent Delivery System; Waters Assoc.) and absorbance monitoring was performed at 254nm (Model 440 Absorbance Detector; Waters Assoc., AUFS=0.1). Retention times for the internal standard and acetaminophen were 7 and 12 minutes respectively. Sample run time was 18 minutes and the chart speed was set at 10cm/hr.

For each sample, a minimum of three peaks appeared. The first was identified as a peak that contained proteinaceous endogenous compounds that remained after extraction. The second peak was the internal standard peak and the third peak was the acetaminophen peak. A fourth commonly seen peak appeared at 16 minutes and was determined to have the same retention time as caffeine. The peak heights of all acetaminophen and internal standard peaks were measured. Dividing the acetaminophen peak height by the height of the internal standard peak normalized each acetaminophen peak. A standard curve was obtained by performing linear regression on the plot of normalized peak height ratios versus acetaminophen concentration. The equation obtained from linear regression was used to convert normalized peak ratios of sample unknowns into acetaminophen concentrations. Standard curves were prepared daily with each set of samples. Figure 2.2 shows a typical HPLC profile.

Figure 2.2: HPLC Saliva Profile for Subject taking Acetaminophen Formulation.



Subject Data:

Subjects ranged in age from 22-54 years of age. Three males and seven females participated in the study. The subjects ranged in height from 59 to 75 inches.

Table 2.2 is a summary of the subject characteristics.

Table 2.2: Summary of Subject Characteristics Including Age, Height, Weight, and Gender.

Subject #	Age (yr)	Height (in)	Sex	Weight (kg)
1	25	65	M	59
2	37	75	M	107
3	28	64	F	77
4	29	66	F	57
5	54	67	M	85
6	26	62	F	50
7	25	59	F	59
8	20	67	F	61
9	37	64	F	73
10	22	61	F	100
AVERAGE	30.3	65	3M/7F	72.8

Each of the ten subjects was randomly assigned to one of four treatments.

Each treatment period lasted one day with a six day acetaminophen free period between treatments. At the end of treatment one, subjects were randomly assigned to one of the three remaining treatments. This pattern was repeated until all ten subjects had completed all four treatments. Table 2.3 shows the assignment of treatments for each of the ten subjects.

Table 2.3: Random Treatment Assignments for the 10 Subjects

Subject #	Treatment Period 1	Treatment Period 2	Treatment Period 3	Treatment Period 4
1	SR 7.5	SR 5.0	ER	IR
2	SR 7.5	SR 5.0	ER	IR
3	SR 7.5	IR	SR 5.0	ER
4	SR 7.5	IR	SR 5.0	ER
5	SR 7.5	SR 5.0	ER	IR
6	IR	ER	SR 5.0	SR 7.5
7	ER	SR 5.0	IR	SR 7.5
8	IR	SR 5.0	SR 7.5	ER
9	ER	IR	SR 7.5	SR 5.0
10	IR	ER	SR 7.5	SR 5.0

Where

ER = 2 x 650mg Tylenol Extended Relief®

IR = 2 x 500mg Tylenol Extra Strength®

SR 5.0 = 2 x 650mg Sustained Release 5.0% HPMC

SR 7.5 = 2 x 650mg Sustained Release 7.5% HPMC

Saliva samples were analyzed as previously described and the data collected.

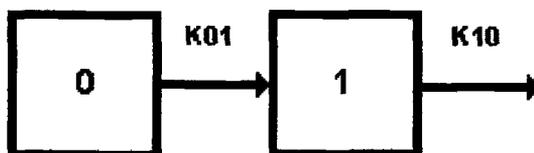
Each pharmacokinetic profile for each subject was evaluated using WinNonlin® and the data recorded.

PHARMACOKINETIC MODEL FITTING

WinNonlin Kinetic Fitting:

All data were fit using one of four compiled models supplied with the program.

Figure 2.3: Model #4: 1 compartment first order input, lag time, and first order elimination.



$$C(T) = D \cdot K_{01} / (V)(K_{01} - K_{10}) * (\text{EXP}(-K_{10} \cdot T) - \text{EXP}(-K_{01} \cdot T))$$

Estimated Parameters:

1. Volume/F
2. K_{01} = absorption rate
3. K_{10} = elimination rate
4. LT = lag time

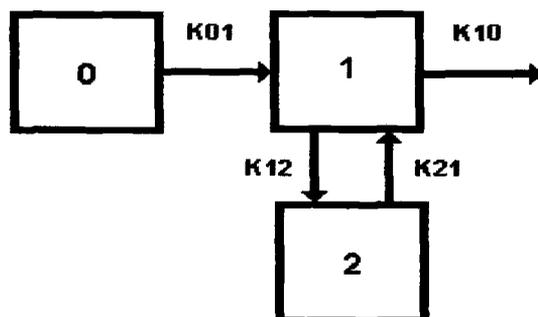
Constants in input:

1. # doses
2. dose 1 (mg)
3. time of dose 1

Secondary Parameters:

1. AUC = $D / (V)(K_{10})$
2. K_{01} half-life
3. K_{10} half-life
4. T_{max} = time of maximum concentration
= $\ln(K_{01}/K_{10}) / (K_{01} - K_{10})$
5. C_{max} = maximum concentration
= $C(T_{max})$

Figure 2.4: Model #12: 2 compartment first order input, micro-constants as primary parameters, lag time, and first order elimination.



$$C(T) = A \cdot \text{EXP}(-\text{ALPHA} \cdot T) + B \cdot \text{EXP}(-\text{BETA} \cdot T) + C \cdot \text{EXP}(-K01 \cdot T)$$

Where ALPHA and BETA are roots of the quadratic equation:

$$r^2 + (K12 + K21 + K10) \cdot r + K21 \cdot K10 = 0$$

Estimated Parameters:

1. Volume/F
2. K01 = absorption rate
3. K10 = elimination rate
4. K12 = transfer rate, 1 to 2
5. K21 = transfer rate, 2 to 1
6. LT = lag time

Constants in input:

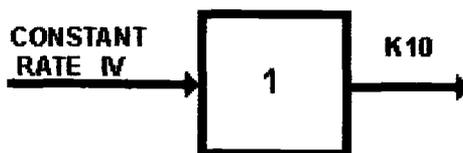
1. # doses
2. dose 1 (mg)
3. time of dose 1

Secondary parameters:

- | | |
|---------------------|-------------------|
| 1. AUC = D/(V)(K10) | 7. BETA half-life |
| 2. K10 half-life | 8. A |
| 3. K01 half-life | 9. B |
| 4. ALPHA | 10. Tmax* |
| 5. BETA | 11. Cmax* |
| 6. ALPHA half-life | |

*Estimated for the compiled (internal) library only.

Figure 2.5: Model #2: 1 compartment IV-infusion (zero order input), no lag time, first order elimination.



$$C(T) = (D/VI)/(V)(K10) * (EXP(-K10*TSTAR) - EXP(-K10*T))$$

where TI = time of infusion
 TSTAR = T-TI for T>TI
 = 0 for T<TI

Estimated parameters:

1. V = Volume
2. K10 = elimination rate

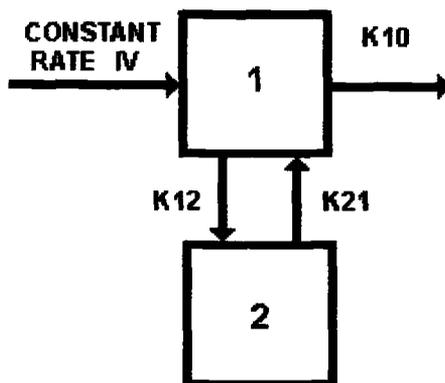
Constants in input:

1. # doses
2. dose 1 (mg)
3. start time of infusion
4. end time of infusion

Secondary Parameters:

1. AUC = D/(V)(K10)
2. K10 half-life
3. Cmax = C(TI)
4. CL
5. AUMC
6. MRT
7. Vss

Figure 2.6: Model #10: 2 Compartment IV-Infusion (zero-order input), macroconstants as primary parameters, no lag time, first order elimination.



$$C(T) = A_1 (\text{EXP}(-\text{ALPHA} * T) - \text{EXP}(-\text{ALPHA} * T\text{STAR})) + B_1 (\text{EXP}(-\text{BETA} * T) - \text{EXP}(-\text{BETA} * T\text{STAR}))$$

where $T\text{I}$ = time of infusion
 $T\text{STAR}$ = $T - T\text{I}$ for $T > T\text{I}$
 = 0 for $T \leq T\text{I}$

$$A_1 = (D / (T\text{I} * V)) * ((K21 - \text{ALPHA}) / ((\text{ALPHA} - \text{BETA}) * \text{ALPHA}))$$

$$B_1 = (-D / (T\text{I} * V)) * ((K21 - \text{BETA}) / ((\text{ALPHA} - \text{BETA}) * \text{BETA}))$$

Estimated Parameters:

1. Volume
2. $K21$
3. ALPHA
4. BETA

Constants in input:

1. # doses
2. dose 1 (mg)
3. start time of infusion
4. end time of infusion

Secondary Parameters:

1. K_{10}
2. K_{12}
3. K_{10} half-life
4. AUC
5. ALPHA half-life
6. BETA half-life
7. A^*
8. B^*
9. C_{max}
10. Cl
11. AUMC
12. MRT
13. V_{ss}

*A and B are the zero time intercepts following IV injection.

TYLENOL EXTRA STRENGTH

This formulation was included in the experiment as a baseline formulation. As the pharmacokinetics of immediate release acetaminophen have been extensively studied, this formulation serves as a double check that the study design and analysis yield data that are reasonably consistent with results obtained by other scientists.

Measured concentration versus time data for the ten subjects taking the Tylenol Extra Strength Product are listed in Appendix 2B. Saliva concentrations from the ten subjects were averaged for each time point and analyzed as an overall "average" profile for the immediate release formulation. Also, data from each subject were first fitted with equal weight on each point using both 1-compartment and 2-compartment open models with first order input and first order elimination. The fitted data were examined for appropriateness and goodness of fit and the compartmental model that fitted the majority of individual subjects was selected for additional study. Special consideration was given to the pharmacokinetic fitting of the "average" curves, which will be used for overall comparison among products because it is expected to represent the average pharmacokinetic behavior of the general population. A compartmental model was selected using the Schwartz Criteria, visual inspection of the data, and using an F-test.

Approximate hand calculations were also performed for AUC, K_{el} , and $t_{1/2}$ on the average data to verify fitting appropriateness. AUC was calculated using the trapezoidal rule. K_{el} was determined using linear regression of the elimination portion

of the data curve. The $t_{1/2}$ and V_d were calculated using standard pharmacokinetic formulas. Both T_{max} and C_{max} were estimated by visual inspection of the graphed data. These hand calculated values were compared to the computer generated profiles for both the one and two compartment models.

The computer generated parameters were also compared with literature values. A general literature search provided a fairly comprehensive list of pharmacokinetic parameters for acetaminophen. As it is been widely shown that acetaminophen exhibits linear kinetics at therapeutic dosage ranges, some literature values were scaled to a 1000mg dose to provide an easier basis for comparison.

Once a compartment model was selected, data were fitted again weighting the data $1/y$. The two models were compared using both visual inspection and an F-test to select the best model. Table 2.4 is a summary of pharmacokinetic parameters obtained from fitting a one compartment open model with equal weight on all points, first order input, and first order elimination. Pharmacokinetic parameters obtained from each fitting include area under the curve (AUC in $mg \cdot h/L$), time of maximum concentration (T_{max} in h), the maximum concentration value (C_{max} in mg/L), the quotient of the apparent volume of distribution (V_d in L) over the fraction of the dose absorbed (F), the lag time (T_{lag} in h), the calculated elimination half-life ($t_{1/2}$ in h), and the Schwartz Criteria (SC).

Notes about Pharmacokinetic Data

1. V_d/F - acetaminophen is an extremely well absorbed drug. The drug has continuous absorption throughout the gastrointestinal tract². It is therefore expected

that the value of F will be very close to one and the Vd/F quotient may be treated as Vd .

2. AUC - Values should be closely examined as in several individual subjects, the fitted lines predicted by the models do not return to zero. Erroneous K_{10} values may result for these models in these individual subjects. Since AUC is primarily calculated by this program using the equation $D/Vd/K_{10}$, AUC values may be affected. This is especially true in the case of the Tylenol Extra Strength® and Tylenol Extended Relief® products. In some individual subjects taking these formulations, the data return to zero but the fitted lines do not, therefore data from these individual subject was not used. In the 5% and 7,5% HPMC sustained release products this phenomenon is of less concern. The fact that the lines predicted by the model does not return to zero may be an indication that input from the dosage form is still occurring as the product passes though the gastrointestinal tract.
3. $t_{1/2}$ - calculated by $\ln 2/K_{10}$. As mentioned above, several fitted models predict lines with plasma concentrations that do not return to zero. Erroneous K_{10} values may result for these models. Profiles exhibiting this condition are marked with an asterisk (*) and are not included in the average calculations.

Table 2.4: Summary of pharmacokinetic parameters resulting from fitting Tylenol Extra Strength Data with a 1-compartment open model with equally weighted data points, first order input, and first order elimination.

SUBJ #	AUC	Tmax	Cmax	Vd/F	K ₁₀	t _{1/2}	SC
Units	mg*h/L	H	mg/L	L	1/h	h	
1	41.00	1.03	14.96	19.75	0.825	0.84	15.83
2	46.45	0.66	12.30	32.63	0.330	2.10	11.18
3	63.68	1.12	6.81	63.88	0.122	5.64	23.08
4	36.76	1.11	10.03	35.25	0.533	1.30	9.12
5	45.38	1.20	5.02	85.07	0.129	5.35	9.33
6	46.23	0.39	14.47	29.91	0.362	1.91	31.58
7	54.85	0.62	16.09	24.71	0.387	1.79	19.41
8	44.61	0.57	7.51	53.41	0.380	1.82	9.08
9	85.15	1.08	15.54	24.95	0.235	2.94	43.30
10	48.64	0.80	10.99	36.17	0.285	2.43	16.75
AV. DATA	52.82	0.80	10.87	35.42	0.330	2.10	9.50
AV. OF 10 SUB	51.27	0.85	11.37	40.57	0.358	1.93*	-----

* value calculated using harmonic mean.

$$x = \ln 2 / \text{average } K_{10}$$

This model does an excellent job of fitting most of the subject data. The three worst fitting examples are for subjects three (SC=23.08), six (SC=31.58), and nine (SC=43.30). For all three subjects, the fitted model predicts a line that falls below both the peak value (Cmax) and the elimination curve (K₁₀). The three best fitting examples are subjects four (SC=9.12), five (SC=9.33), and eight (SC=9.08). Figure 2.7 is the graph of the average data for this model, and the fit is quite good.

Figure 2.7: Graph of Tylenol Extra Strength Average Data fitted with a 1-compartment open model with equally weighted data points, first order input, and first order elimination.

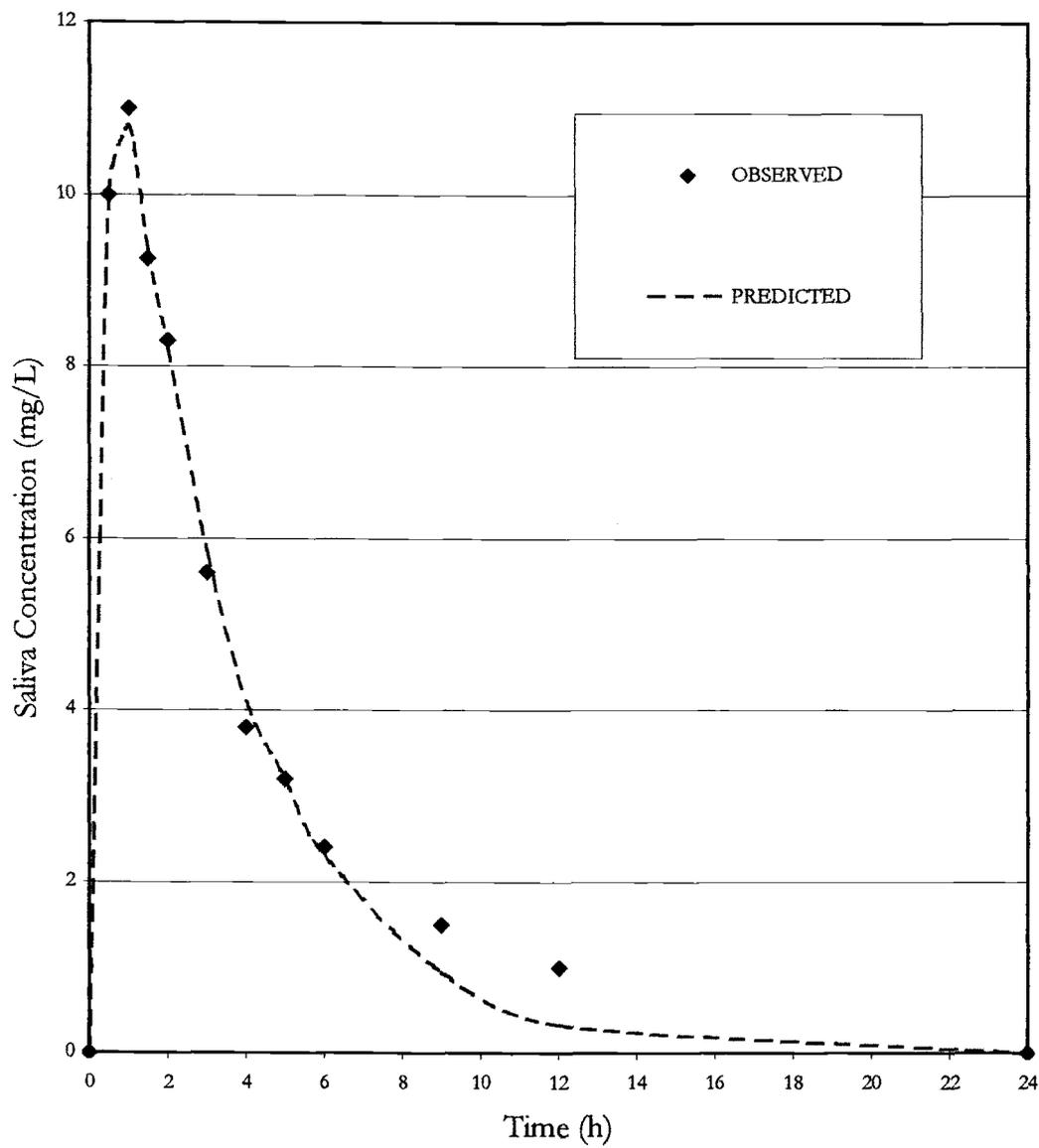


Table 2.5: Summary of pharmacokinetic parameters resulting from fitting Tylenol Extra Strength Data with a 2-compartment open model with equally weighted data points, first order input, and first order elimination.

SUBJ#	AUC	Tmax	Cmax	Vd/F	K ₁₀	t _{1/2}	SC
Units	mg*h/L	H	mg/L	L	1/h	h	
1	34.64	1.02	15.03	20.25	0.714	0.97	18.05
2	46.91	0.66	12.32	2.62	0.331	2.09	45.86
3	95.76	0.90	7.57	31.07	0.168	4.12	6.45
4*	68.08	0.82	11.42	37.15	0.198	3.50	1.75
5*	65.34	0.25	7.75	58.87	0.008	80.7	1.85
6	65.82	0.29	17.08	23.68	0.320	2.16	2.03
7*	64.73	0.53	16.44	25.03	0.309	2.24	18.72
8	31.53	0.70	7.79	26.63	0.597	1.16	3.87
9	133.3	0.53	16.38	27.08	0.138	5.00	12.10
10	80.26	0.42	14.52	30.10	0.207	3.34	3.23
AV. DATA	51.76	0.84	11.08	29.60	0.326	2.12	-5.77
AV. OF 7 SUB	69.74	0.64	12.95	23.06	0.353	1.96**	-----

* profile fitted with a line that does not converge to zero. AUC, t_{1/2}, and other pharmacokinetic parameters are not reasonable values and represent mathematical artifacts. These data are therefore not included in the analysis of in the average of 10 subjects data.

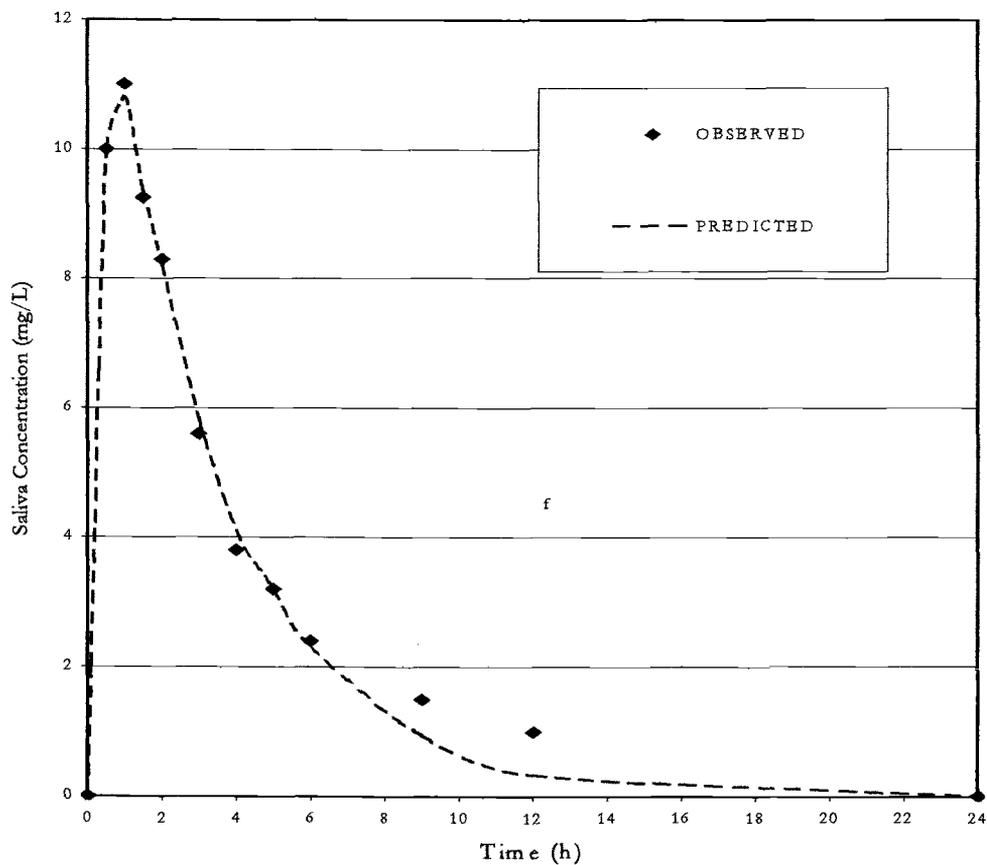
** value calculated using harmonic mean.

$$x = \ln 2 / \text{average } K_{10}$$

Subjects 4, 5, and 7 were not included in the average of 10 subjects data as described above. Although the equations generated for these data are an excellent fit to the experimental data points, the profiles generated are tangent to, not convergent

with a zero saliva concentration. This suggests that the drug stays in the body indefinitely which is not consistent with physical data for an immediate release formulation. Overall, this model appears to fit the data better than the 1 compartment model because of an overall better fit to the elimination portion of the curve. However, only 7 of the ten profiles yield reasonable data. Figure 2.8 shows fitted data for the average data for this model, and the fit is better than for a one-compartment model (compare to Figure 2.7).

Figure 2.8: Graph of Tylenol Extra Strength Average Data fitted with a 2-compartment open model with equally weighted data points, first order input, and first order elimination.



Comparison of Fitted Parameters to Hand Calculated Parameters:

As a double check of the fitting program, parameter estimates were calculated by hand stripping and compared to fitted data from the program. The average data curve was selected as a representative profile. Linear regression was performed on the 4, 5, 6, 9, and 12 hour time points to estimate k_{el} . AUC was estimated using the trapezoidal rule. Values of Vd and $t_{1/2}$ were calculated using $Vd=D/(AUC)(k_{el})$ and $t_{1/2}=\ln 2/k_{el}$ respectively. T_{max} and C_{max} were obtained by visual inspection of the graphed data.

Table 2.6 Comparison of Computer Fitted Parameters to Hand Calculated Parameters

Fitting Method	AUC	Tmax	Cmax	Vd/F	K_{10}	$t_{1/2}$
Units	mg*h/ L	H	mg/L	L	1/h	H
Computer 1 Comp	52.82	0.80	10.87	35.42	0.330	2.10
Computer 2 Comp	51.76	0.84	11.08	29.60	0.326	2.12
Hand Calculated	50.71	1.0	11.04	46.75	0.211	3.28

Computer generated parameters of averaged data for both the one compartment and the two compartment models were very close to the hand-calculated parameters. The larger values of Vd/F and $t_{1/2}$ for the hand calculated parameters may be the result of excluding the 24 hour time point from the linear regression process. This may have resulted in an under estimation of k_{el} and a corresponding over estimation of Vd/F and $t_{1/2}$. Overall, the similarity of the values supports the computer simulations and lends confidence to the program output.

Model Selection:

Table 2.7: Comparison of Fitted Pharmacokinetic Parameters to Literature Values

	S/ B	AUC	Tmax	Cmax	t1/2	Kel	Ka
1 ^a	B	52		16			
2 ^b	S	64.6	0.67	20.6			
3 ^c	S	58.6	1.42	15.8			
4 ^d	B	33.3			1.97		
5 ^e	S	47.1	1.24	15.5	1.92	0.361	9.757
6 ^f	S	60.5		22.5	3.39	0.454	15.2
7 ^g	B		0.5-1	11.4	1.8	0.385	
8 ^h	B		0.7	13.2	1.8	0.376	3.25
9 ⁱ	B		0.9	9.71	1.8	0.390	2.20
10 ^j	S	58.85	1.22	20.8	2.47	0.295	
11 ^k	S	58.81	0.97	18.10	2.21	0.314	
12 ^l	S	63.0			2.67	0.259	
13 ^m	S	64.3	0.82	21.0	2.60	0.267	
10 ⁿ	S	52.82	0.8	10.87	2.10	0.329	3.20
11 ^o	S	51.76	0.84	11.08	2.12	0.326	2.33
Mean ± SD		55.47 ±8.89	0.96 ±0.26	16.78 ±4.21	2.26 ±0.52	0.344 ±0.06	7.60 ±6.06
Range		33.3- 64.6	0.5- 1.42	9.71- 22.5	1.8-3.39	0.259- 0.454	2.20- 15.2

- a. Values adjusted to 1000mg. Original data for 450mg³.
- b. Values adjusted to 1000mg. Original data for 500mg. Fasted subjects⁴.
- c. Values adjusted to 1000mg. Original data for 500mg. Fed subjects⁴.
- d. Values adjusted to 1000mg. Original data for 12mg/kg. Assume 70kg person = 840mg⁵.
- e. Values adjusted to 1000mg. Original data for 1500mg. Fitted with 1 compartment model with first order input and first order elimination⁶.

- f. Values adjusted to 1000mg. Original data for 1500mg. Fitted with 2 compartment model with first order input and first order elimination⁶.
- g. Values adjusted to 1000mg. Original data for 10mg/kg. Assume 70kg person = 70kg. data in children age 1.7-6 years⁷.
- h. Values adjusted to 1000mg. Original data for 10mg/kg. Assume 70kg person = 70kg. data in children age 2-7 years⁸.
- i. Values adjusted to 1000mg. Original data for 10mg/kg. Assume 70kg person = 70kg. data in children age 2-11 years⁹.
- j. Multiple dose pharmacokinetic parameters¹⁰.
- k. Multiple dose pharmacokinetic parameters¹¹.
- l. Non-compartmental analysis. Multiple dose pharmacokinetic parameters¹².
- m. Compartmental analysis. Multiple dose pharmacokinetic parameters¹².
- n. From average data fitted with 1 compartment model with first order input and first order elimination
- o. From average data fitted with 2 compartment model with first order input and first order elimination
- * Average of literature values \pm SD

Table 2.7 clearly shows that both the one compartment and the two compartment fitted models provide parameters that are close to the average and well within the ranges of previously reported literature values for acetaminophen. Likewise, the literature data are relatively equally divided in use of one and two compartment models. Despite the better Schwartz Criteria for the two compartment model, the two compartment model failed to predict reasonable model parameters for 3 of the 10 fitted kinetic profiles. Therefore, this author has selected the 1 compartment model for additional analysis.

Another interesting item is to note that the literature is also split on its use of saliva and serum data. Those studies using saliva samples arrived at pharmacokinetic parameters that were similar to the parameters obtained from studies using serum samples. Since saliva samples may be collected using a non-invasive sampling technique and appear to yield similar pharmacokinetic results, it is appropriate to use them for testing of acetaminophen products.

Since one of the main sources of error in the one compartment model above was underestimation of data points in the elimination curve, it was decided to fit the data again weighing the points by a factor of $1/y$ and to consider weighting of $1/y^2$. This change in weighing scheme increases the significance of the elimination points in the fitting process, sometimes resulting in a better estimation of the elimination portion of the curve. Table 2.8 summarizes the pharmacokinetic parameters resulting from fitting the data points with a 1-compartmental open model with the data points weighed $1/y$, first order input, and first order elimination. Figure 2.9 is the graph of the fitted data for the average data with first order input, first order elimination, and data points weighed $1/y$.

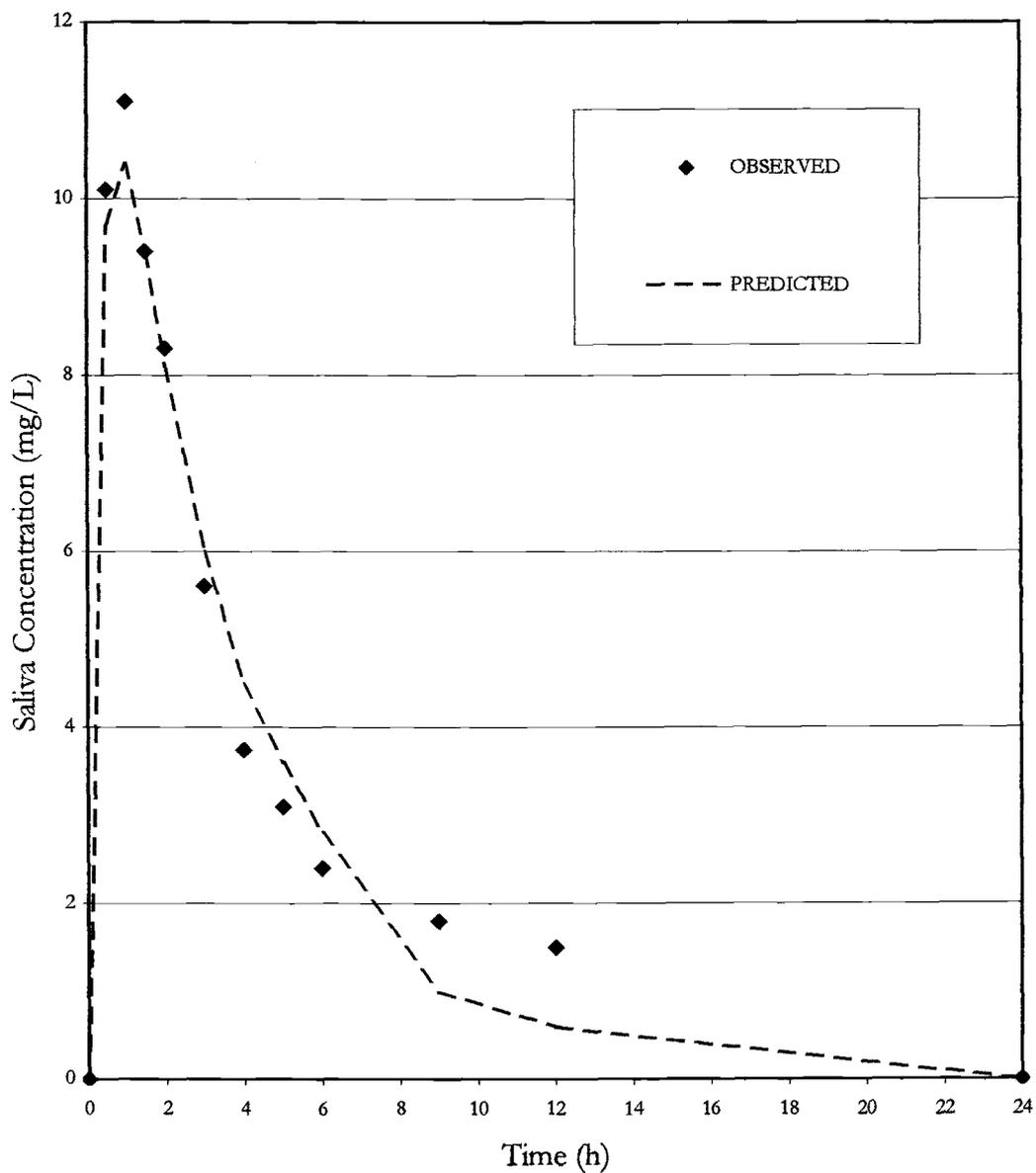
Table 2.8: Summary of pharmacokinetic parameters resulting from fitting Tylenol Extra Strength data with a 1-compartment open model with the data points weighed 1/y, first order input, and first order elimination.

SUBJ#	AUC	Tmax	Cmax	Vd/F	K ₁₀	t _{1/2}	SC
Units	Mg*h/L	h	mg/L	L	1/h	h	
1	30.74	1.00	15.11	20.59	0.796	0.87	-8.14
2	45.45	0.69	12.33	31.92	0.344	2.01	0.63
3	76.46	1.21	6.27	71.2	0.091	7.55	22.39
4	27.49	1.13	9.72	36.94	0.495	1.40	-10.20
5	24.68	0.74	6.84	55.88	0.362	1.91	0.65
6	52.11	0.42	12.53	35.50	0.270	2.56	26.88
7	55.50	0.62	15.74	25.41	0.355	1.95	-5.97
8	23.50	0.54	7.33	55.12	0.387	1.79	4.35
9	97.04	1.16	14.44	27.91	0.184	3.75	36.41
10	54.67	0.46	10.74	42.23	0.216	3.20	14.70
AV. DATA	44.91	0.81	10.45	37.52	0.297	2.33	13.56
AV. OF 10 SUB	48.76	0.79	11.10	40.27	0.350	1.98*	-----

* value calculated using harmonic mean.

$$x = \ln 2 / \text{average } K_{10}$$

Figure 2.9: Graph of Tylenol Extra Strength Average Data fitted with a 1-compartment open model with data points weighted $1/y$, first order input, and first order elimination.



Weighing the data points by $1/y$ during the fitting process appears to have improved the fit on some of the subject data. The cost of the improved fit during the elimination portion of the curve is the fit around the peak area and the C_{max} values. Most of the fitted models using the $1/y$ weighing scheme underestimate the C_{max} values. Table 2.9 compares the measured C_{max} with the C_{max} values estimated by the 1-compartment open models with the data points weighed 1 and $1/y$.

Table 2.9: Comparison of Estimated C_{max} values for the Tylenol Extra Strength data fitted with 1-compartment open models with different data points weighing schemes.

SUBJ #	Exp. C_{max}	Est. C_{max} $W=1$	Exp.-Est. C_{max} for $W=1$	Est. C_{max} $W=1/y$	Exp.-Est. C_{max} for $W=1/y$
1	15.22	14.96	0.26	15.11	0.11
2	12.21	12.30	-0.09	12.33	-0.12
3	7.61	6.81	0.80	6.27	1.34
4	10.61	10.03	0.58	9.72	0.89
5	7.35	5.02	2.33	6.84	0.51
6	15.88	14.47	1.41	12.53	3.35
7	16.45	16.09	0.36	15.74	0.71
8	7.55	7.51	0.04	7.33	0.22
9	16.66	15.54	1.12	14.44	2.22
10	11.59	10.99	0.60	10.74	0.85
AV. DATA	11.04	10.87	0.17	10.45	0.59

The models with data points weighed by $1/y$ underestimated the C_{max} value by an average of 1.025mg/L but, models with the data points weighed by 1 underestimated the C_{max} by only 0.741mg/L.

Finally, the fit for the average data was compared for the two models. Both modeling schemes appear to fit the data reasonable well upon visual inspection, however the model with equally weighted data points has a slightly better fit ($SC=9.50$) than the model with data points weighted $1/y$ ($SC= 13.56$). Any further analysis on these data will be done using a one-compartment open model with equally weighed data points, first order input and first order elimination.

Since the $1/y$ weighting scheme did not significantly improve the fit of the model, fitting with $1/y^2$ was not performed. The $1/y^2$ weighting scheme, while expected to put even more emphasis on the elimination portion of the curve, would further exacerbate the poor fit of the model around the peak. This weighting scheme was therefore not applied to the data.

TYLENOL EXTENDED RELIEF

The Tylenol Extended Relief® product is expected to differ from the Tylenol Extra Strength Product® because of the manufacturer claims of "extended relief". Each tablet is composed of 325mg of immediate release acetaminophen and 325mg of acetaminophen in a sustaining hydrophilic matrix. The analysis process described above in the Tylenol Extra Strength section was repeated for the Tylenol Extended Relief product. The raw acetaminophen saliva data are available in Appendix 2B. Figure 2.10 shows the Tylenol Extended Relief Product fitted with a one compartment open model with first order input and first order elimination. All data points are given equal weight during the fitting.

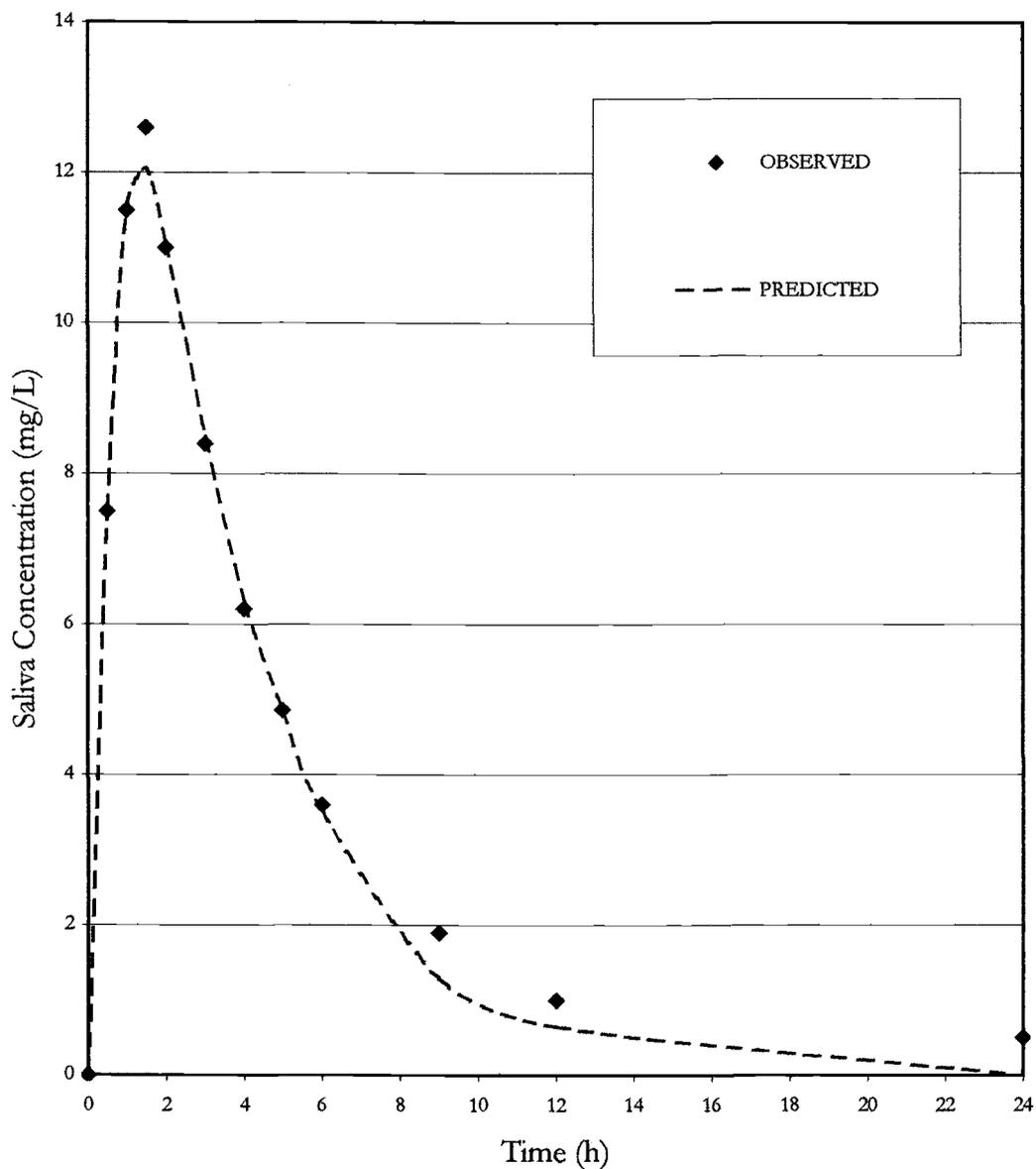
Table 2.10: Summary of pharmacokinetic parameters resulting from fitting Tylenol Extended Relief Data with a 1-compartment open model with equally weighted data points, first order input, and first order elimination.

SUBJ#	AUC	Tmax	Cmax	Vd/F	K ₁₀	t _{1/2}	SC
Units	Mg*h/L	h	mg/L	L	1/h	h	
1	48.59	1.19	14.46	41.50	0.322	2.15	29.39
2	79.33	1.58	12.39	37.37	0.152	4.56	24.73
3	25.62	0.82	8.72	57.45	0.444	1.56	13.28
4	81.06	1.67	12.69	39.75	0.202	3.43	41.38
5	45.50	0.73	9.22	59.01	0.242	2.86	31.46
6	67.58	1.70	12.10	32.29	0.298	2.32	25.46
7	74.89	1.41	15.61	30.65	0.284	2.44	31.67
8	76.64	0.96	16.02	31.22	0.271	2.55	51.38
9	84.69	0.79	14.84	41.17	0.186	3.71	21.58
10	39.15	0.40	12.05	48.00	0.346	2.00	9.53
AV. DATA	67.32	1.34	12.15	37.54	0.302	2.29	6.28
AV. OF 10 SUBJ.	62.30	1.12	12.81	41.84	0.274	2.52*	-----

* value calculated using harmonic mean.

$$x = \ln 2 / \text{average } K_{10}$$

Figure 2.10: Graph of Tylenol Extended Relief Average Data fitted with a 1-compartment open model with equally weighted data points, first order input, and first order elimination.



Many of the data profiles could not be fit for a 2 compartment model. Table 2.11 lists the fitted parameters for those profiles that the computer was able to fit. All data points received equal weight during the fitting.

Table 2.11: Summary of pharmacokinetic parameters resulting from fitting Tylenol Extended Relief Data with a 2-compartment open model with equally weighted data points, first order input, and first order elimination.

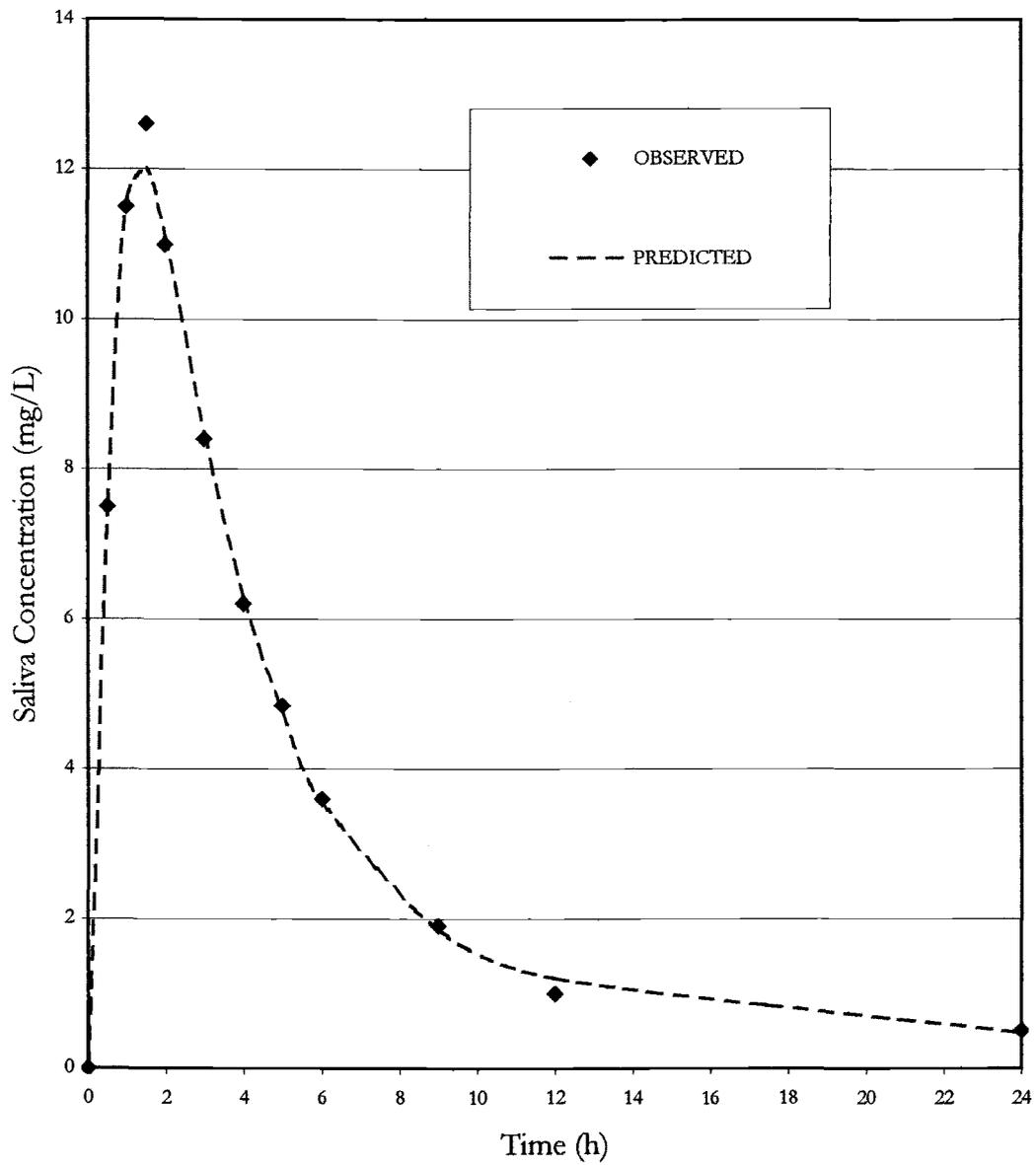
SUBJ#	AUC	Tmax	Cmax	Vd/F	K ₁₀	t _{1/2}	SC
Units	mg*h/L	h	mg/L	L	1/h	h	
2	79.99	1.58	12.39	37.27	0.218	3.17	27.13
4	136.3	1.54	16.62	20.16	0.236	2.93	4.55
5	53.26	0.60	10.79	46.09	0.265	2.61	3.90
7*	336.5	1.58	15.70	15.87	0.121	5.69	22.35
8*	119.5	0.95	16.05	31.04	0.175	3.95	25.88
AV. DATA	73.29	1.33	12.28	35.32	0.251	2.76	-2.90
AV. OF 3 SUBJ.	89.85	1.24	13.26	34.50	0.239	2.90**	-----

* profile fitted with a line that does not converge to zero. AUC, t_{1/2}, and other pharmacokinetic parameters are not reasonable values and represent mathematical artifacts. These data are therefore not included in the analysis of in the average of 10 subjects data.

** value calculated using harmonic mean.

$$x = \ln 2 / \text{average } K_{10}$$

Figure 2.11: Graph of Tylenol Extended Relief Average Data fitted with a 2-compartment open model with equally weighted data points, first order input, and first order elimination.



Of the five profiles that the computer was able to fit as a two compartment model, two fitted curves are tangential to, not convergent with a zero concentration profile. Those profiles did not provide reasonable estimates for some parameters (AUC) and were excluded from the average of three subjects portion of the data. Since this model could describe such a small number of profiles, it was discarded as unsuitable for this formulation.

Again, the profiles were re-fit using a one compartment open model with first order input and first order elimination with the data points weighted $1/y$ in an effort to produce curves that better describe the elimination portion of the pharmacokinetic curve. Table 2.12 describes the data from this fitting model.

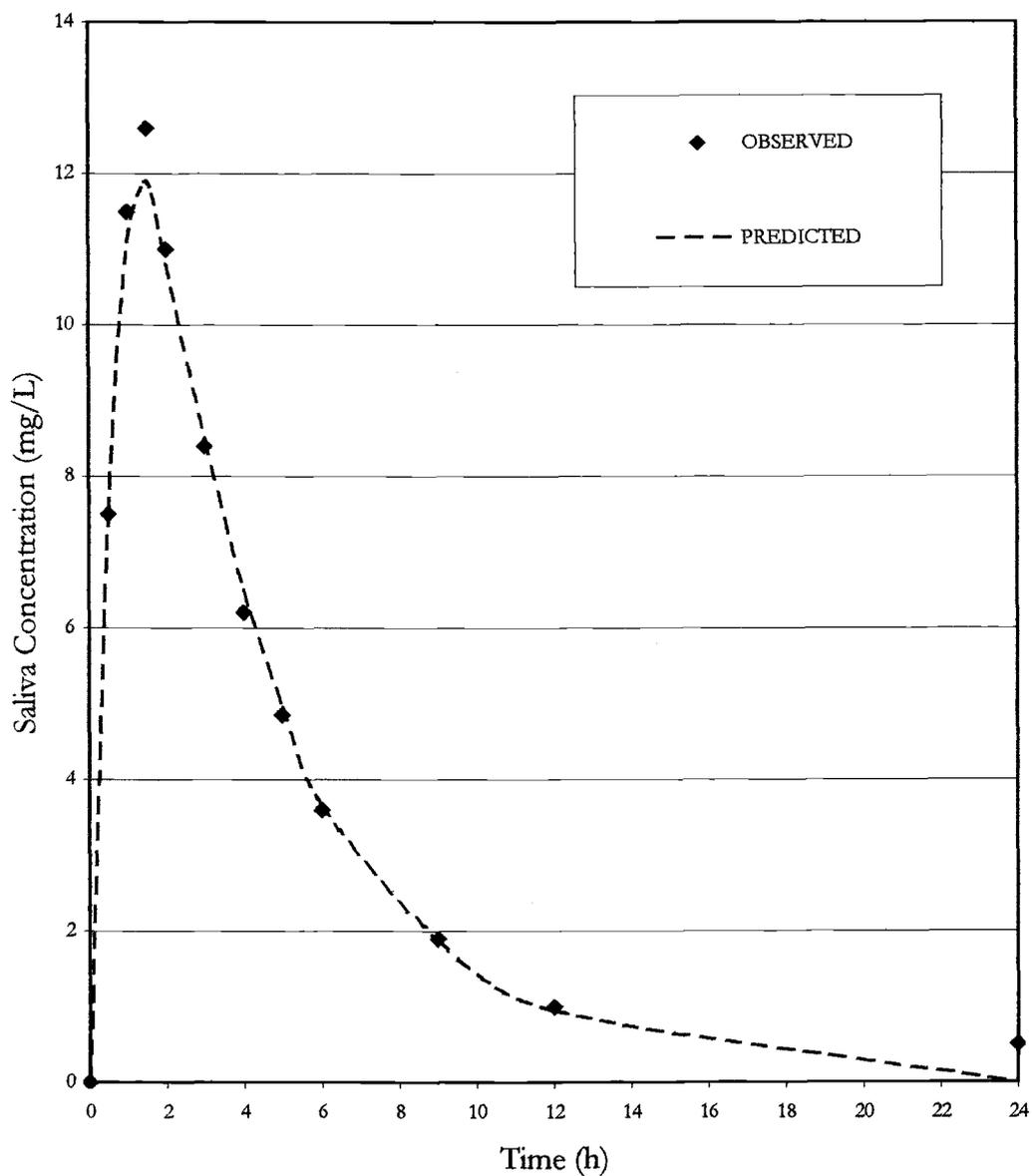
Table 2.12: Summary of pharmacokinetic parameters resulting from fitting Tylenol Extended Relief data with a 1-compartment open model with the data points weighed 1/y, first order input, and first order elimination.

SUBJ#	AUC	Tmax	Cmax	Vd/F	K₁₀	t_{1/2}	SC
Units	Mg*h/L	h	mg/L	L	1/h	H	
1	34.36	1.55	11.55	20.65	0.924	0.75	13.04
2	79.33	1.58	12.39	37.37	0.219	3.16	24.73
3	28.25	0.67	8.52	60.28	0.382	1.81	-17.76
4	67.03	1.70	10.49	48.08	0.202	3.43	33.17
5	36.14	0.65	10.13	50.82	0.355	1.95	6.76
6	66.73	1.71	11.98	32.43	0.301	2.30	16.95
7	123.2	1.55	10.44	53.36	0.098	7.01	44.12
8	94.28	1.23	10.79	50.89	0.353	1.96	42.73
9	76.08	1.04	14.67	38.52	0.222	3.12	-9.27
10	42.17	1.17	11.18	50.08	0.308	2.25	-30.65
AV. DATA	60.61	1.22	13.07	38.02	0.282	2.45	19.93
AV. OF 10 SUBJ	64.82	1.28	11.21	44.24	0.336	2.06*	-----

* value calculated using harmonic mean.

$$x = \ln 2 / \text{average } K_{10}$$

Figure 2.12: Graph of Tylenol Extended Relief Average Data fitted with a 1-compartment open model with data points weighted $1/y$, first order input, and first order elimination.



When comparing the profile of the data fitted with equal and $1/y$ weight on the data points, little difference is seen in the tabulated data, but as before, the $1/y$ weighted data have lower predicted peaks and a more gently sloping elimination phase. However, when looking at the average data results for both fitting methods, it becomes clear that the equally weighted data ($SC=6.28$) fits better than the $1/y$ weighted data ($SC=19.93$). As with the Tylenol Extra Strength Data, it is felt that the one compartment open model with first order input, first order elimination, and equally weighted data points best describes the data.

Since this product is 325mg of immediate release combined with 325mg of "extended release" formulation it was difficult to know what to expect of the release profile. It would be reasonable to expect a rapid increase in drug concentration followed by a well sustained or extended, relatively "flat", drug concentration vs. time profile. These two profiles would combine to form an overall profile that could be best described by a multiple input model. In reality, it appears that a one compartment open model with first order input can easily and accurately describe the combined release of the two elements. Rather than being unique, results for the Tylenol Extended Relief® are nearly identical to results for the Tylenol Extra Strength® tablets after scaling for the difference in the dose (see Figure 2.13).

The nearly identical pharmacokinetic results for the Tylenol Extra Strength® and the Tylenol Extended Relief® products suggests that the "Extended Relief" product behaves as an immediate release product, not as a sustained release product. The 325mg hydrophilic matrix portion of the Tylenol Extended Relief® product is

not successful in extending the release of the acetaminophen from the product. The increase in the recommended dosing interval from 4-6 hours (Tylenol Extra Strength®) to every 8 hours (Tylenol Extended Relief®) appears to be possible not because of any sustained release character of the formulation, but because of the increase in the dose. Even the 2 hour extension between doses is suspect since the drug concentration at 6 hours from 1000mg of the immediate release product is higher than the drug concentration at the 8 hours from the larger dose, extended relief product.

Data provided in United States Patent 4,820,522 compares average plasma acetaminophen levels for a 1000mg dose of "Non-sustained Release Acetaminophen 500mg tablets in 12 subjects" to a 1300mg dose of "Sustained Release (SR) Acetaminophen Bi-layered 650mg tablets". Figure 2.13a shows a plot of the data published for that comparison. Figure 2.13b shows that same plot comparison after the immediate release (IR) data points were proportionally adjusted to a 1300mg dose. At 8 hours, the difference between the plasma concentrations is 2.6µg/ml and 2.3µg/ml respectively for the SR and adjusted IR products. Calculating the time it would take the Tylenol Extended relief product to decline from 2.6 to 2.3µg/ml can be accomplished using the equation $C_t = C_o e^{-kt}$. C_t is the drug concentration at time t , C_o is the original drug concentration, k is the elimination rate constant, and t is the time in hours it takes for C_o to decline to C_t . First, a k for the Tylenol extended relief product must be calculated using known data points. Published data shows a plasma concentration of 2.6µg/ml, 8 hours after the dose and a plasma concentration of

1.6 $\mu\text{g}/\text{ml}$, 10 hours after the dose.

Plugging in the equation we have:

$$1.6 = 2.6e^{-k(2)}$$

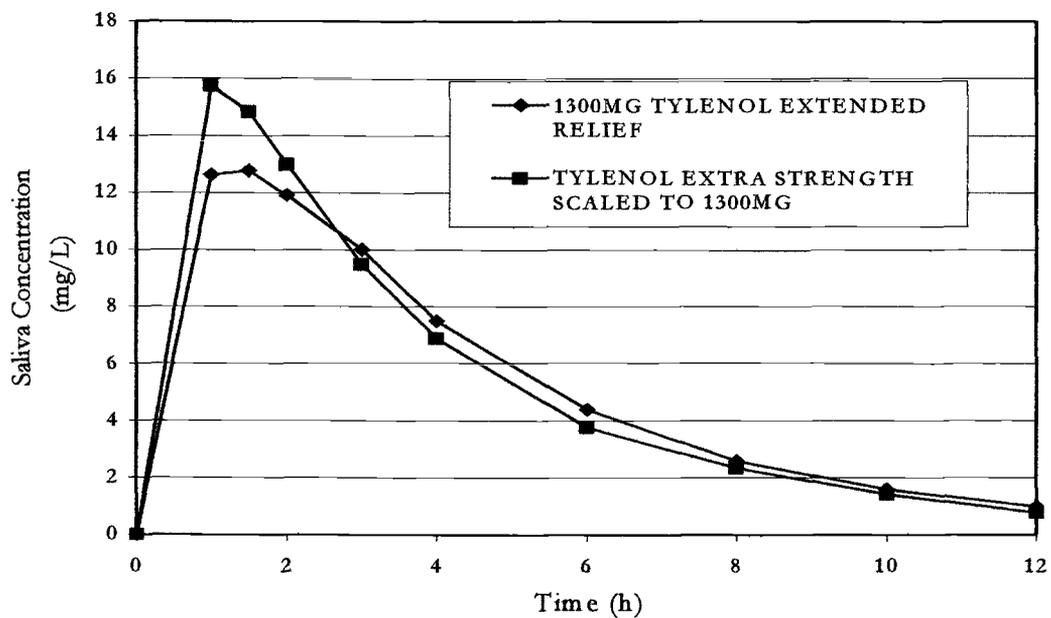
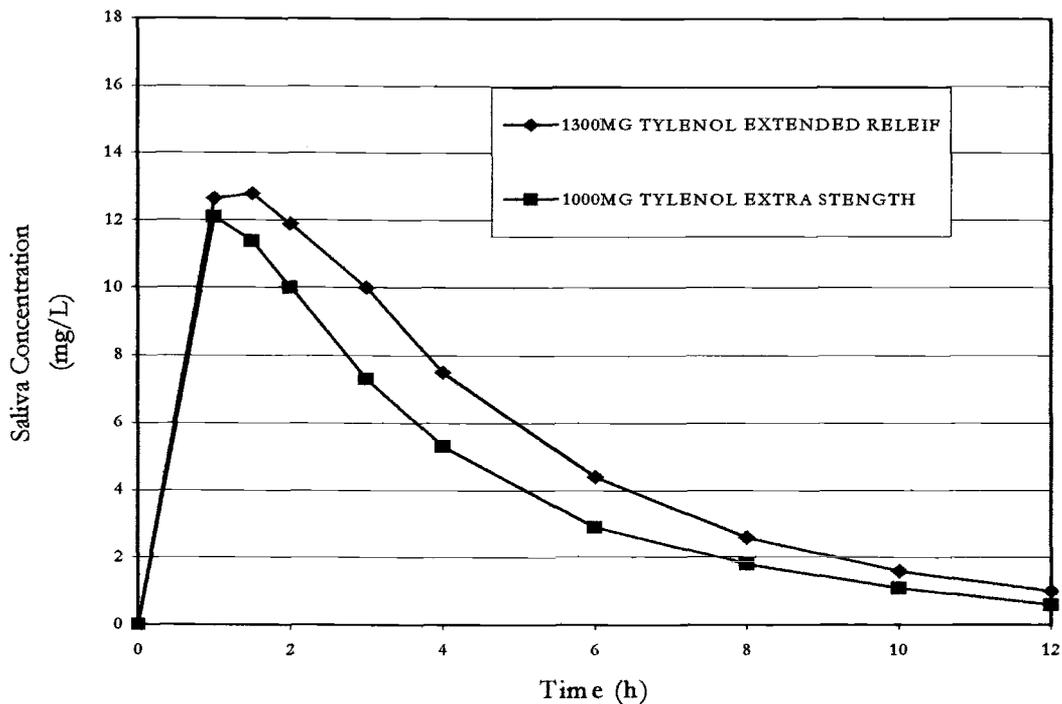
from which k can be determined to be 0.2427h^{-1} . Using this calculated k , we can now solve for the time for the plasma concentration to decrease from $2.6\mu\text{g}/\text{ml}$ to $2.3\mu\text{g}/\text{ml}$.

$$1.3 = 2.6e^{-(0.2427)t}$$

This equation yields a value for t of 0.50 hours or 30 minutes. This means that the acetaminophen release is only extended by only 30 minutes. In light of this, this investigator considers the term "Extended Relief" to be a misnomer as patients could achieve essentially the same plasma acetaminophen levels by taking 1300mg of generic immediate release product rather than pay for the poorly formulated and expensive brand name Tylenol Extended Relief® product.

Figure 2.13: a. Published Average Plasma Concentrations for a 1000mg dose of Non-sustained Release Acetaminophen 500mg tablets compared to Average Plasma Levels for a 1300mg dose of Sustained Release Acetaminophen Bi-layered 650mg tablets in twelve Subjects.

b. Data in a. after proportionally adjusting immediate release data to a total acetaminophen dose of 1300mg.



5% HPMC SUSTAINED RELEASE PRODUCT

Release of acetaminophen from matrix tablets is expected to be a combination of kinetic release profiles. Initially, the profile is expected to show a small burst of drug release. This small burst is the result of drug being released from the surface of the tablet during initial wetting of the tablet surface. As the surface begins to hydrate, diffusion of drug out of the wetted and gelled tablet is expected to be the dominant kinetic factor. Lastly, drug release from surface erosion of the tablet will be added to the profile as the tablet is forced through the gastrointestinal tract via peristaltic contractions of the small and large intestines. The three kinetic profiles are expected to combine to form a kinetic profile that has a lower and broader peak than was seen in the immediate release Tylenol Extra Strength® and the Tylenol Extended Relief profiles. The lower peak is expected to gradually decline back to baseline resulting in a much smaller apparent k_{el} and therefore a longer apparent $t_{1/2}$ value. The actual magnitude and proportion of the three kinetic patterns, and therefore the sum, will determine the overall release profile.

Since the exact release pattern from the sustained release products was unknown and unpredictable, fitting was attempted to a larger number of pharmacokinetic models in terms of drug input. Data from each subject were fitted to four models. All models were open models with equally weighted data points and first order elimination. Models used included: a one compartment model with first

order input, a one compartment model with zero order input from time zero to T_{max} , a two compartment model with first order input, and a two compartment model with zero order input from time zero to T_{max} . Tables 2.13-2.16 display results of fitting the four models. Figures 2.14-2.17 are graphs of average data for each of the four models.

Table 2.13: Summary of pharmacokinetic parameters resulting from fitting 5% HPMC Sustained Release Acetaminophen with a 1-compartment open model with equally weighted data points, first order input, and first order elimination.

SUBJ#	AUC	T_{max}	C_{max}	Vd/F	K_{10}	$t_{1/2}$	SC
Units	Mg*h/L	h	mg/L	L	1/h	h	
1	89.83	3.21	5.63	91.15	0.079	8.73	12.41
2	66.73	3.55	6.86	52.74	0.184	3.75	33.58
3	86.44	3.56	4.61	120.3	0.062	11.1	20.74
4	65.26	3.96	10.5	36.76	0.271	2.55	37.10
5	27.94	2.84	4.69	51.03	0.456	1.52	27.06
6	95.90	2.15	6.89	80.42	0.084	8.22	22.20
7	63.57	3.87	6.42	37.14	0.276	2.51	19.93
8	34.63	3.68	3.96	60.06	0.313	2.21	26.72
9	132.0	4.41	4.83	110.3	0.044	15.5	0.905
10	49.16	2.97	5.64	66.72	0.198	3.49	16.99
AV. DATA	69.18	3.73	5.62	60.84	0.133	5.2	13.50
AV. OF 10 SUBJ	71.14	3.42	6.00	70.66	0.196	3.5*	-----

* value calculated using harmonic mean.
 $x = \ln 2 / \text{average } K_{10}$

Figure 2.14: Graph of 5% HPMC Sustained Release Acetaminophen Average Data fitted with a 1-compartment open model with equally weighted data points, first order input, and first order elimination.

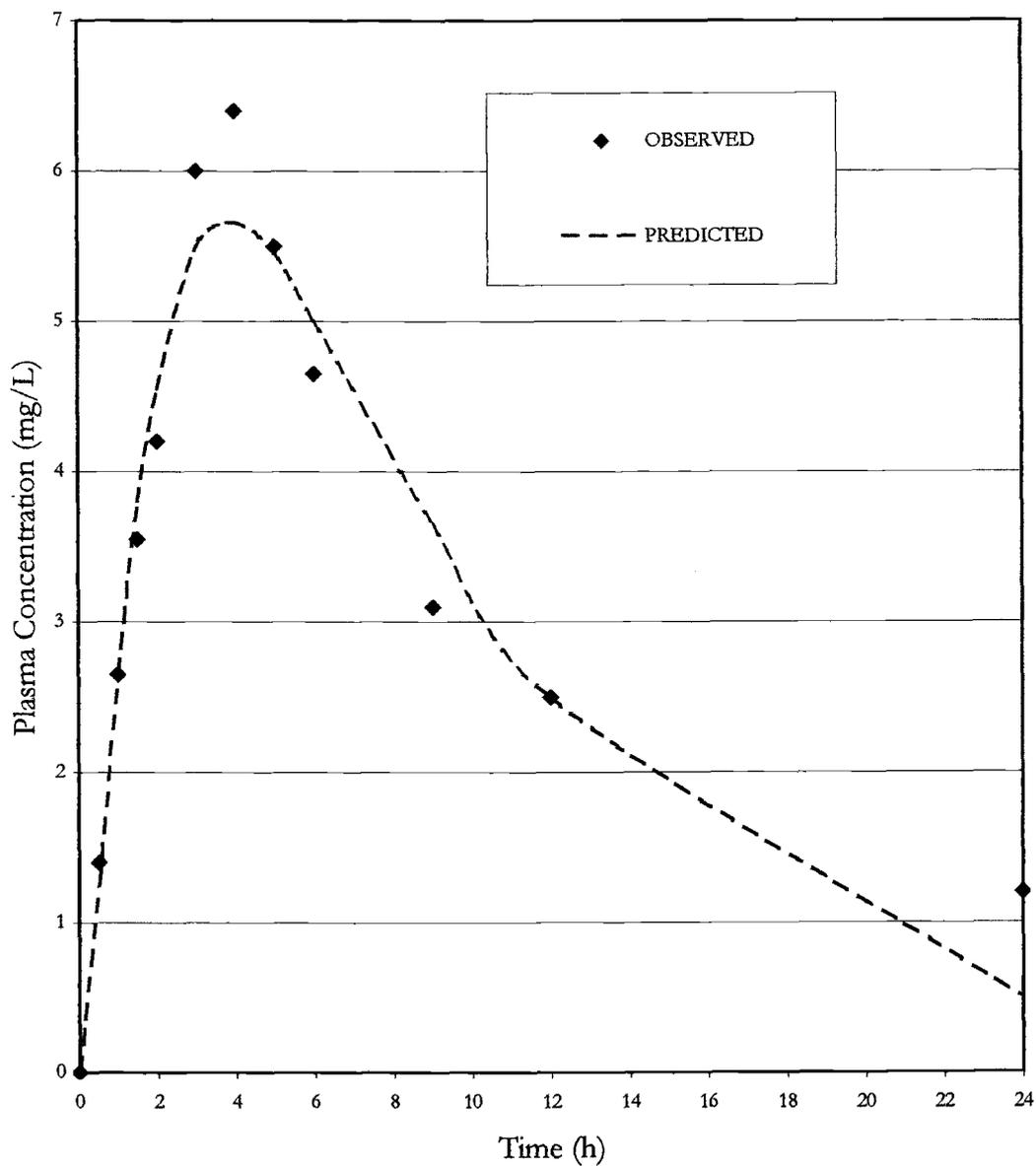


Table 2.14: Summary of pharmacokinetic parameters resulting from fitting 5% HPMC Sustained Release Acetaminophen with a 2-compartment open model with equally weighted data points, first order input, and first order elimination. The computer was unable to fit many of the profiles using this model.

SUBJ#	AUC	Tmax	Cmax	Vd/F	K ₁₀	t _{1/2}	SC
Units	Mg*h/L	h	mg/L	L	1/h	h	
4	269.05	4.12	8.91	27.76	0.087	7.96	42.59
6	147.64	2.44	7.24	39.13	0.112	6.16	20.67
8	34.81	3.67	3.96	58.62	0.319	2.17	29.25
AV. DATA	230.21	3.70	5.63	47.22	0.060	11.5	11.65
AV. OF 3 SUBJ	150.5	3.41	6.70	41.83	0.172	4.02*	-----

* value calculated using harmonic mean.

$$x = \ln 2 / \text{average } K_{10}$$

Figure 2.15: Graph of 5% HPMC Sustained Release Acetaminophen Average Data fitted with a 2-compartment open model with equally weighted data points, first order input, and first order elimination. The computer was unable to fit many of the profiles using this model.

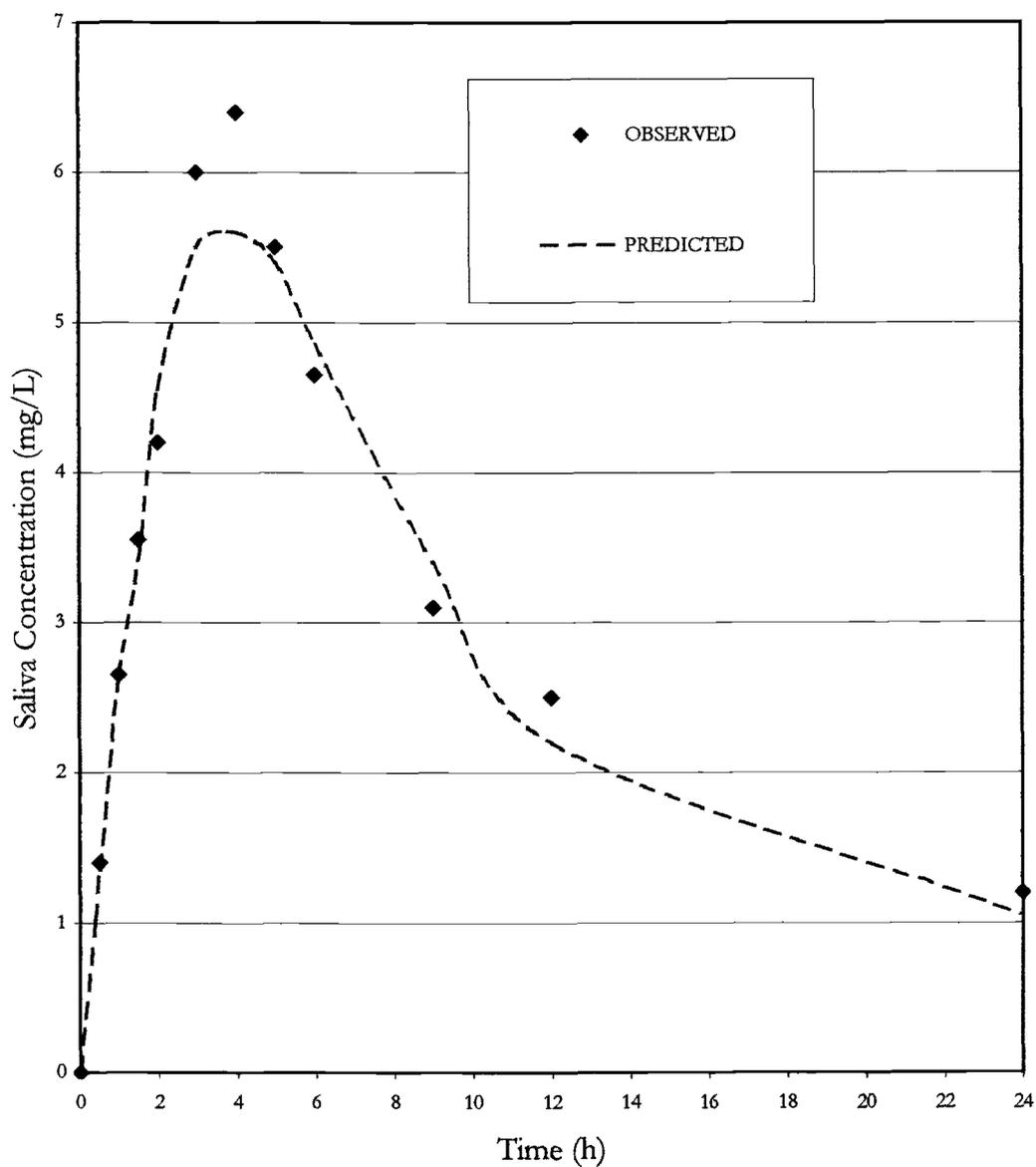


Table 2.15: Summary of pharmacokinetic parameters resulting from fitting 5% HPMC Sustained Release Acetaminophen with a 1-compartment open model with equally weighted data points, zero order input from 0 to T_{max_data} hours, and first order elimination. T_{max_data} was defined as the time associated with the highest saliva concentration for each subject.

SUBJ#	AUC	T_{max_data}	MRT	Vol.	Cl	$t_{1/2}$	SC
Units	Mg*h/L	h	h	L	L/h	h	
1	65.11	4	7.10	70.94	9.98	4.92	26.31
2	59.66	4	4.87	53.08	10.89	3.37	24.95
3	73.58	4	12.14	107.24	8.83	8.41	19.78
4	74.71	5.083	4.81	41.90	8.70	3.33	38.53
5	29.48	3	3.73	82.25	22.04	2.58	16.18
6	66.38	3	6.02	59.00	9.79	4.17	33.17
7	55.40	4	4.74	55.61	11.73	3.28	-1.00
8	30.37	5	3.47	74.34	21.40	2.40	12.73
9	124.7	3.083	21.17	110.39	5.21	14.6	15.73
10	47.01	3	5.21	72.05	13.82	3.61	8.36
AV. DATA	59.47	4	6.49	70.96	10.92	4.50	13.03
AV. OF 10 SUBJ	62.63	3.81	7.32	72.68	12.23	5.06	-----

Figure 2.16: Graph of 5% HPMC Sustained Release Acetaminophen Average Data fitted with a 1-compartment open model with equally weighted data points, zero order input from 0 to T_{max_data} hours, and first order elimination. T_{max_data} was defined as the time associated with the highest saliva concentration for each subject.

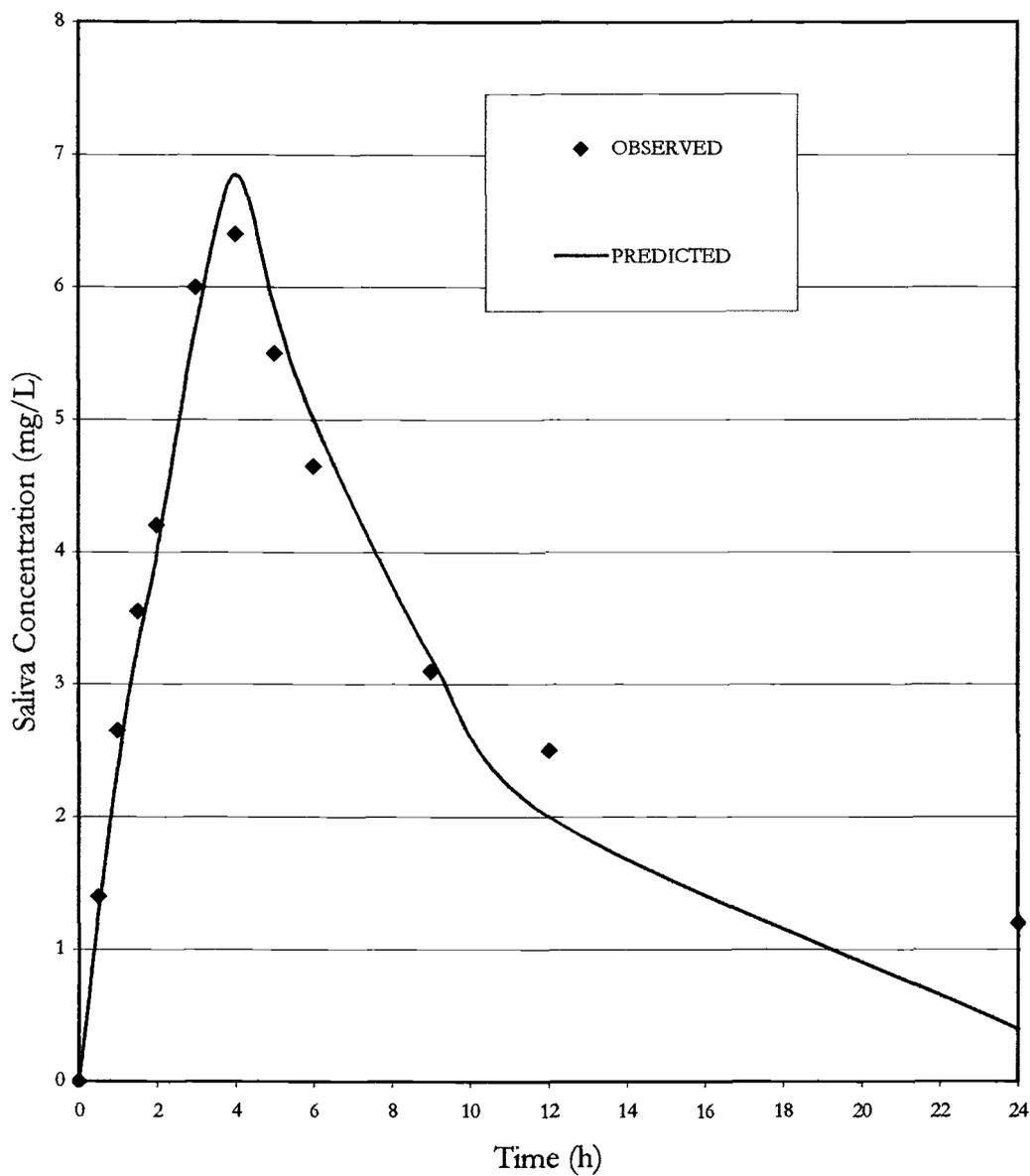
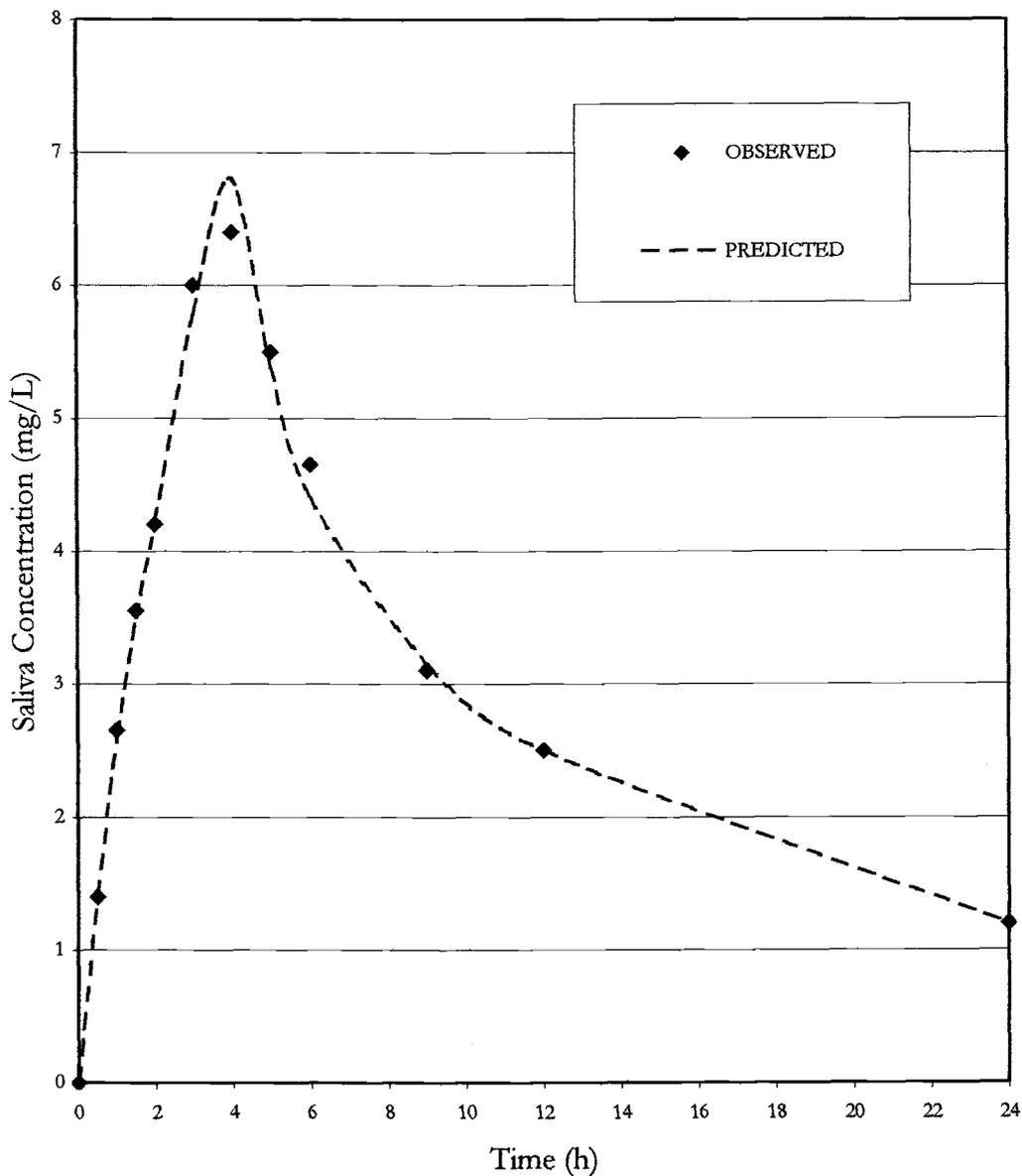


Table 2.16: Summary of pharmacokinetic parameters resulting from fitting 5% HPMC Sustained Release Acetaminophen with a 2-compartment open model with equally weighted data points, zero order input from 0 to T_{max_data} hours, and first order elimination. T_{max_data} was defined as the time associated with the highest saliva concentration for each subject. Some profile could not be fit using this model.

SUBJ#	AUC	T_{max_data}	MRT	Vol.	Cl	$t_{1/2}$	SC
Units	Mg*h/L	h	h	L	L/h	h	
1	105.67	4	16.98	32.26	6.15	3.63	4.74
2	128.08	4	26.13	42.41	5.07	5.79	17.13
3	224.92	4	72.89	73.16	2.88	17.54	17.13
5	22.94	3	1.13	85.48	28.3	2.09	18.07
6	113.77	3	15.62	29.26	5.71	3.55	23.70
7	62.11	4	15.01	55.48	10.4	3.67	1.12
8	28.75	5	2.65	76.57	22.6	2.34	15.05
AV. DATA	86.00	4	13.83	53.81	7.55	4.93	-4.12
AV. OF 8 SUBJ	98.03	3.85	21.48	56.37	11.6	5.44	-----

Figure 2.17: Graph of 5% HPMC Sustained Release Acetaminophen Average Data fitted with a 2-compartment open model with equally weighted data points, zero order input from 0 to T_{max_data} hours, and first order elimination. T_{max_data} was defined as the time associated with the highest saliva concentration for each subject.



Discussion of Model fitting for the 5% HPMC Sustained Release Acetaminophen Formulation:

1 Compartment Models: First Order Input and Zero Order Input:

Both one compartment models fit the data relatively well. Statistically, the Schwartz Criteria is slightly better for the zero-order input model than for the first-order input model (13.03 compared to 13.50 respectively). However, the difference is not significant.

The one area where both 1-compartment models fail is around the peak. Most of the fitted profiles underestimate the peak concentration by ten percent. One possible explanation is that the peak concentration values are artificially elevated. Most subjects began the bioavailability study between eight and nine am. By the 3-4th hour into the study most subjects were eating lunch. It has been previously shown that eating can deplete the saliva production in a subject resulting in artificially elevated concentrations of drug. It is possible that some if not all of the peak values may have been affected in this manner. Another possible explanation is that the input function is complex and cannot accurately be described by a single input function. While the literature describes multitudes of complex distribution and elimination functions, relatively less study has been devoted to complex input functions. It would be interesting to study the contributions of the drug dissolved off the surface of the tablet, the drug released through diffusion out of the tablet, and the drug released by erosion of the tablet to the total input process. Molecular disentanglement theory promises to address these and other issues in HPMC tablets.

Another more significant difference between the two input models is the fitting of the elimination portion of the curve. For most profiles, the model with zero-order input more closely describes the elimination portion of the curve. The average curves (shown in figures 2.14 and 2.16) are an exception to that observation, however it should be noted that the curve predicted for the zero-order input curve does not appear to return to zero in a reasonable time period. The fact that the predicted line does not return to zero is not particularly disturbing for a true sustained release product and may reflect a flaw in the modeling process. During modeling, the program was instructed to continue zero-order input from time zero to time $T_{max_{data}}$ only. If input continued beyond this artificially selected peak time as an apparent slow first-order process the apparent elimination curve may be deceptive. As the tablet is retained in the gastrointestinal (GI) tract until a bowel movement occurs, it is possible that slow input from the tablet may occur beyond 24 hours. After the tablet is expelled from the GI tract and input from the tablet ceases, the elimination of drug from the body would be expected to resemble the elimination curve for the immediate release product, *i.e.* rapid elimination and declination to zero. In this case, there may be insufficient data points in the terminal portion of the elimination curve to allow the modeling program to perceive the change in apparent slope.

2 Compartment Models: First Order Input and Zero Order Input

As previously seen with the immediate release and the extended release products, the two compartment models, both zero and first order input, were unable to fit several of the data sets. In the case of the first-order input model, the computer

was able to fit only 3 subjects plus the average data. The zero-order input model performed slightly better fitting 8 subject profiles plus the average data. In addition, some sets from both input models that yielded pharmacokinetic parameters that were not consistent with expectations or hand calculations. Therefore it is assumed that the relatively simple 2 compartment models tested do not well describe the release of drug from this dosage form in individual subjects.

Model selection:

Although the zero-order, 2-compartment model fit the average data well, both of the 2-compartment models failed to fit the individual subject data. They were therefore discarded as unsuitable. Of the two 1-compartment models, both fit relatively well. Since neither 1-compartment models fits better than the other, the simpler of the two models was chosen for further study. The one compartment open model with first order input and first order elimination will be used to describe the data for the 5% HPMC sustained release acetaminophen formulation. As discussed earlier, it is recognized that the input function is not a simple first order function for this formulation. However, it is concluded that this simple assumption results in adequate prediction and description of the drug concentration versus time curve for acetaminophen absorption from the 5% HPMC formulation involved.

Selection of this model provides the following estimates for pharmacokinetic parameters for the fit of average data.

Volume/F	= 60.84L
K01	= absorption rate = $K_a = 0.5292\text{h}^{-1}$
K10	= elimination rate = $K_{el} = 0.1331\text{h}^{-1}$
LT	= lag time = 0.25h
AUC	= area under the curve = $69.18\mu\text{g}\cdot\text{h}/\text{ml}$
Tmax	= time to maximum concentration = 3.73h
Cmax	= maximum estimated concentration = $5.62\mu\text{g}/\text{ml}$

Since this dosage form exhibits sustained release character, the possibility that the rate constant may be interchanged must be investigated. The phenomenon is termed the flip-flop model and can occur any time that the rate constants are estimated using oral data. This phenomenon is possible in this case because the sustained release character of the tablet may artificially slow the absorption of the drug resulting in a K_a that appears to be smaller than the K_{el} . This occurs most commonly with drugs that have a rapid elimination ($K_{el} > K_a$). The only way to be sure is to compare the orally derived rate constants to intravenously derived rate constants in the same subjects. This was not possible in this study because acetaminophen is not available in an intravenous form in the United States. For the remainder of the analysis it will be assumed that the flip-flop model has occurred since the true $t_{1/2}$ for acetaminophen is reported to be 1-2 hours. The apparent $t_{1/2}$ for this formulation based on the terminal slope of the data is therefore estimated to be 5.2 hours for this dosage form. The true $t_{1/2}$ for the drug in this model based on K_a is then calculated to be 1.3 hours which is consistent with a flip-flop model effect.

7.5% HPMC SUSTAINED RELEASE PRODUCT

Like the 5% HPMC data, the model that would fit the 7.5% data was unknown. It is expected that these data should exhibit a slower overall release pattern than the 5% HPMC data because of the higher HPMC content. It has been well documented in the literature that as the percentage of HPMC in the formulation increases, drug release from the dosage form decreases. Chapter 1 contains *in vitro* testing demonstrating this concept. Eventually this trend results in incomplete release of the drug from the dosage form. *In vitro*, the 7.5% HPMC formulation did not achieve complete release of the acetaminophen from the dosage form in 12 hours. Its *in vivo* performance is expected to be slightly better. This expectation is based on the premise that more surface erosion of the matrix will occur in the gastric track than occurred in the *in vitro* dissolution. Although the dissolution apparatus sometimes simulates the tumble of the matrix through the gastric tract, this requires that tablets remain free-floating within the dissolution chamber. Unfortunately, the hydrated surface of the tablets often became like a glue, sticking the tablets firmly to the side of the dissolution flask. This had two basic effects on the dissolution of drug from the tablet. One, it prevented the tumbling motion of the tablet that might simulate the motion of the tablet as it passed through the gastrointestinal tract via peristaltic muscle contractions. Two, the side of the tablet that was attached to the glass of the dissolution chamber was protected from erosion and changed the overall surface area of the tablet that was available for diffusion of drug out of the tablet.

Note: This concept of changing the release from the tablet matrix by preventing release from various surfaces of the tablet is a liability in the current study, but has been successfully used to the advantage of other scientists in the development of the Geomatrix® system of drug release. *In vivo*, the sticking of the tablet to the GI mucosa should not occur, therefore *in vivo* release from the tablet is expected to be more rapid and complete than in the *in vitro* test.

Data from each subject were fitted to four models. All models were open models with equally weighted data points and first order elimination. Those models were a one compartment model with first order input, a one compartment model with zero order input from time zero to T_{max} , a two compartment model with first order input, and a two compartment model with zero order input from time zero to T_{max} . Tables 2.17-2.20 display results of fitting the four models. Figures 2.18-2.21 display the data and fitted curves for the average data for each of the four models fitted.

Table 2.17: Summary of pharmacokinetic parameters resulting from fitting 7.5% HPMC Sustained Release Acetaminophen with a 1-compartment open model with equally weighted data points, first order input, and first order elimination.

SUBJ#	AUC	Tmax	Cmax	Vd/F	K ₁₀	t _{1/2}	SC
Units	Mg*h/L	h	mg/L	L	1/h	h	
1	17.04	2.73	1.56	292.79	0.130	5.32	-10.96
2	34.52	1.82	3.82	131.06	0.143	4.82	3.72
3	151.2	4.96	1.63	374.67	0.011	60.4	-17.67
4	15.09	4.84	1.92	124.66	0.346	2.00	9.89
5	11.05	1.74	1.88	242.16	0.243	2.85	13.19
6	59.36	4.86	3.51	125.91	0.086	7.97	6.19
7	76.27	3.01	3.21	183.09	0.046	14.9	-18.10
8	60.71	2.49	3.87	149.01	0.071	9.64	0.66
9	35.57	3.61	2.74	159.92	0.114	6.06	17.03
10	59.65	3.62	3.99	115.54	0.094	7.34	19.06
AV. DATA	44.61	3.47	2.58	194.58	0.074	9.25	-14.30
AV.OF 10 SUB	52.04	3.36	2.81	189.88	0.128	5.41*	-----

* value calculated using harmonic mean.

$$x = \ln 2 / \text{average } K_{10}$$

Figure 2.18: Graph of 7.5% HPMC Sustained Release Acetaminophen Average Data fitted with a 1-compartment open model with equally weighted data points, first order input, and first order elimination.

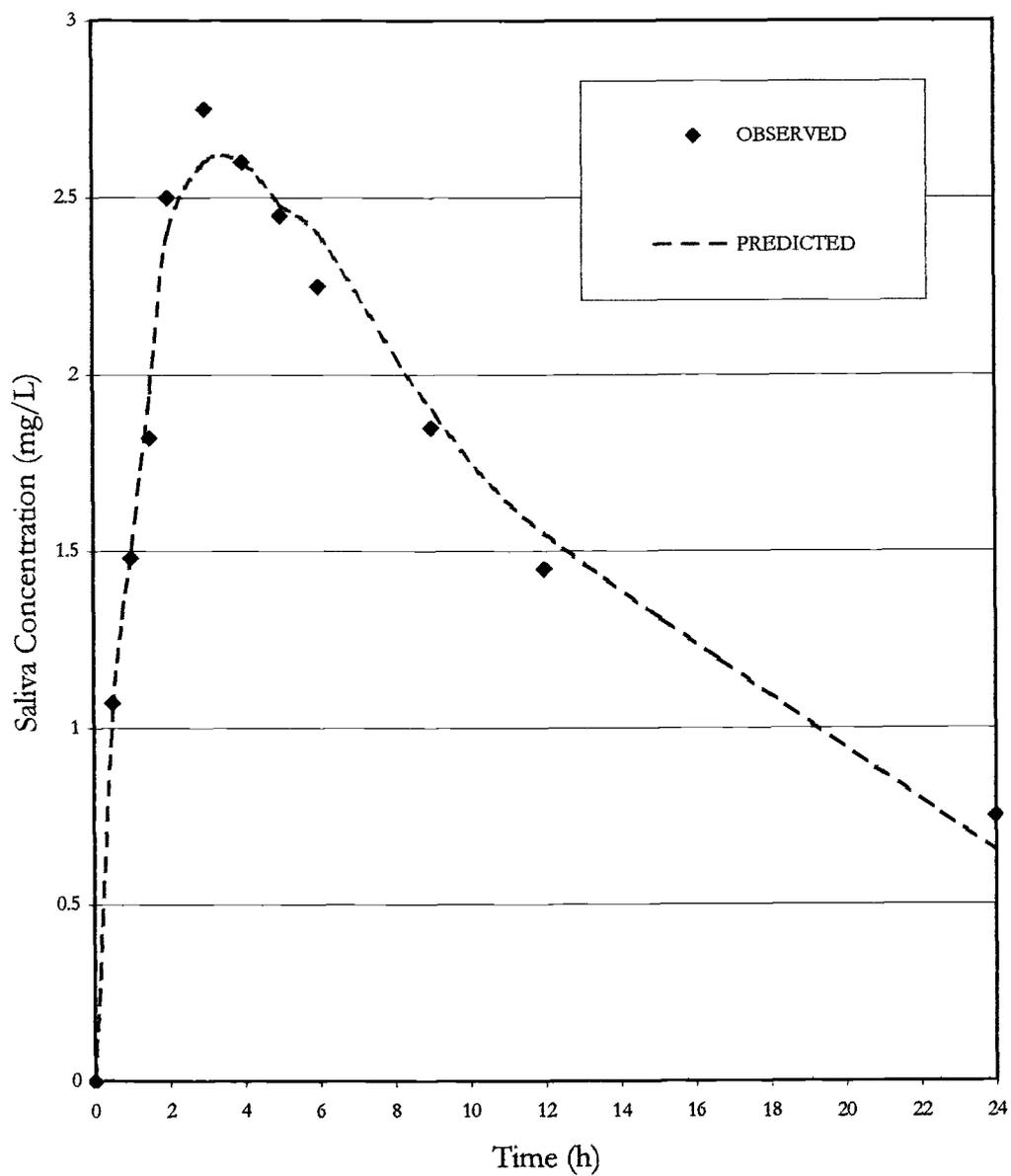


Table 2.18: Summary of pharmacokinetic parameters resulting from fitting 7.5% HPMC Sustained Release Acetaminophen with a 2-compartment open model with equally weighted data points, first order input, and first order elimination. The computer was unable to fit many of the profiles using this model.

SUBJ#	AUC	Tmax	Cmax	Vd/F	K ₁₀	t _{1/2}	SC
Units	mg*h/L	h	mg/L	L	1/h	H	
1	331.48	1.59	2.81	164.81	0.011	58.2	-15.04
2	43.22	1.89	3.94	71.17	0.211	3.28	2.51
5	86.47	1.73	1.89	138.57	0.054	12.7	11.71
10	85.53	3.37	3.81	79.70	0.095	7.27	16.71
AV. DATA	53.53	3.51	2.63	113.00	0.107	6.45	-15.84
AV. OF 4 SUB	115.06	2.14	3.11	113.56	0.092	7.53*	-----

* Value calculated using harmonic mean.

$$x = \ln 2 / \text{average } K_{10}$$

Figure 2.19: Graph of 7.5% HPMC Sustained Release Acetaminophen Average Data fitted with a 2-compartment open model with equally weighted data points, first order input, and first order elimination. The computer was unable to fit many of the profiles using this model.

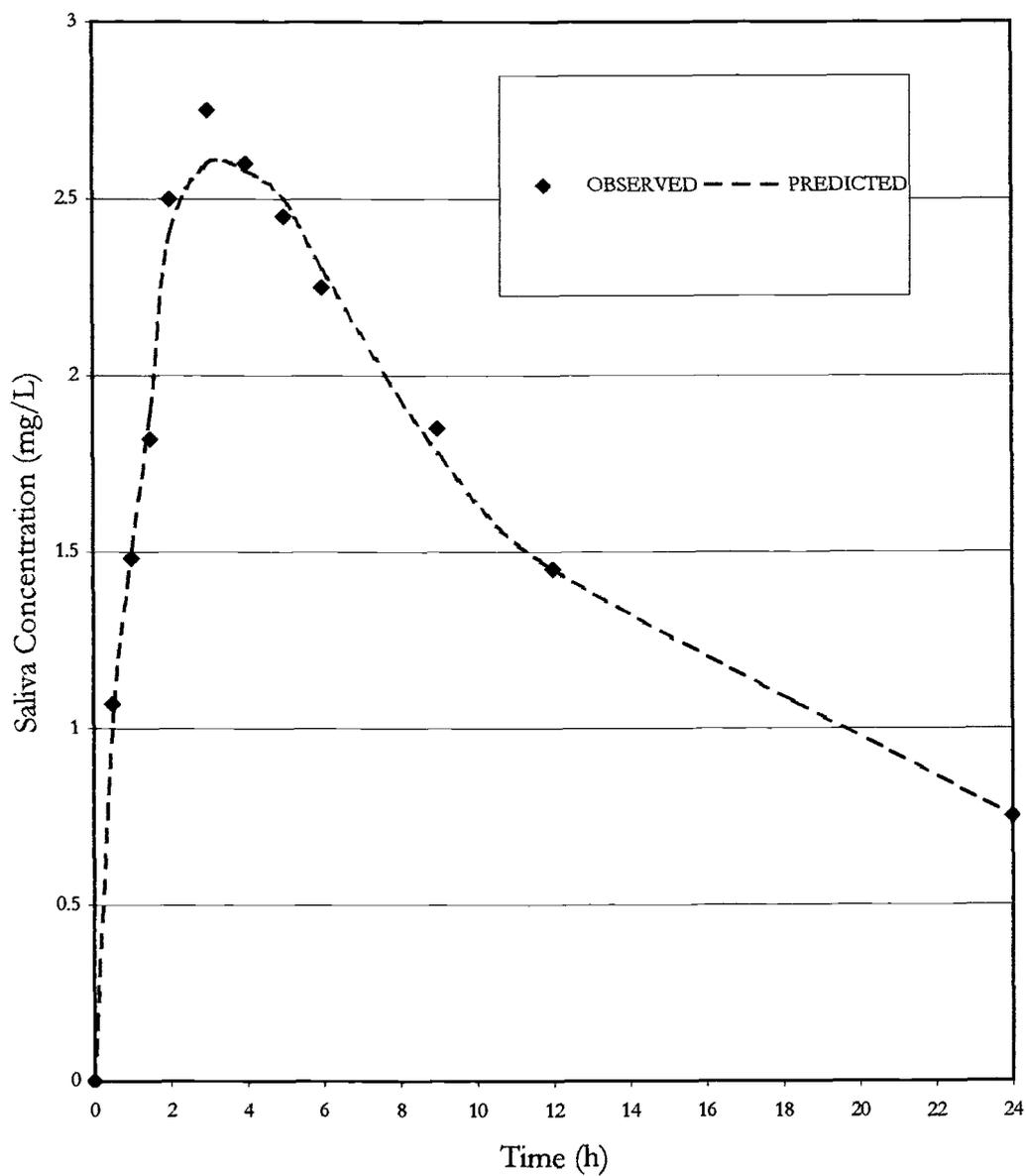


Table 2.19: Summary of pharmacokinetic parameters resulting from fitting 7.5% HPMC Sustained Release Acetaminophen with a 1-compartment open model with equally weighted data points, zero order input from 0 to $T_{max,data}$ hours, and first order elimination. $T_{max,data}$ was defined as the time associated with the highest saliva concentration for each subject.

SUBJ#	AUC	T_{max} data	MRT	Vol.	Cl	$t_{1/2}$	SC
Units	mg*h/L	h	h	L	L/h	h	
1	14.16	3	5.56	255.38	45.9	3.85	-5.36
2	23.30	3	2.93	81.7	27.9	2.03	23.01
3	82.08	4	40.8	323.39	7.91	28.3	4.16
4	16.84	5.16	6.04	233.20	35.6	4.18	8.67
5	9.62	3	2.63	178.27	67.5	1.83	16.00
6	61.96	4	13.6	142.46	10.5	9.41	-2.20
7	70.50	3	18.3	169.20	9.21	12.7	-0.63
8	66.85	2	16.4	159.89	9.72	11.4	7.76
9	34.64	3	8.96	168.12	18.7	6.21	6.98
10	61.74	4	10.3	108.48	10.5	7.14	24.8
AV. DATA	40.36	3	11.6	187.47	16.1	8.07	-0.32
AV. OF 10 SUBJ	44.16	3.41	12.5	182.00	24.3	8.71	-----

Figure 2.20: Graph of 7.5% HPMC Sustained Release Acetaminophen Average Data fitted with a 1-compartment open model with equally weighted data points, zero order input from 0 to T_{max_data} hours, and first order elimination. T_{max_data} was defined as the time associated with the highest saliva concentration for each subject.

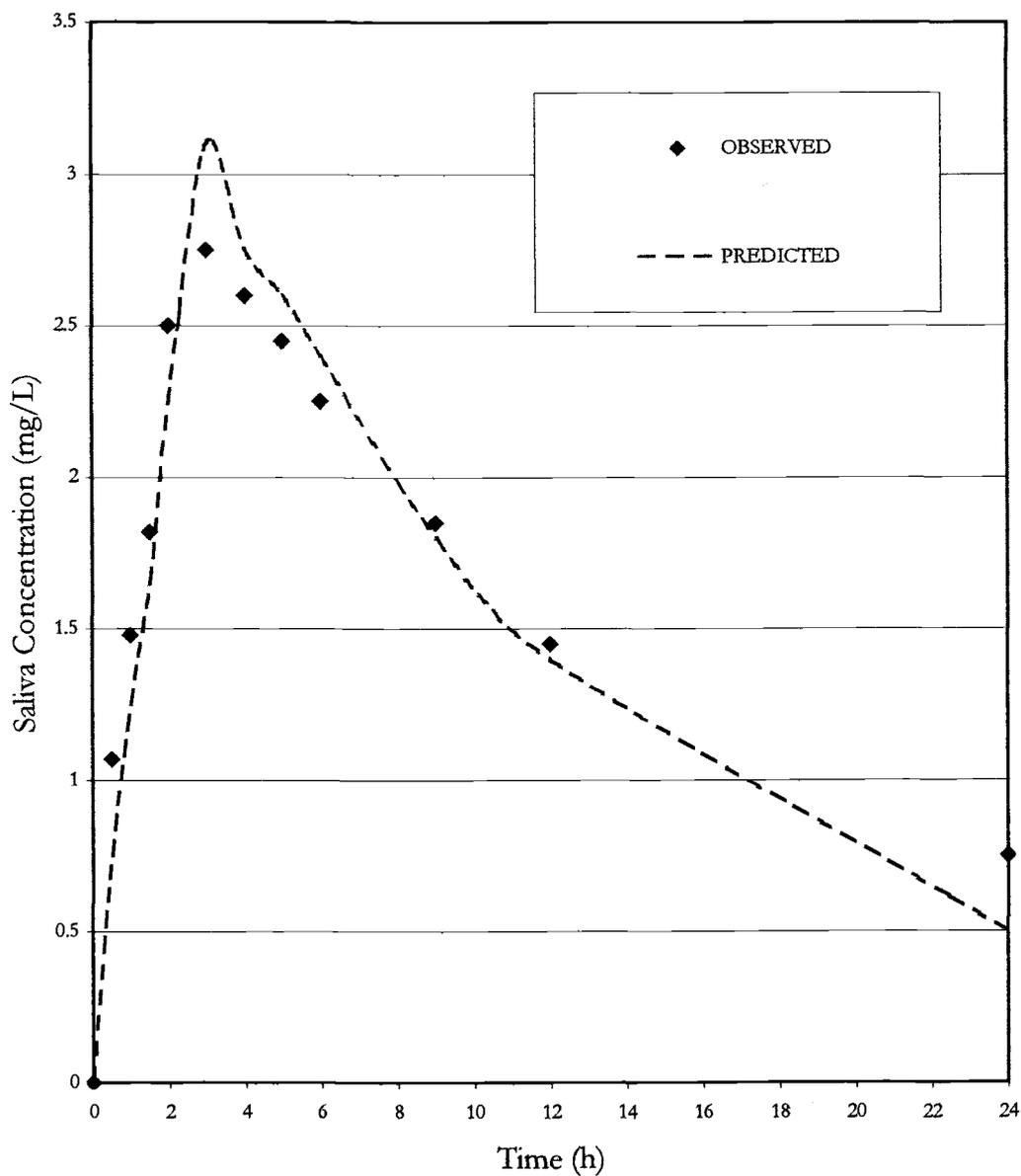
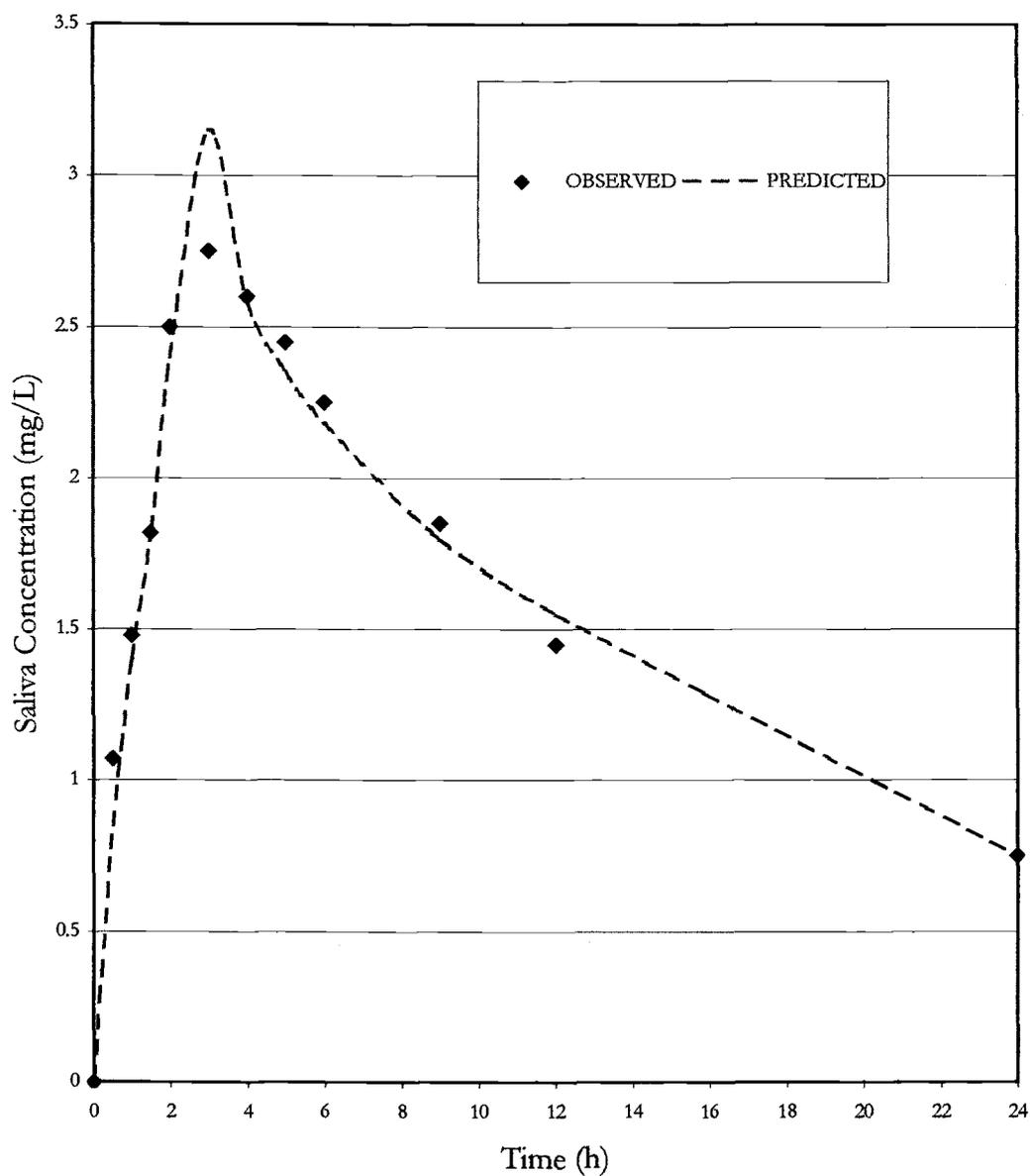


Table 2.20: Summary of pharmacokinetic parameters resulting from fitting 7.5% HPMC Sustained Release Acetaminophen with a 2-compartment open model with equally weighted data points, zero order input from 0 to T_{max_data} hours, and first order elimination. T_{max_data} was defined as the time associated with the highest saliva concentration for each subject. Some profiles could not be fit using this model.

SUBJ#	AUC	T_{max_data}	MRT	Vol.	Cl	$t_{1/2}$	SC
Units	mg*h/L	h	h	L	L/h	H	
1	19.94	3	10.45	116.0	32.58	7.84	-16.3
2	41.19	3	9.67	14.01	15.80	7.81	2.55
5	54.32	3	70.51	85.25	11.96	53.2	11.15
6	67.48	4	15.87	128.9	9.63	11.27	-1.06
9	38.66	3	10.75	47.30	16.80	7.64	7.59
10	93.02	4	21.87	27.23	6.98	16.14	15.78
AV. DATA	49.82	3	16.47	109.7	13.04	11.80	-9.45
AV. OF 6 SUBJ	52.43	3.33	23.18	69.79	15.62	17.31	----

Figure 2.21: Graph of 7.5% HPMC Sustained Release Acetaminophen Average Data fitted with a 2-compartment open model with equally weighted data points, zero order input from 0 to T_{max_data} hours, and first order elimination. T_{max_data} was defined as the time associated with the highest saliva concentration for each subject.



Discussion of Model fitting for the 7.5% HPMC Sustained Release Acetaminophen Formulation:

Selection of a model for the 7.5% HPMC sustained release formulation followed the same criteria and observations as the 5% HPMC sustained release formulation. As before, both two-compartment models were discarded as unsuitable because of the inability to fit several individual subject profiles with the model. The 2-compartment model with first order input performed the poorest, fitting only four subject profiles plus the average curve. The 2-compartment model with zero-order input performed only slightly better fitting six subject profiles plus the average curve.

The 1-compartment models fit all subject data and the average curves for both input functions. The model with first order input still underestimated the peak in contrast to the zero-order input function that overestimated the peak. Both profiles describe the data fairly well but the Schwartz Criteria for the first order input model is significantly better than for the zero-order input model (-14.40 as compared to -0.32 respectively). The one compartment open model with first order input and first order elimination will also be used to describe the data for the 7.5% HPMC sustained release acetaminophen formulation.

Model selection:

Selection of this model provides the following estimates for pharmacokinetic parameters for averaged data fitted with this model.

Volume/F = 194.58ml
K01 = absorption rate = $K_a = 0.750609\text{h}^{-1}$ *
K10 = elimination rate = $K_{el} = 0.074867\text{h}^{-1}$ *
LT = lag time = 0.06h
AUC = area under the curve = $44.61\mu\text{g h/ml}$
Tmax = time to maximum concentration = 3.47h
Cmax = maximum estimated concentration = $2.58\mu\text{g/ml}$

* See previous discussion of the flip-flop model. Apparent $t_{1/2}$ for this formulation = 9.25 hours. Calculated $t_{1/2}$ for the drug = 0.92 hours.

Selection of a Sustained Release Acetaminophen Product for Phase Two Clinical Trials

Comparison of the *in vivo* bioavailability of the 5% and the 7.5% HPMC Sustained Release Acetaminophen Formulations:

By comparing the AUC of the sustained release product to the AUC of an immediate release product, a relative *in vivo* estimation of the bioavailability for the two sustained release acetaminophen formulations can be made. The Tylenol Extra Strength® and the Tylenol Extended Relief® products may be used as reference formulations.

First, bioavailability is compared for the two reference formulations. AUC for the 1000mg dose of immediate release Tylenol Extra Strength Product® was 52.82µg/ml (for the data averaged before fitting with a 1-compartment model with first order input and first order elimination). AUC for the 1300mg dose of the Tylenol Extended Relief Product® was 67.32µg/ml (for data averaged before fitting with a 1-compartment model with first order input and first order elimination). Assuming that K_{el} , V_d , and F remain constant, then changes in dose should produce proportional changes in AUC. Since the same subjects were used to test both formulations, similar pharmacokinetic parameters should be expected. Differences in the AUC values should therefore reflect changes in the bioavailability of the formulation and not changes in the subject pharmacokinetic parameters.

To compare products, AUC for the Tylenol Extra Strength® product must be proportionately adjusted for a 1300mg dose. Proportionally, an AUC of

68.66 $\mu\text{g}/\text{ml}$ would be expected if a 1300mg dose of Tylenol Extra Strength[®] were given. This is consistent with the 67.32 $\mu\text{g}/\text{ml}$ AUC from the Tylenol Extended Relief[®] product. From this it can be assumed that an AUC value of approximately 67-68 $\mu\text{g}/\text{ml}$ represents complete absorption of a 1300mg dose of acetaminophen in this subject population.

The literature surveyed in Table 2.7 displayed an average AUC of 55.47 \pm 8.89 $\mu\text{g}/\text{ml}$ for a 1000mg dose. That average converts to a range of 46.58-64.36 $\mu\text{g}/\text{ml}$. Once adjusted to a 1300mg dose, the average becomes 72.11 $\mu\text{g}/\text{ml}$ with a range of 60.55-83.66 $\mu\text{g}/\text{ml}$. The AUC of the Tylenol Extra Strength[®] and the Tylenol Extended Relief[®] products are well within the range.

In comparison, the fitted values of AUC for the 5% HPMC sustained release product and the 7.5% HPMC sustained release acetaminophen products are 69.18 $\mu\text{g}/\text{ml}$ and 44.61 $\mu\text{g h}/\text{ml}$ respectively. The AUC for the 5% HPMC falls within the estimated range suggesting that release of drug from the tablet is essentially complete. The AUC for the 7.5% HPMC sustained release acetaminophen formulation is only 44.61 $\mu\text{g h}/\text{ml}$ suggesting that only 48-74% of the drug is released from the formulation. This incomplete drug release from the 7.5% HPMC sustained release formulation does not make this formulation a good candidate for continued study. Although, true fraction of the dose absorbed values (F) are obtained by comparing drug absorption in an oral formulation to that in an intravenous dose of the same drug, relative F values can be obtained by comparing the two HPMC sustained release formulations to the immediate release formulation known to have a

$F=1$. Using the average literature AUC value of $72.11\mu\text{g/ml}$ as 100%, relative F values can be estimated for the 5% HPMC product ($F_{\text{rel}} = 0.96$) and for the 7.5% HPMC product ($F_{\text{rel}} = 0.61$).

Selection of a Sustained Release Acetaminophen based on Target Formulation Criteria:

Recall that 5 overall target criteria were outlined in chapter one. They were:

1. Pharmaceutically acceptable size, shape, and palatability.
2. Sustained release character: zero-order release preferred but pseudo zero-order release or combination release acceptable.
3. Minimum plasma concentration at steady state of $5\mu\text{g/ml}$.
4. Overall maximum daily dose of 2.6gm of acetaminophen per day
5. Convenient dosing interval of once-twice daily

First consider the size and palatability of the tablets. The compressed HPMC tablets of the 5% and the 7.5% formulations both measure 14mm in diameter and 6mm in height with no perceptible taste. Each dose consists of two tablets. No difficulties in swallowing the tablets were reported by subjects in this study.

The sustained release character of both HPMC formulations was found to be a combination release that could be adequately described by a simple one-compartment open pharmacokinetic model with first order absorption and first order elimination.

The last three of the development goals are intertwined and depend on estimates of the behavior of the sustained release acetaminophen formulations upon

multiple dosing. The target steady state plasma concentration of 5 μ g/ml is desired. Using the *in vivo* pharmacokinetic data from the single dose studies, multiple dose simulations can be performed to evaluate the feasibility of achieving this goal. Since the model chosen slightly underestimates the concentrations observed at the peak and during the elimination portion of the curve, multiple dose estimations should also slightly underestimate steady state concentrations.

The superposition principle was used to predict drug accumulation in plasma for the sustained release acetaminophen products. Recall that this principle assumes that early doses of drug do not affect the pharmacokinetics of subsequent drug doses. It will further assume the desired dosing interval (τ) is 12 hours. Overall daily dose using this dosing regimen is = 1300mg every 12 hours which further complies with the target goal of total daily acetaminophen dose of less than or equal to 2.6 grams acetaminophen per day. The C_{ssmin} is the minimum plasma concentration at steady state. It can be calculated using the equation

$$C_{ssmin} = \frac{(S)(F)(Dose)}{V} * \frac{1}{(1-e^{-k\tau})} * e^{-k\tau}$$

Where S = salt fraction
 F = fraction of the dose absorbed
 V = Volume of distribution
 k = elimination rate constant
 τ = the dosing interval

S is assumed to be 1 for both formulations, and τ is selected to be 12 hours. Relative F values for 5% and 7.5% HPMC formulations were previously calculated to be 0.96 and 0.61 respectively.

For the 5% HPMC formulation:

$$\begin{aligned}
 &= [(1)(0.96)(1300\text{mg})/60.84] * [1/(1-e^{-(0.133)(12)})] * [e^{-(0.133)(12)}] \\
 &= (20.51) * (1.2542) * (0.2027) \\
 &= 5.21\mu\text{g/ml}
 \end{aligned}$$

For the 7.5% HPMC formulation:

$$\begin{aligned}
 &= [(1)(0.61)(1300\text{mg})/194.58] * [1/(1-e^{-(0.074)(12)})] * [e^{-(0.074)(12)}] \\
 &= (4.075) * (1.6991) * (0.4114) \\
 &= 2.84\mu\text{g/ml}
 \end{aligned}$$

While the 5% HPMC formulations meets and slightly exceeds the target steady state minimum plasma concentration, the 7.5% HPMC formulation falls short of the goal. Figures 2.22 and 2.23 show simulated multiple dose profiles for the 5% HPMC and 7.5% HPMC products. Clearly, the incomplete drug release from the 7.5% HPMC sustained release formulation combined with sub-therapeutic estimate of C_{ss} make it a poor candidate for additional study. Conversely, the apparently complete release of drug from the 5% HPMC sustained release formulation combined with the favorable estimate of C_{ss} make it a logical choice for Phase II clinical trials.

Figure 2.22: Simulate Plasma Acetaminophen Concentrations for Multiple Dosing of the 5% HPMC Sustained Release Acetaminophen formulation.

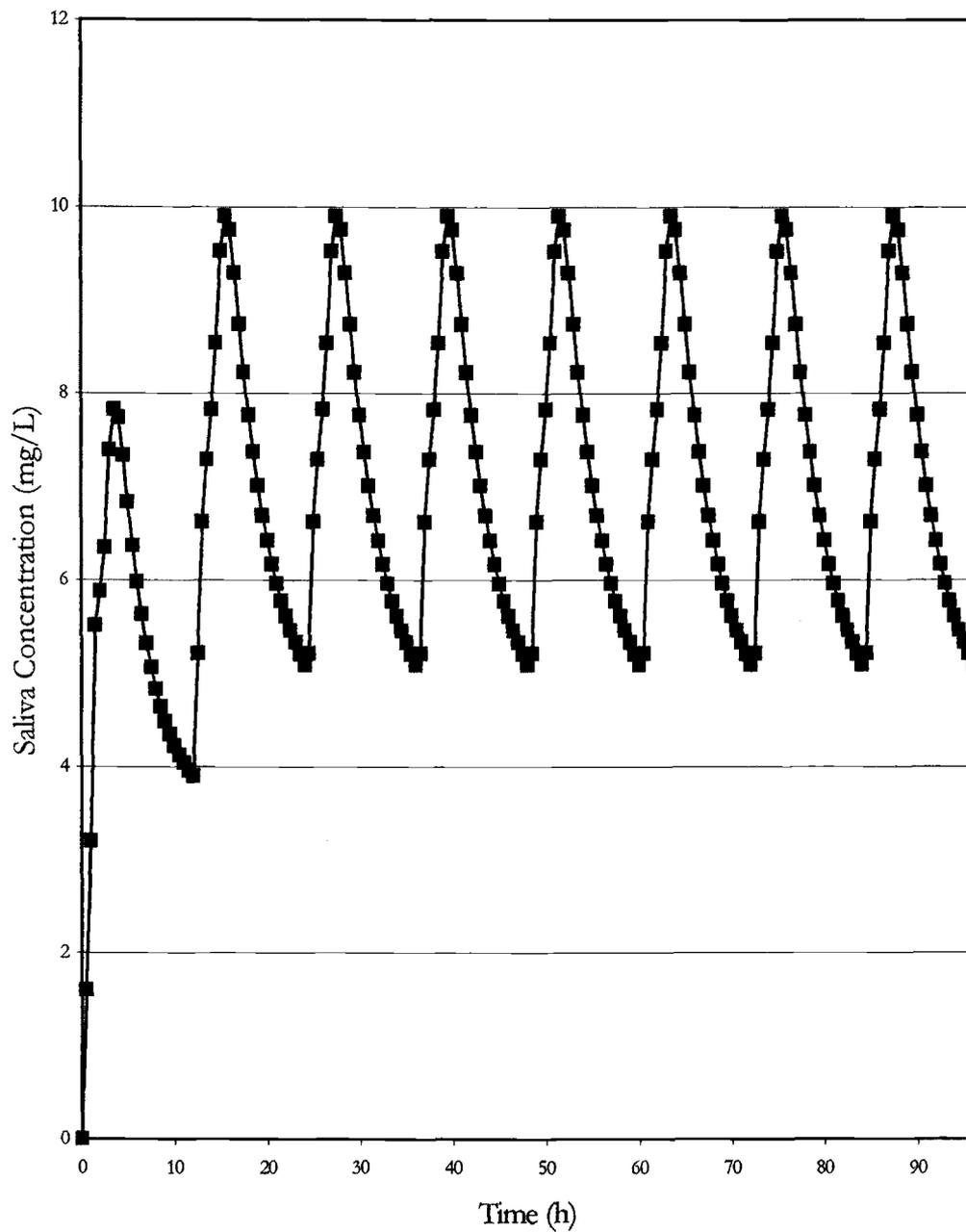
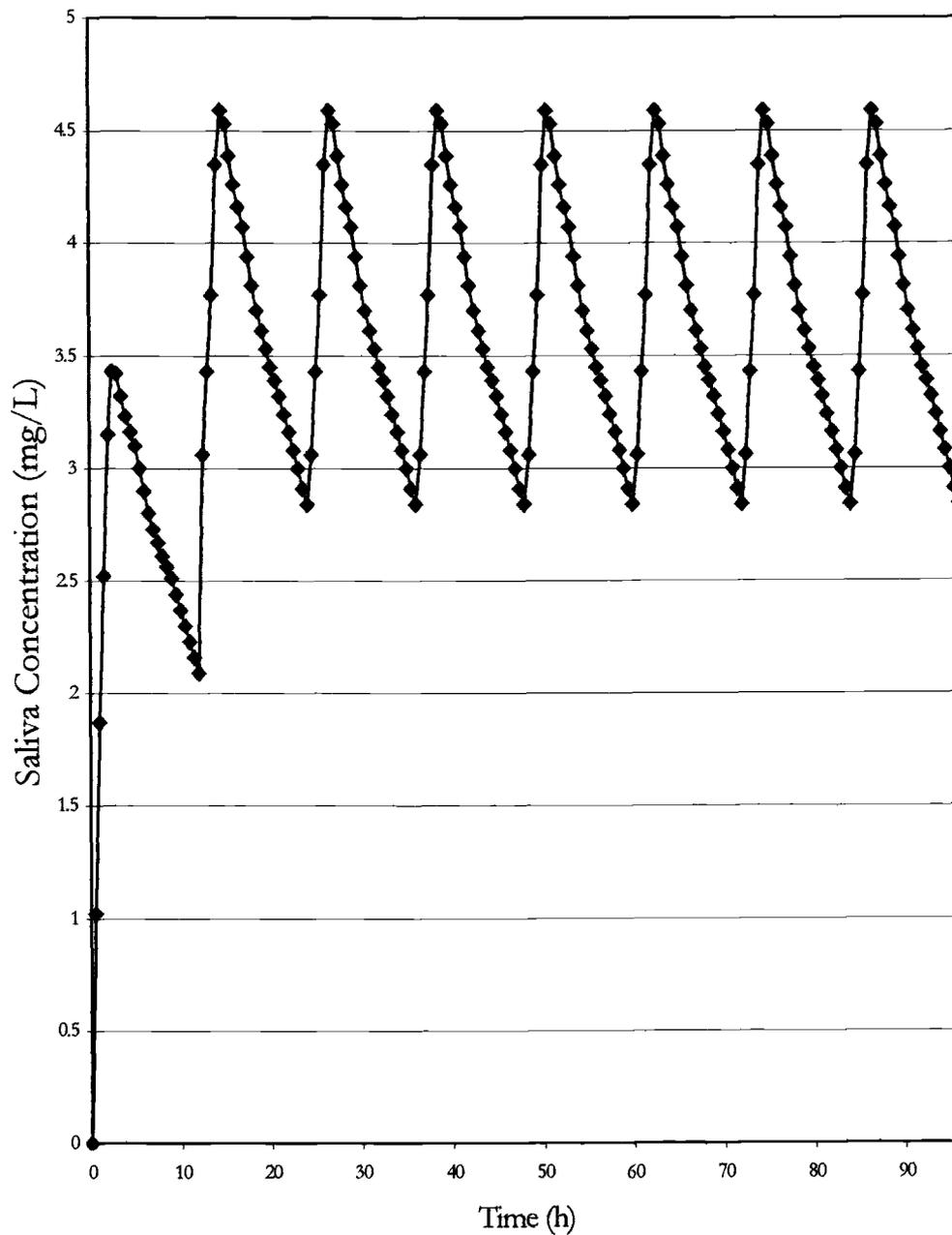


Figure 2.23: Simulate Plasma Acetaminophen Concentrations for Multiple Dosing of the 7.5% HPMC Sustained Release Acetaminophen formulation.



CONCLUSIONS

Tylenol Extra Strength® and Tylenol Extended Relief® produce single dose in vivo pharmacokinetic profiles that were best described by a one-compartment open model with equally weighted data points, first order absorption, and first order elimination. Pharmacokinetic parameters estimated agreed with literature data reported by other scientists.

Both the 5% and the 7.5% HPMC sustained release acetaminophen formulations produced in vivo pharmacokinetics that were most consistent with a one-compartment open model with first order input and first order elimination when fitting individual subject data. Two-compartment models did not adequately describe individual subject data and were unsuitable to either formulation. One-compartment models with zero-order input could be applied to the data but did not provide the optimum fit.

Comparison of the sustained release formulations to the immediate release data collected from the literature suggests that the 7.5% HPMC sustained release acetaminophen formulation released only 48-74% of the total drug from the formulation. In contrast, the 5% HPMC sustained release acetaminophen product was found to have released nearly all of the drug contained within the tablet. C_{ss} was estimated for both sustained release formulations with $\tau=12$ hours. Estimates of C_{ss} for both products yielded a C_{ss} of 5.59 $\mu\text{g}/\text{ml}$ for the 5% formulation and a C_{ss} of 3.71 $\mu\text{g}/\text{ml}$ for the 7.5% HPMC formulation.

Comparing these data to the original target criteria for development of the sustained release acetaminophen product, the 5% HPMC sustained release acetaminophen formulation was found to comply with all five target criteria and has been selected to continue to Phase II clinical trials.

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CHAPTER 3**FORMULATION OF A SUSTAINED RELEASE ACETAMINOPHEN****PRODUCT: PHASE II CLINICAL TRIALS**

ABSTRACT

Phase II clinical trials were conducted to compare a novel sustained release acetaminophen (SR) formulation to a conventional immediate release (IR) acetaminophen formulation for treatment of pain due to osteoarthritis in the knee. Thirty male patients between the ages of 44 and 76 were recruited from the Veterans Administration (VA) Outpatients clinic in Portland, Oregon. The study was a randomized, placebo controlled, double blind crossover study. Baseline surveys were performed on the enrolled patients. A pain and disability question was administered and the time to walk 50 feet was measured. Saliva samples were also collected at evaluation periods two and three. Each patient was randomly assigned to either the SR or IR formulations for the first treatment period. Patients took 2 tablets of study medication 4 times a day for 4 weeks. After 4 weeks, patients returned for a second evaluation. After a 7 day washout period, patients were then crossed over to the other formulation for treatment period two. Upon completion of the second medication period, patients repeated a third final evaluation. Rescue analgesic tablets (ibuprofen 200mg) were provided to patients for use during the washout period and for pain not relieved by the administered acetaminophen treatment.

Seventeen patients completed the study. All seventeen were verified as meeting the minimum compliance standards (missed no more than 10% of total doses) and rescue analgesic guidelines (no more than 4 tablets/day) during the

treatment periods. Saliva acetaminophen concentrations were determined using standard HPLC techniques. Data from the questionnaires was collated and prepared for analysis.

Average saliva concentrations were decayed to estimated trough values. The SR formulation produced an estimated steady state trough concentration of 5.11mg/L and the IR formulation produced a significantly lower level of 1.34mg/L. ANOVA comparison of the questionnaire results between the IR and SR products showed that the SR formulation was equally effective as the IR formulation in reducing pain and improving mobility in patients with osteoarthritis of the knee ($\alpha=0.05$). The 2.6 gram/day SR product was equally effective as the 4 gram/day IR product despite the large difference in dose. Reported side effects were similar for the two formulations and included drowsiness, headache, nausea, GI upset, and diarrhea.

Subsequent comparison of the SR formulation to the baseline treatment exhibited more dramatic results. ANOVA evaluations performed on the baseline treatments and the SR treatments showed statistically significant improvements in the patients average overall rating of their pain levels, the ability of these patients to stand without help from another person, and in the duration of pain relief that these patients received from their treatment medication. Other areas that improved but were not statistically significant included a decrease in pain after the SR treatment and an increase in the overall relief that the SR treatment provided to these patients.

Overall, the novel sustained release acetaminophen formulation performed well. It achieved the formulation goal of an estimated minimum steady state

acetaminophen goal of 5mg/L. It also reduced the average overall pain rating and improved the duration of the pain relief in patients compared to the baseline treatments. Time to walk 50 feet was reduced by 1.65 seconds and patients required less assistance in standing while using the SR treatment as compared to the baseline treatment . These results suggest that the sustained release formulation is equally as effective as the IR treatment and superior to the baseline treatments in these patients with osteoarthritis of the knee. These effects occurred while reducing the dose of acetaminophen to 2.6 grams/day from 4 grams/day. Additional studies with larger number of patients are needed to verify these results, but initial results are promising.

INTRODUCTION

Pharmacodynamic analysis suggests that a plasma acetaminophen concentration of 5mg/L is necessary to provide analgesic relief to patients^{1,2}. Chapter 1 focused on formulation and dissolution studies performed to produce an acetaminophen product with predetermined *in vitro* drug release parameters. Chapter 2 involved Phase I clinical trials to establish *in vivo* performance and pharmacokinetic parameters. Those studies suggested that a new 5% hydroxypropylmethyl-cellulose (HPMC) sustained release acetaminophen formulation would provide the necessary *in vivo* release to maintain a steady state plasma concentration of 5mg/L with a dose of 1300mg given every 12 hours. This chapter investigates the effectiveness of this formulation in patients with a chronic pain syndrome. Osteoarthritis patients were selected as a model disease state.

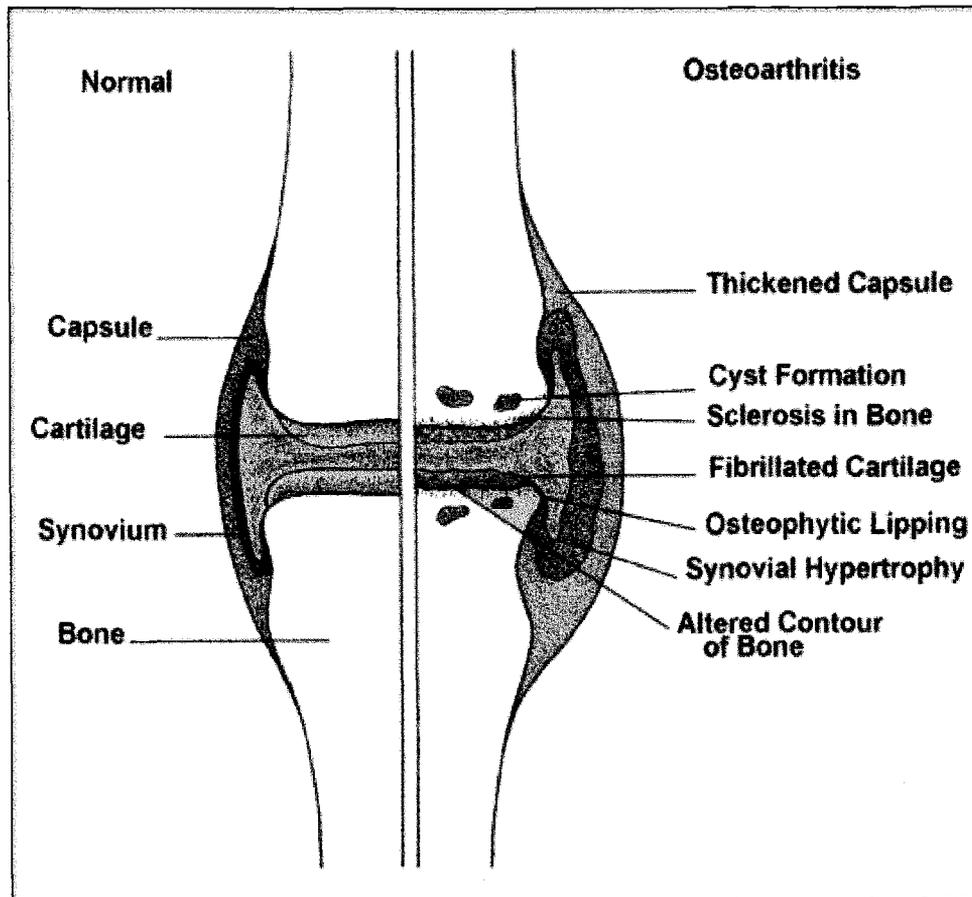
Osteoarthritis:

Osteoarthritis affects nearly 10% of the population over age 60 and is second only to cardiovascular disease in causing severe chronic pain and disability³.

Osteoarthritis occurs when the catabolic functions of chondrocytes exceed the anabolic functions. The result is a breakdown of the protective cartilage in the joint surface. The activated chondrocytes produce increased amounts of collagenase, stromelysin, and water, while producing decreased amounts of cartilage matrix, proteoglycans, chondrocytes, and bone formation. The resulting anatomic changes include cartilage erosion, subchondral bone microfractures, bone cysts, thickening of

the subchondral bone, osteophytes, and fibrocartilage repair abnormalities⁴ (see Figure 3.1).

Figure 3.1: Diagram of physical changes that take place in an osteoarthritic knee



Osteoarthritis occurs most commonly in hands, hips, feet, neck, and spine. It is linked to age, obesity, occupation, and genetic predisposition^{3,5}. Clinically, sufferers describe loss of function, chronic pain, and increasing disability in the affected joints⁶.

Therapy is therefore aimed at pain relief, increased mobility, and reduction of disability while minimizing side effects³.

Due to limited time and resources available for the current study, patients with osteoarthritis of the knees were selected as a target population. Justification of this choice includes the availability of a published and validated pain/disability questionnaire for this subtype of the disease, documentation concerning effectiveness of immediate release acetaminophen in treatment of the disease, quantitative nature of the walking time measurements, and significant incidence of the disease in the recruitment population/area.

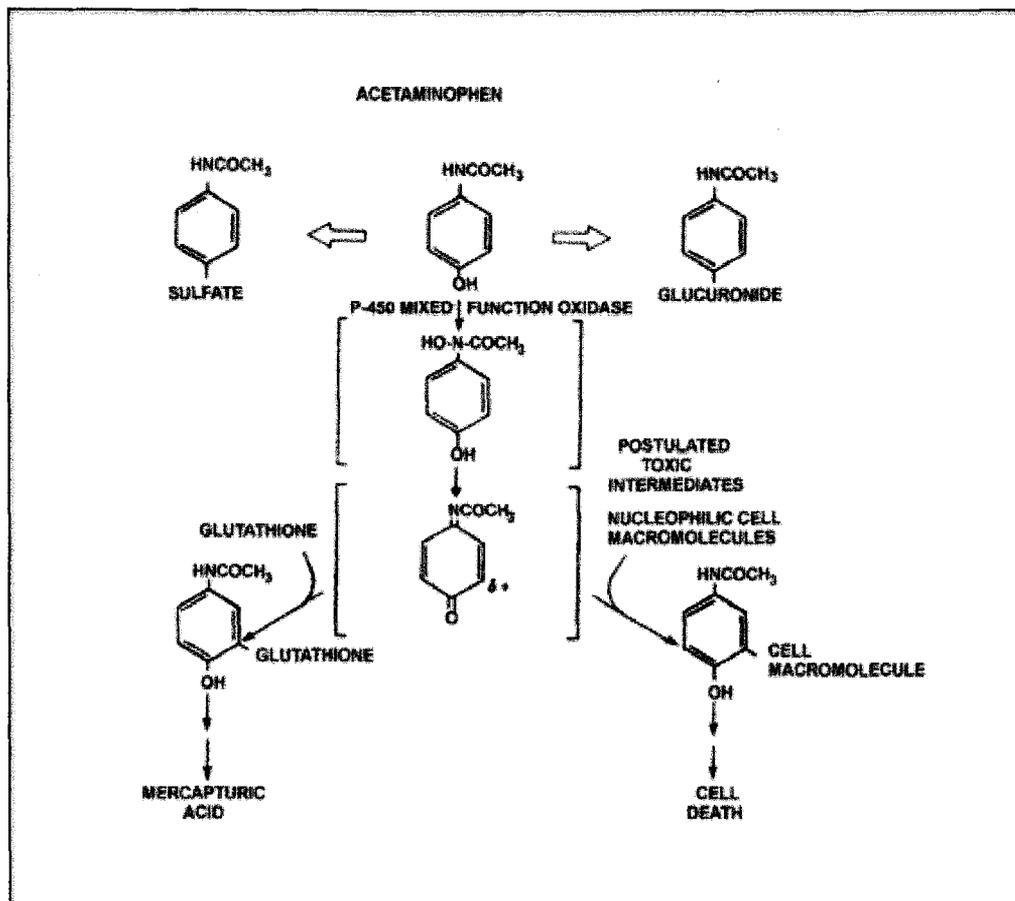
Study Design:

Investigational Review Board (IRB) applications were approved by the Human Studies Committees of both Oregon State University and the Portland branch of the Veterans Administration (VA) Hospital. An Investigational New Drug Application (IND) was filed with the Federal Food and Drug Administration. Copies of these documents are found in Appendices 3A, 3B, and 3C respectively. The IRB board at the VA Hospital expressed concern about acetaminophen toxicity and its relationship to hepatic toxicity. The question was addressed by an review of acetaminophen metabolism and literature concerning acetaminophen induced hepatotoxicity.

History and review of acetaminophen toxicity and alcohol consumption.

Review of Acetaminophen: Structure and Metabolic pathways:

Figure 3.2: Acetaminophen structure and metabolic pathways



Acetaminophen is preferentially conjugated into glucuronide or sulfate and excreted from the body via renal elimination^{7,8}. Once these pathways are saturated, the remaining acetaminophen is oxidized by the cytochrome P450 mixed function oxidases (primarily P450 2E1) to *N*-acetyl-*p*-benzoquinoneimine (NAPQI)^{9,10}. NAPQI is usually rendered nontoxic by conjugation with glutathione. Once glutathione stores are exhausted, NAPQI remains in the liver causing hepatic toxicity.

In normal patients, approximately 2% of the dose is excreted unchanged in the urine, 95% is conjugated to the sulfate or glucuronide, leaving only 3% of the dose to be oxidized to NAPQI¹¹. There are several possible causes of glutathione depletion. The first is chronic depletion over time. The constant drain of the store of glutathione by chronic administration of acetaminophen (greater than 4 grams/day) can deplete the glutathione store. A second cause is acute depletion. This occurs when the amount of acetaminophen taken at a single time exceeds the amount of glutathione present¹². A third cause of glutathione depletion is insufficient dietary intake. People who do not intake sufficient sources of protein in their diet cannot produce as much glutathione. Alcoholics are known to possess decreased amounts of glutathione^{13,14}. Whether that is a result of poor nutrition or some intrinsic effect of the ethanol is unclear at this time. Alcoholics are also at increased risk of toxicity because of the stimulating effect of ethanol on the cytochrome P450 3A system¹⁵⁻¹⁶. This system is thought to increase the rate of formation of NAPQI and increase the risk of hepatic damage.

Table 3.1: Literature reports of acetaminophen toxicity and alcohol.

REFERENCE	# PT	AGE/SEX	AMOUNT OF APAP	AST	ETOH	TOTAL BILIRUBIN	PT	OUTCOME
	n	yrs	g/24h	U/L	A/C/N	mg/dL	s	
Emby and Fraser ¹⁷ , 1977	2	31/F 52/M	10.0 14.0	3,561 13,610	C C	59 68	16 2	died died
Barker et. al. ⁸ , 1977	3	59/M 67/F 50/W	7.5 5.2 5.2-6.5	6,200 1,040 400	C N ?	9.5 1.3 0.6	19 12 10	alive alive alive
Goldfinger et.al. ²⁴ , 1978	1	36/F	9.75	1,960	A	18.6	28.9	alive
McClain et. al. ¹⁹ , 1980	3	48/M 53/M 43/M	5.0 10 16.5	6,960 9,940 7,720	C C C	17.0 8.0 7.0	35 50 16.6	alive died alive
Licht et. al. ²⁰ , 1980	1	53/M	2.6-3.9	19,710	C	13.0	12	alive
LaBrecque and Mitros ²¹ , 1980	2	36/M 29/F	4.5 3.0	3,300 3,300	C C	5.9 6.9	alive alive
Gerber et.al. ²² , 1980	2	36/F 27/F	6.4 4.0	8,460 4,590	A C	13.0 8.7	12 21	alive alive
Johnson et. al. ²³ , 1981	1	23/F	6.0	4,320	C	10.0	13.1	alive
Black et. al. ²⁴ , 1982	1	37/F	10.0	14,500	C	8.7	20.0	died
Levinson ²⁵ , 1983	1	41/M	10.0	6,500	C	3.5	6.0	alive

ETOH key A=acute ingestion, C=chronic ingestion, N=denies ingestion, ?=alcohol ingestion unknown.

Table 3.1: Literature reports of acetaminophen toxicity and alcohol (cont.)

REFERENCE	#PT	AGE/SEX	AMOUNT OF APAP	AST	ETOH	TOTAL BILIRUBIN	PT	OUTCOME
Himmelstein et. al. ²⁶ , 1984	1	27/M	4.0	5,178	C	6.4	20.0	alive
Fleckenstein ²⁷ , 1985	1	45/M	7.0	10,100	C/A	9.6	27.0	alive
Leist et. al. ²⁸ , 1985	3	28/M	7.0	29,700	C	5.1	63	alive
		28/M	6.0	19,750	C	23.9	27	died
		40/M	9.0	2,396	C	4.2	17	alive
Seeff et. al. ²⁹ , 1986	6	53/M	2.6-3.9	19,710	C	13.0	24	alive
			12.5	10,000	C	2.4	17	alive
		30/M	3.8	5,640	C	16.5	21	alive
		39/M	4.0-6.0	2,870	A	3.6	14	alive
		58/M	26,900	C	0.9	...	alive
		34/F	3.6	6,888	C	6.6	22	alive
		49/F						
Kartsonis et. al. ³⁰ , 1986	2	39/M	5.0	6,494	C	4.2	21	alive
		38/M	4.4	13,496	C	6.1	30	alive
Kumar and Rex ³¹ , 1991	6	66/M	20.0	9,240	C	4.0	23	alive
		65/F	6.0	3,199	C	2.4	alive
		43/F	5.0	14,920	C	7.4	46	alive
		55/M	6.0	7,225	C	2.0	15	alive
		59/M	5.0	3,000	C	7.7	19	died
		34/M	10.0	4,052	C	6.0	37	died
Eriksson et. al. ¹³ , 1992	2	25/M	5.0-6.0	5,759	C	7.2	alive
		46/F	3.0-4.0	14,997	C	4.4	alive

ETOH key A=acute ingestion, C=chronic ingestion, N=denies ingestion, ?=alcohol ingestion unknown.

Table 3.1: Literature reports of acetaminophen toxicity and alcohol (cont.)

REFERENCE	# PT	AGE/SEX	AMOUNT OF APAP	AST	ETOH	TOTAL BILIRUBIN	PT	OUTCOME
Whitcomb and Block ⁹ , 1994	21	29/F	5.0-7.0	10,400	N	alive
		43/F	4.0-6.0	14,520	N	alive
		40/M	6.0	19,916	C	alive
		55/F	5.0-8.0	6,457	N	alive
		45/F	6.0-9.0	5,727	N	alive
		29/F	6.0-10	3,117	C	died
		41/F	4.0-6.0	30,000	C	alive
		40/F	7.0-8.0	17,585	N	alive
		47/F	3.5-5.0	3,990	C	alive
		15/F	7.0	9,735	N	alive
		34/F	8.0-15	2,060	C	alive
		35/M	20-25	9,881	C	alive
		26/M	10-15	7,824	A	alive
		51/M	16-24	1,318	C	alive
		49/M	12-18	13,740	C	died
		40/F	12-18	10,000	C	alive
		27/F	>13	15,720	C	alive
36/F	13-16	13,860	C	died		
60/M	?	2,289	C	alive		
67/F	>5.0	12,740	C	alive		
26/F	?	21,691	C	alive		
Bonkovsky. ² ³² , 1995	1	67/M	1.0-3.0	N	alive

ETOH key A=acute ingestion, C=chronic ingestion, N=denies ingestion, ?=alcohol ingestion unknown.

Discussion of literature review on acetaminophen toxicity and alcohol:

Out of the 60 case studies reviewed here only 9 patients (15%) showed toxicity at less than or equal to 4 grams of acetaminophen per day. Eight of the nine patients were documented alcoholics. There is little evidence that doses of less than or equal to 4 grams of acetaminophen per day causes toxicity in nonalcoholic patients.

Three other studies not included above are of note in the history of acetaminophen induced hepatotoxicity. The first is a study done by Rumack et. al. in 1983³³. They found that administration of 4 grams of acetaminophen daily for 14 days did not cause elevated hepatic aminotransferase levels or induce hepatic necrosis in a group of patients with chronic active hepatitis and cirrhosis. This article is extensively cited and appears in multiple letters to the editors of several journals including *Annals of Internal Medicine*³⁴, *Digestive Diseases and Sciences*³⁵, and *Journal of the American Medical Association*³⁶. The second article is a 1986 look at factors that may effect mortality in acetaminophen overdose. Read et. al's look at 247 patients concludes that "While there was a trend for the alcoholic patients to deteriorate more rapidly and to develop higher prothrombin times than the nonalcoholic group, neither of these differences reached statistical significance ($0.2 > p > 0.10$). Likewise there was no significant difference in the clinical course or outcome between patients who took alcohol concomitantly with the paracetamol overdose³⁷." This article is also extensively cited and appears in the previously mentioned letters to the editors. Lastly, the 1981 findings of Rumack et. al. in 662 cases of acetaminophen overdose, they subdivided patients into several groups. These groups consisted of patients with toxic blood concentrations and patients without toxic blood concentrations. These groups

were further divided based on a history of chronic or acute alcohol consumption.

Their findings show that alcohol consumption, both chronic and acute intake had no significant effect on the maximum prothrombin ratio, maximum serum bilirubin ratio, or the elevation of the SGOT or SGPT ratio when the acetaminophen blood level was in the non-toxic range. When the acetaminophen blood level was measured in the toxic range, statistical differences were seen in maximum prothrombin time and maximum serum bilirubin ratio between patients who had a history of chronic alcohol intake and those with no history of chronic alcohol intake³⁸. They also associated acute alcohol consumption with a hepatic protective effective. A mechanism for this protective effect is not discussed nor is this effect mentioned in any of the other papers.

Conclusions concerning acetaminophen and hepatotoxicity:

1. Chronic alcoholics may be at increased risk for developing toxic effects from acetaminophen when it is taken in doses greater than 4 grams per day. The mechanism is probably a combination of reduced glutathione production and cytochrome P450 enzyme induction. Few reports of toxicity occur in patients who are not alcoholic and consume less than or equal to 4 grams of acetaminophen per day.

2. Few reports of toxicity have occurred in patients taking recommended doses of the drug (4 grams/day). Of those reports, a majority of those patients were chronic alcoholics.

Based on those two statements, all efforts will be made to effectively screen out patients who are at risk of increased toxicity. By eliminating patients with a documented history of alcohol abuse, the increased risk they may represent is

documented history of alcohol abuse, the increased risk they may represent is eliminated in this study. Recognizing that an accurate history of alcohol consumption may be difficult to obtain from these patients, the remainder will be evaluated for preexisting liver disease using liver enzyme assays performed in the last 6 months, and patients will be counseled as to the increased risk of side effects and adverse reactions when alcohol is used in conjunction with any analgesic medication. Participants will be advised to limit their alcohol intake but will not be restricted in their alcohol intake beyond the FDA's recommended two drinks per day limit.

The study design was a double blind crossover comparing two treatments of acetaminophen, each of which were administered as two tablets taken four times a day for four weeks per treatment. Treatments were separated by a 7 days "washout" period during which patients did not receive acetaminophen. One treatment consisted of 1000mg (2x500mg tablets) of an immediate release (IR) commercially available product (URL corp. Lot 15448, exp. 7/97). The second treatment consisted of 1300mg (2x650mg tablets) of the sustained release (SR) product developed as described in chapter two, alternated with two placebo, identically appearing doses for a total of four doses per day. The placebo tablets were made to appear identical to the sustained release tablets. All tablets used in the study were approximately 12mm in diameter, white in color, and had an imprint of three numbers and three letters. During the sustained release treatment, doses 1 and 3 contained active medication, while doses 2 and 4 were the placebo. Total daily dose of acetaminophen for the SR treatment was 2.6 grams and it was 4.0 grams for the IR treatment.

Table 3.2: Comparison of dose placement in the SR and IR treatment packets.

Treatment	Dose 1	Dose 2	Dose 3	Dose 4
Sustained Release	Drug 1300mg	Placebo	Drug 1300mg	Placebo
Immediate Release	Drug 1000mg	Drug 1000mg	Drug 1000mg	Drug 1000mg

All medications were pre-packaged into medication cards. The Redi-Pak®

medication packaging system (MOCORP INC. Smithtown, NY) consists of clear plastic bubbles in which each dose of the medication is placed. The card is then sealed to the backing using a peel and stick mechanism. No heat is involved in the packaging. After packaging, each card holds $7 \times 4 = 28$ doses of medication.

Appropriate labels were placed in the areas that displayed the drug and dosing regimen. For this study, each card of study medication was also labeled across the top of the bubbles as Dose 1, Dose 2, Dose 3, and Dose 4. Down the side of the bubbles, each card was labeled with the days of the week. Packaging was done to increase compliance with the dosing regimen.

Initial concern was expressed that the Redi-Pak® system might be difficult for the target population to use. However, patients stated they had no trouble pushing tablets out of the cards. Several patients even stated that they were easier to use than standard "child resistant caps". Two patients participating in the study were of increased concern because they had above the elbow amputations of one arm. During the first evaluation, these patients pushed tablets out of the cards without problems, despite their disability.

A rescue analgesic (Advil® brand ibuprofen 200mg tablets lot 95 AG 1019 exp. 4/97) was provided to patients for use during the washout period and for pain not relieved by acetaminophen treatments. A maximum of 400mg could be taken up to three times a day. Patients were asked to record any doses of ibuprofen needed in the provided log. The rescue analgesic was packaged into medication cards that held

28 doses of two tablets each. One card of rescue analgesic was included in each treatment package.

Acetaminophen treatments were also packaged in medication cards that each held a one weeks supply of medication. Each card held 28 doses of two tablets each. Groups of four cards of acetaminophen were placed into opaque envelopes with one card of rescue analgesic according to a randomization list and sealed. Each packet was labeled with the subject number and the treatment number and was dispensed without opening. Patients were asked to return all cards once the treatment had been completed. The coded randomization list was kept confidential from the recruiter/investigator.

Evaluation of each patient's pain was performed at three intervals throughout the study. The first evaluation was slightly more extensive than the subsequent evaluations. During the first evaluation, patients were asked for such demographic data as age, height, weight, number of joints affected by the osteoarthritis, length of time since diagnosis, etc. Patients were also questioned about overall health, allergies, and other inclusion and exclusion criteria. Once patient eligibility was confirmed, consent forms were filed and prescriptions written and filled for both the study treatment and the rescue analgesic. A questionnaire consisting of 12 questions was administered to patients and time to walk 50 feet measured. The questionnaire was modified from the Stanford HAQ test³⁹. This test was selected because it had been previously validated and use on osteoarthritis patients to measure pain and disability⁴⁰⁻⁴⁶.

Subsequent visits after treatments two and three were identical in nature. Patients repeated the questionnaire and walking test. Patients were also asked to

supply a saliva sample for analysis. Saliva samples were immediately frozen for future analysis. All empty cards of study medication and cards of rescue medication were collected at the end of each visit. The returned packets remained sealed until completion of the study.

SAMPLE SIZE CALCULATION

Literature searches were conducted to locate previous studies that might contain information that would be useful in estimating the sample size needed for the study. These studies were examined to provide initial estimates of the type of data collected, methods of evaluation, and of results and conclusions. Information about analysis methods, strength, and power of the tests performed on data were also gathered. Prior to performing a sample size calculation, a study design must be selected. For this study a randomized double blind 2X2 crossover design was selected.

Of all the literature examined⁴⁶⁻⁴⁸, a study by Bradley et al. (1991) was selected as the study that would provide the most accurate estimates for sample size calculations⁴⁶. The Bradley study examined 3 different drug treatments and used a timed walking test and pain questionnaire to evaluate the outcome of drug treatments in osteoarthritis patients. The study was not a crossover design. This study was thought to be statistically representative because of its use of acetaminophen in osteoarthritic patients and because of similar evaluation methods.

Dr. Dave Birkes (Oregon State University, Department of Statistics) was consulted concerning the sample size calculation. First, a table of Standard Deviations (SD) of within-subjects differences was calculated from Table 3 of the Bradley paper.

Table 3.3: Estimated standard deviation used for sample size calculation

	Acet. 4000	Ibup. 1200	Ibup. 2400	Average
HAQ pain score	0.74	0.82	0.86	0.81
50-ft-walk-time	1.94	3.71	3.32	2.99
HAQ dis. Score	0.31	0.33	0.49	0.38

Then, the magnitude of difference that was desirable to detect was chosen.

Since the purpose was to compare treatments, the magnitude that must be detected must be at least the mean difference between the treatments.

Table 3.4: Estimated magnitude of difference used for sample size calculation.

	Acet. 4000	Ibup. 1200	Ibup. 2400	Average
HAQ pain score	0.33	0.30	0.35	0.33
50-ft-walk-time	0.50	0.50	0.70	0.57
HAQ dis. score	0.08	0.08	0.11	0.09

Next, the means and SD of differences in the proposed study are assumed to be similar to those listed above. Therefore the sample size needed for a 2X2 crossover design in order to detect the assumed mean differences with 90% probability would be:

Table 3.5: Estimated sample size for 2x2 crossover design used in study sample size calculation.

	Total sample size n
HAQ pain score	66
50-ft-walk-time	294
HAQ dis. Score	186

Lastly, the corresponding powers or probabilities of detection were calculated for the assumed mean differences.

Table 3.6: Estimated powers or probabilities of detection used in sample size calculation.

	n=50	n=100	n=150	n=200
HAQ pain score	0.81	0.98	0.99+	0.99+
50-ft-walk-time	0.25	0.47	0.64	0.76
HAQ dis. Score	0.38	0.66	0.83	0.92

A sample size of approximately 50 people was estimated to be appropriate for the proposed study.

PATIENT RECRUITMENT AND ENROLLMENT

Recruitment was performed from the Veterans Administration (VA) Outpatient clinic in Portland, OR. Medical charts for patients with scheduled appointments in the general medicine clinic were screened 1 day prior to the appointment for study suitability. Charts were reviewed for proper diagnosis documentation and for inclusion/exclusion criteria.

Inclusion criteria:

1. Documented diagnosis of osteoarthritis in one or both knees.
2. Age 40-90 inclusive
3. Permission of Primary Care Provider

Exclusion criteria:

1. Renal dysfunction - elevated BUN or serum creatinine.
2. Hepatic dysfunction - elevated SGOT, SGPT, alkaline phosphatase, or total serum bilirubin.
3. Allergy to either acetaminophen or ibuprofen.
4. Diagnosis of ethanol abuse or consumption of > 3 alcoholic beverages per day.
5. Diagnosis of infectious disease - HIV, hepatitis B or C, tuberculosis, etc.
6. Drug interactions - phenytoin, carbamazepine, cyclosporine, lithium, rifampin, chloramphenicol, diflunisal, oral contraceptives, metoclopramide, or cisapride.
7. Mental incompetence or diagnosis of dementia.
8. Trauma to the knees in the last 3 months - surgery, acute injury, or intra-articular injections of the joint.

9. Pregnancy or inability to verify birth control/menopausal status.
10. Inability to walk 50 feet without assistance or assistive devices.
11. Concurrent diagnosis of a disease state that might affect the ability to walk or might constitute a contra-indication for acetaminophen or ibuprofen therapy. Includes, but is not limited to, rheumatoid arthritis, unstable angina, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), peripheral vascular disease, fibromyalgia, bursitis, active peptic ulcer disease (within the last 12 months), and chondromalacia.
12. Any documented behavior that might constitute a risk to the investigator or the patient themselves. Includes, but is not limited to, documented suicidal ideation, previous attempts to commit suicide, use of illegal or recreational drugs, and previous history of threatening behavior towards other medical personnel.

When patients arrived for their appointments, permission of the attending physician was obtained prior to approaching the patient about enrollment. After the physician addressed immediate health concerns of the patient, the patient was approached concerning enrollment into the study. If interested, patients were enrolled. Patients were counseled to restart their previous analgesic regimens at the conclusion of the study.

Recruitment lasted for the period between May 20th, 1996 and December 31st, 1997. During that time, a total of 13,483 medical charts of patients scheduled for visits were screened for possible patient inclusion into the study. A documented diagnosis of osteoarthritis of the knee was made in 708 patients. This represents 5.25% of the screened patients. Inclusion/Exclusion criteria were then applied to this population to identify eligible participants.

A total of 349 patients were excluded from the study for failure to meet one or more inclusion/exclusion criteria. Table 3.1 is a summary of the distribution of those

patients. Justification and explanation of each exclusion criteria follows the table.

Table 3.7: Number of Patients Excluded from the Study Categorized by the Exclusion Criteria

Excluding factor	Level	# patients	
Renal Dysfunction	Mild ($1.4 < \text{Scr} < 2.0$)	33	
	Moderate ($2.1 < \text{Scr} < 3.0$)	8	
	Severe ($\text{Scr} > 3.0$)	4	
Hepatic Dysfunction	Alk. Phosphatase > 100	31	
	SGOT > 35	10	
	Total Bilirubin > 1.0	5	
Combined Renal and Hepatic Dysfunction		9	
Allergy to Drug	Acetaminophen	3	
	Ibuprofen	20	
Ethanol Abuse	Greater than 3 Drinks/Day	19	
Infectious Disease	Hepatitis B	2	
	Tuberculosis	1	
Drug Interactions	Phenytoin	2	
	Cyclosporine	1	
Mental Status	Dementia	5	
	Mentally Incompetent	3	
Recent Trauma to Knees	Injections or surgery	18	
Birth Control	Unable to verify	1	
Assistive Device or Inability to Walk 50 Feet	Cane or Walker	16	
	CVA with hemiparesis	1	
	Cellulitis	1	
	Foot Ulcers	1	
	Parkinson's disease	1	
	Blindness	2	
	Concomitant Diseases	Rheumatoid Arthritis	13
		Bursitis	1
Unstable Angina		3	
Chondromalacia		3	
Peptic Ulcer Disease		4	
High Risk Patients	Threat w/firearms	3	
	Drug seeking behavior	8	
	Suicidal Ideation	1	
Misc. Exclusions	Dysphagia	1	
	Other Clinical Study	3	
Age	Age > 90	19	

	Age<40	1
MD Declination	See Table 3.7	92

Justification and Explanation of Excluded Patients:

1. Renal Dysfunction:

Normal Scr ranges from 0.7 to 1.3 mg/dL with most adults having a Scr of 1.0mg/dL⁴⁹. Forty-five patients were excluded for isolated renal insufficiency (Scr>1.3). Thirty-three had mild renal dysfunction (1.4<Scr<2.0), eight had moderate renal dysfunction (2.1<Scr<3.0), and four had severe renal dysfunction (Scr>3.0). Another 9 patients were excluded for combined renal and hepatic dysfunction. Adequate renal function is essential in patients taking ibuprofen (the rescue analgesic), as the potential for renal toxicity from ibuprofen increases as renal function decreases.

2. Hepatic Dysfunction:

Normal liver enzymes for healthy adults range from alkaline phosphatase between 50-100 but it can vary dependant on assay method, SGOT between 8-42 IU/L, and total bilirubin between 0.3 and 1mg/dL⁴⁹. Forty-six patients were excluded for elevated alkaline phosphatase (31 patients), SGOT (10 patients), or total bilirubin (5 patients). Acetaminophen is primarily metabolized in the liver. Adequate hepatic function is essential to the metabolism of acetaminophen and the removal by conjugation of hepatotoxins produced during the metabolism of acetaminophen.

Nine additional patients were excluded for combined renal and hepatic insufficiency.

3. Allergy to Acetaminophen or Ibuprofen:

Twenty-three patients were excluded for listed allergies to either acetaminophen (3 patients) or to ibuprofen (20 patients). Allergy listings were taken at face value and no attempt was made to document true "allergic" reaction versus adverse drug reaction.

4. Ethanol Abuse:

Nineteen patients were excluded for a documented diagnosis of ethanol abuse or for the known consumption of 3 or more alcoholic beverages per day. It has been shown that alcoholic patients or heavy alcohol consuming patients had reduced amounts of the conjugate needed during acetaminophen metabolism. Consequently, they are at increased risk of acetaminophen induced hepatotoxicity.

5. Infectious Disease:

Three patients were excluded because of infectious disease considerations. Two patients were carriers of Hepatitis B, while a third was undergoing treatment for active tuberculosis. Since this study involves collection of saliva samples for analysis these patients were excluded from the study as possible sources of biohazardous samples.

6. Drug Interactions:

Three patients were eliminated for drug interactions. Two patients were taking phenytoin and 1 was taking cyclosporine. Acetaminophen is highly protein bound and may compete with these medications for protein binding sites.

7. Mental Status:

Five patients were excluded for a diagnosis of dementia and three more had been ruled by the court as mentally incompetent. This study was not designed to legally accommodate these groups of patients.

8. Recent Trauma to Knees:

Eighteen patients were excluded for trauma or intra-articular injections in the knee in the last 3 months.

9. Birth Control:

Nearly 99% of the patients seen at the VA Outpatient clinic are male. Of the females screened only one patient was excluded for insufficient birth control methods. The patient was still peri-menopausal and therefore at risk of possible pregnancy.

10. Assistive Devices or Inability to Walk 50 Feet:

Twenty-two patients were excluded for inability to walk 50 feet without assistance or assistive devices. Sixteen of those required a cane or walker. One patient had hemi-paresis secondary to a recent CVA, 1 patient had severe bilateral cellulitis of the lower extremities, 1 had diabetic foot ulcers, 1 patient had Parkinson's disease, and 2 patients were legally blind.

11. Concomitant Diseases:

Twenty-four patients were excluded for concomitant disease states. Thirteen

patients also had rheumatoid arthritis in the knees, 1 patient had bursitis, 3 patients had unstable angina, 3 patients had chondromalacia, and 4 patients had active peptic ulcer disease.

12. High Risk Patients:

Twelve patients were excluded because they represented a danger to themselves or to the investigator. Three were excluded for threatening medical personnel with firearms, eight for drug seeking behavior, and 1 for suicidal ideation.

13. Miscellaneous exclusions:

One patient was excluded for dysphasia that prevented swallowing of the tablets and 3 patients were excluded because they were actively enrolled in another clinical study.

The last two categories are listed as "Age" and "MD Declines Enrollment".

These are not part on the exclusion criteria *per se*. Rather they can be best classified as "Failures to Comply with the Inclusion Criteria."

14. Age:

Twenty people fell outside the age range. Nineteen of those were greater than 90 years of age and 1 was less than 40 years of age.

15. MD Declines Enrollment:

Permission for enrollment was declined for 92 patients. Thirty-two physicians did not specify a reason for declining enrollment. Most reasons for declining enrollment were a direct result of the acute problem that had brought the patient to the clinic. Table 3.8 outlines all stated reasons for declining enrollment.

Table 3.8: Physician Reasons for Declining Enrollment

Reason	#Pt
Recent surgery – eye	1
Recent surgery – urology	1
Recent surgery – ankle	2
Recent surgery - plastic surgery	4
Recent surgery – cardiac	2
Cancer	2
Foot ulcer	1
Infection	1
Deep Venous Thrombosis	5
Pancreatitis	1
Transient Ischemic Attack	1
Cerebral Vascular Accident	4
GI Bleed	1
Mental Health Issues	2
Rash	1
Eye Issues	1
Atrial flutter/tachycardia/angina	9
No Ibuprofen	1
Nurse Practitioner	7
Not Primary Care Provider	10
New Patient	3
Not Specified	32

After eliminating the 349 patients that did not satisfy all inclusion/exclusion criteria, 359 patients remained. Every attempt was made to contact these patients regarding enrollment in the study. One hundred twenty five of these patients were

unable to be contacted because they cancelled their appointments, did not show up for their appointment at all, or were "missed" because of the interview or enrollment of another patient. Of those patients approached, two hundred and four of them declined enrollment in the study for reasons that ranged from "not interested" to "not having pain at this time". Table 3.9 summarizes the reasons stated for non-enrollment.

Table 3.9: Patient Reasons for Non-enrollment into the Study.

Reason	#Pt
Cancelled Appointment	20
Did Not Show for Appointment	46
Recruiter Missed the Patient	59
Not interested	22
Not enough time	3
Too Many Pills	5
Doesn't want to change Meds	5
Leaving area for trip	2
Too far to Drive	103
Too much pain	25
No pain at this time	39

It should be noted that over half of the 204 patients approached declined because it was too far for them to drive back to the clinic for follow-up evaluations. The VA hospital outpatient clinic services a huge area of Oregon and Washington. Patients are expected to travel several hundred miles for service at the clinic. Table 3.10 is a table of the cities that these 103 patients commute from to go to the clinic.

Table 3.10: Home City of 103 Declined Patients who Stated "Too far to Drive" as the Reason for not Enrolling in the Study

City	# Patients	City	# Patients
Albany, OR	8	Oregon City, OR	1
Astoria, OR	3	Otis, OR	1
Banks, OR	1	Parkdale, OR	1
Bend, OR	2	Redmond, OR	1
Boring, OR	2	Rockaway, OR	2
Brownsville, OR	1	Salem, OR	22
Canby, OR	1	Sandy, OR	1
Condon, OR	1	Seaside, OR	2
Corvallis, OR	3	Silverton, OR	1
Eagle Creek, OR	1	South Beach, OR	1
Eugene, OR	2	Stayton, OR	2
Forest Grove, OR	1	St. Helens, OR	1
Garibaldi, OR	1	Sweet Home, OR	1
Gervais, OR	1	The Dallas, OR	1
Idanha, OR	1	Tillamook, OR	5
Jefferson, OR	1	Troutdale, OR	1
Junction City, OR	1	Woodburn, OR	1
Klamath Falls, OR	1	Battleground, WA	2
Keizer, OR	1	Camos, WA	1
Lapine, OR	1	Kelso, WA	1
Lebanon, OR	3	Longview, WA	1
Lincoln City, OR	1	Rainier, WA	2
Manzanita, OR	1	Ridgefield, WA	1
Mcminnville, OR	1	Stevenson, WA	1
Monmouth, OR	2	Vancouver, WA	1
Newberg, OR	1	Washougal, WA	1
Newport, OR	3	Woodland, WA	1

Study Management:

An often ignored subject in the medical literature is the huge amounts of time, effort, and true costs that are put into subject recruitment. Months of effort are often reduced to a sentence that states "X number of patients were recruited over a XX month period." Strict documentation must be kept on all patients screened for the study, all excluded patients, all participating patients, and all patient withdrawals from the study. The mechanics of this screening and documentation process are

tremendously complicated and tedious. Therefore, a small section of this thesis is dedicated to the mechanics of the actual process.

Getting the Word Out:

The first step is notifying and educating the providers about the existence and purpose of the study. Large signs were posted around the VA outpatient clinic. The signs were a succinct listing of the name of the project, the inclusion/exclusion criteria, and the contact personnel. In addition, short announcements were made during clinic "grand rounds" for each group of physicians and one page protocol summaries were passed out for staff reference. Lastly, "study cards", fashioned after the business cards seen in the corporate world were printed and distributed to each participating M.D.

Identifying patients:

Patients recruited for this study all had appointments with physicians at the VA Outpatient Clinic. In preparation for these appointments, medical charts of each patient were sent to the clinic on the day prior to the appointment. Using the VA computer system, a list of all patients with appointments for the next day could be printed for each physician. Once printed, patient online records were examined for a diagnosis of osteoarthritis, basic patient information (age, weight, address, and phone number), and laboratory values screened. Promising patient charts could then be examined. On an average day, 60-80 names were printed on the M.D. lists. Of those, about 10 could be eliminated on the basis of their age or diagnosis. An additional 40-

60 could be eliminated for not having the disease or for lab abnormalities. The remaining 10-20 charts were reviewed for all inclusion/exclusion criteria. Those charts belonging to eligible patients were marked with "Patient Identification Forms" to notify the M.D. of the patient's eligibility for the study. A daily "HIT List" was prepared. The physician of each targeted patient was approached at the beginning of rounds and followed up with after the patient had been seen. Many patients also required the permission of the attending physician as well as that of the resident MD. Several physicians gave "blanket" authorization to their patients fitting the criteria, while other refused participation to all their patients.

Patient Paperwork:

Packets were prepared in advance for the patient enrollment. Each enrollment packet contained a checklist, a consent form, a questionnaire, prescriptions, "Study cards", and study medication. The initial visit packet was fifteen pages in length. Smaller packets of only 3 pages were needed for visits 2 and 3. Also, withdrawal forms, patient progress lists, and completed study checklists were needed for each patient. All in all, each patient's final file contained up to 30 pages of information that must be kept organized and confidential. A dedicated, securable filebox was utilized for the security and organization of all the forms and patient files. Folders containing copies of all blank forms were kept inside. Each patient was assigned a separate folder to minimize confusion.

Time and Estimated cost:

Each day of patient screening used 40-60 pages of paper. The VA clinic was kind enough to donate the paper and ink for all the printed documents as well as the use of their computers and printers. All other secretarial supplies were provided out-of-pocket by the investigator. All chart review and drug dispensing was performed by a licensed pharmacist. Each recruitment day began with 7:00am rounds with the resident MD's and ended at 5:30pm with the closing of the clinic. This adds up to a total of 180 working days each 10 hours in length (minus 30 minute lunch daily).

For the sake of example, it is assumed that the investigator would provide all supplies. Supply charges would include 50 pages paper/day with a misc. supply charge of \$5.00/week. Paper charges = \$3.75/144 pages. Let it also be assumed that the pharmacist performing the chart review and dispensing was reimbursed at normal market rate (\$27.00/hr). Also assume that physician and patient participation were not compensated. This study consisted of 180 working days each 10 hours in length.

Table 3.11: Estimated Cost of Study

	Per Month	For This Study
Average of 50 pages/day	\$26.04	\$234.38
Misc. office supplies	\$20.00	\$180.00
Pharmacist salary	\$5,400.00	\$48,600.00
Estimated total cost	\$5,446.04	\$49,014.38

The estimated cost for the example study is nearly \$50,000.00. Actual funding was significantly less.

Recruitment Note:

An additional side note about the recruitment process. It is important for recruiters to consider the age and social standards of the target population. In this case, a majority of the patients were raised during a generation where women were treated much differently than in today's society. These men responded better to a female recruiter who was wearing "proper dress" i.e. a modest blouse and skirt, or a one-piece dress. Recruitment attempts made while wearing pants were less successful. I feel that similar negative reactions would have been obtained with male recruiters with long hair or with an earring, as both were considered socially unacceptable to this generation.

This particular population also responded poorly to medical personnel that were of Asian descent. There were several incidents where patients refused to see medical interns because their Asiatic appearance triggered flashbacks and made the patient uncomfortable. This is hardly surprising as many of them are veterans of the Korean and Vietnam wars and suffer from Post Traumatic Stress Disorder (PTSD). It is also important to point out that the Veterans could not make a distinction between the different Asiatic groups. Regardless if the person was Vietnamese, Chinese, Japanese, or Laotian, the patients were still disturbed. Patient responses varied from polite requests for a different person to patients hiding under chairs or physically attacking the perceived threat. Factors such as these must be taken into consideration when selecting recruiters as they may have a definite impact on patient response to recruitment.

Patient Enrollment:

After all factors were taken into consideration, only thirty patients from the original 13,483 files examined consented to enrollment in the study. All enrolled patients were Caucasian males. Table 3.12 is a summary of demographic characteristics.

Table 3.12: Demographics of 30 enrolled Patients

Characteristic	Average (range)
Age (years)	61.16 (44-76)
Height (inches)	71.16 (67-79)
Weight (pounds)	221.3 (145-268)
Sex	All Male
Race	All Caucasian
Smokers (percent)	40% (12 subjects)

These statistics are consistent with the published data on osteoarthritis of the knee. The disease is known to increase as the patient ages^{3,5,6}. The prevalence increases from 4% in patients age 18-24 up to 85% in patients between 75-79 years of age⁶. The incidence is also a function of weight and race. Americans and Europeans have a higher incidence than Chinese or East Indians^{3,6}. Weight is an aggravating factor in the disease process³. In the 30 enrolled patients, all but 1 were at least 20 pounds over their ideal body weight with 19 subjects being 50 or more pounds above ideal body weight. The incidence of osteoarthritis is generally greater in females than in males³. As the population of patients at the VA Hospital is primarily male, no estimates on female patients were available for comparison.

Severity and Grading of Osteoarthritis of the Knee:

All 30 patients had diagnostic radiological reports on file. Those reports that were not available by computer could be found by accessing the older paper chart of the patient.

Table 3.13: Distribution of enrolled patients by Severity and Radiological grading of the Osteoarthritic Disease.

Grade of Osteoarthritic Disease	Number of Patients
Mild	7
Mild – Moderate	3
Moderate	7
Moderate - Severe	5
Severe	4
Total Knee Replacement secondary to severe disease	4

Discussions with the radiology department at the VA hospital resulted in the following guidelines for radiological interpretation⁴². Films are examined for the presence of lateral or medial osteophytes, joint space narrowing, sclerosis, and cysts. Each category is graded on a scale of 0-2, where 0=absent, 1=questionable, and 2=present. A rating of mild indicates the presence of osteophytes but no joint space narrowing, sclerosis, or cysts. A rating of moderate indicates moderate multiple osteophytes, some sclerosis, some cysts, and definite joint space narrowing. A rating of severe indicates the presence of severe osteophytes, cysts, and sclerosis as well as severe joint space narrowing. The ratings of mild-moderate and moderate-severe are used when some, but not all of the criteria of the upper rating has been met, or to

indicate progression of the disease. In the case where both knees were affected by osteoarthritis, the rating of the higher knee was used.

Withdrawal from the Study and Reported Side Effects:

Of the 30 patients who enrolled in the study, 17 completed the study. The thirteen who withdrew cited a variety of reasons. Two patients withdrew before taking any tablets. One cited a newly diagnosed rash as the reason and the other decided that his moving to another city would not allow enough time.

Two patients were lost to follow-up. One elected to obtain medical care from another facility and the other is missing and presumed dead by local police.

Seven patients withdrew during or after treatment one. Three cited new diagnosis or acute injury as the reason (subject #19 - shoulder injury, subject #30 - emergency knee surgery, subject #23 - new diagnosis of prostate cancer), one cited inability to give up previous narcotic medication (subject #26 - Vicodin®), one cited uncontrolled pain (subject #21), and 2 cited intolerable side effects from the treatment medication. Subject #20 reported drowsiness from the medication while subject #22 reported stomach upset, diarrhea, and insomnia. All are uncommon, but reported side effects to acetaminophen. Four of these seven patients could have experienced withdrawal due to the treatment. For subjects #26, #21, and #22, treatment 1 was the immediate release acetaminophen. For subject #20, treatment #1 was the sustained release acetaminophen formulation.

Two patients withdrew during treatment two. Subject #12 withdrew because of uncontrolled pain. Lastly, Subject #9 withdrew because he experienced nausea,

stomach upset, and heartburn. Side effects for this subject were much worse during treatment two than during treatment one. Treatment two for both subjects was the immediate release acetaminophen formulation.

Side effects from the medication were reported by a total of eleven patients during one or more treatments. Most side effects were reported as occurring for only a short time. Reports were noted but no attempts were made to develop causal relationships between these side effects and treatment during the study.

The incidence of these complaints did not vary significantly between the immediate release and sustained release acetaminophen formulations. Table 3.14 is a summary of reported side effects in all patients regardless of whether they completed the study.

Table 3.14: Incidence of Side Effects to Study Medication By Formulation.

Side Effect	Total # Reports	IR	SR
Drowsiness	5	2	3
Stomach Upset	4	3	1
Nausea	3	1	2
Headache	2	1	1
Diarrhea	2	1	1
Dizziness	1	0	1
Heartburn	1	1	0
Insomnia	1	1	0

Verification of Patient Compliance:

After the end of each treatment, each patient returned the treatment cards in a sealed envelope. Once the study had been completed those envelopes were opened and the number of remaining tablets counted. Patients with treatment cards that contained greater than 10% of the doses remaining were disqualified from the study for non-compliance. Each treatment consisted of 224 total tablets. Patients could miss up to 11 doses or 22 tablets without disqualification. None of the seventeen patients that completed the study were disqualified for non-compliance. The table below shows the number of “missed” doses in the seventeen patients that completed the study. No patient missed more than 8 tablets or 4 doses of medication during any given treatment. The average number of tablets missed during treatment period 1 and treatment period 2 were 1.64 and 1.88 respectively. Several patients stated that the convenient packaging of the medication had improved their compliance with both the study medication and their own regular medications. The packing of the study apparently medication reminded them to take their other medications.

Table 3.15: Number of Tablets Missed by Patients During the Study Treatments

Patient #	# Tablets Missed During Treatment 1	# Tablets Missed During Treatment 2
1	2	4
2	0	0
3	8	8
4	0	0
5	0	0
6	4	0
7	0	6
8	0	0
11	0	0
13	0	0
14	8	4
16	2	0
18	0	0
24	0	0
25	0	4
27	0	0
28	4	6
Average	1.64	1.88

Breakthrough Analgesic Quantification:

For humanitarian reasons, patients were supplied with ibuprofen 200mg (Advil 200mg tablets Lot 95 AG1019, exp. 4/97) tablets as a breakthrough analgesic. This medication was available to the patients for use if the acetaminophen treatment was not effective. A maximum of two ibuprofen tablets (400mg) twice a day was permitted. Most patients did not require the breakthrough analgesia. Some patients admitted to requiring additional analgesia in the evenings. Many stated that their pain was adequately controlled during the day because there were busy working. In the evenings, patients stated that they “stiffened up” and “had nothing else to think about” other than their pain. One patient stated that the acetaminophen treatment

made him feel so much better that he “over did it”. He needed rescue analgesia the next day. Table 3.16 shows the number of ibuprofen tablets taken by the seventeen patients who completed the study.

Table 3.16: Number of Rescue Analgesic Tablets Needed by Patients during the Study Treatments

Patient #	# Tablets used during Treatment 1	# Tablets used during Treatment 2
1	0	0
2	0	0
3	0	2
4	0	0
5	14	10
6	0	0
7	0	0
8	2	0
11	0	4
13	0	0
14	0	0
16	0	0
18	0	9
24	0	0
25	8	0
27	5	3
28	0	5
Average	1.71	1.94

Saliva Samples:

Each patient was asked to produce a saliva sample for analysis at three different points during the study. The first sample was taken during visit 1 and served as a baseline sample. The second sample was collected during visit 2 at the end of the first treatment period. The third and last sample was collected during visit 3 at the end of the second treatment period. Sample two and three should represent steady state

saliva acetaminophen concentrations for their respective treatments. Samples were frozen after collected and analyzed using the techniques in Chapter 2. Salvia acetaminophen concentrations in the seventeen patients completing the study are shown in Table 3. 17. Note: most samples were taken about 4 hours after the second dose and about 2 hours prior to the third dose of the day. The average values must therefore by “decayed” to estimate true saliva troughs. Drug decay is influenced by continued input from the SR dosage form in one case, but not for the IR dosage form in the other case.

Table 3.17: Measured Saliva Acetaminophen Levels in Study Samples

Patient #	Saliva APAP concentration after IR treatment (mg/L)	Saliva APAP concentration after SR treatment (mg/L)
1	2.5	6.7
2	2.8	7.0
3	2.3	6.8
4	1.7	6.8
5	1.9	6.3
6	2.8	6.2
7	3.7	7.4
8	2.7	6.7
11	1.8	5.9
13	3.0	6.4
14	1.9	6.3
16	2.5	6.8
18	4.1	7.9
24	2.4	6.7
25	2.8	6.4
27	2.6	6.4
28	3.0	7.0
Average	2.61	6.68

Decaying the average saliva drug concentrations:

From the single dose studies in Chapter 2, the K_e for the immediate release product was calculated to be 0.3300 h^{-1} and the K_e for the 5% sustained release product was calculated to be 0.1331 h^{-1} . Using these estimates, the saliva concentrations of drug can be “decayed” to approximate trough levels using the equation $C_t = C_o e^{-k_e t}$. In this equation recall that C_t is the concentration at any time t , C_o is the original concentration, K_e is the elimination rate constant, and t is the time in hours that has elapsed between C_o and C_t .

For the estimated IR trough:

$$C_t = 2.61 e^{-(0.3300)(2)} = 1.34 \text{ mg/L (range 0.87 - 1.91mg/L)}$$

For the estimated SR trough:

$$C_t = 6.68 e^{-(0.1331)(2)} = 5.11 \text{ mg/L (range 4.75 - 6.05mg/L)}$$

Recall from chapter 1 that saliva and serum acetaminophen concentrations are approximately equal⁵¹⁻⁵⁴. If the K_e from the single dose study is representative of the multiple dose K_e , then the formulation goal of a minimum acetaminophen plasma level of 5mg/L has been accomplished.

PAIN AND DISABILITY QUESTIONNAIRE

The pain/disability questionnaires consisted of 12 questions plus the walking test time. It was adapted from the Stanford Health Assessment Questionnaire (HAQ).

Three of the twelve questions concerned pain and pain characteristics, six questions concerned disability, and three questions concerned the patient's medication and any side effects from that medication. Raw data for all questions can be found in Appendix 3D. Data analysis was performed only on the 17 patients completing the study. Data were examined first for overall changes in average score for all 17 patients, then by treatment group. Those patients receiving the SR treatment as their first treatment will be designated as treatment group SR-IR (n=8). Likewise those patients receiving the IR treatment as their first treatment will be designated as treatment group IR-SR (n=9).

Pain Evaluation

Question 1: How would you rate your overall pain during the last 4 weeks?

Patients were asked to rate their pain as 1=mild, 2=moderate, or 3=severe.

Table 3.18: Average Score on Question 1 by Treatment Group

Tx Group	Visit 1	Visit 2	Visit 3
Average – All	2.205	1.735	1.558
Average SR-IR	2.250	1.875	1.687
Average IR-SR	2.166	1.611	1.444

Question 2: How would you describe the change in your pain in the last 4 weeks?

Patients were asked to rate their pain as 1=better, 2=no change, or 3=worse.

These ratings were re-coded as -1 = better, 0 = no change, and 1= worse for analysis.

Therefore a negative average change can be interpreted as a reduction the pain or as a change for the "better". Baseline values were set = 0 as a reference point.

Table 3.19: Average Score on Question 2 by Treatment Group.

Tx Group	Visit 1	Visit 2	Visit 3
Average – All	0.000	-0.294	-0.294
Average SR-IR	0.000	-0.250	-0.250
Average IR-SR	0.000	-0.333	-0.555

Question 3: My pain is best described as:

Patients were asked to rate their pain as 1=periodic (comes and goes), 2=daily

(occurs at least once a day), or 3=constant.

Table 3.20: Average Score on Question 3 by Treatment Group.

Tx Group	Visit 1	Visit 2	Visit 3
Average – All	2.352	2.117	2.176
Average SR-IR	2.125	2.125	2.250
Average IR-SR	2.555	2.111	2.111

All three questions in this section were designed to measure the type and severity of pain that osteoarthritis patient experience. During the baseline evaluation (Visit 1), it became clear that on average these patients experience daily to constant pain that is of moderate to severe. Most of these patients have historically treated their symptoms with "as needed" pain medications. Only a few patients took regularly

scheduled pain medications. Questions 1 and 2 show that regardless of the treatment group the severity of the pain decreased with routine pain medication administration. In contrast, Question 3 shows that regardless of the pain medication or regimen prescribed the description of their pain varied little with most patients still describing their pain as occurring on a daily basis.

Disability:

The next 6 questions in the pain and disability questionnaire were targeted at the degree of disability that each patient experiences. As before, data analysis was performed only on the 17 patients completing the study. Data were examined first for overall changes in average score for all 17 patients, then by treatment group. Those patients receiving the SR treatment as their first treatment will be designated as treatment group SR-IR (n=8). Likewise those patients receiving the IR treatment as their first treatment will be designated as treatment group IR-SR (n=9). Patients were asked to rate these tasks as 1=Seldom need help, 2=sometimes need help, or 3= often need help.

The questions were: I need help from another person to do the following:

Question 4: Dress

Table 3.21: Average Score on Question 4 by Treatment Group

TX Group	Visit 1	Visit 2	Visit 3
Average - All	1.117	1.000	1.058
Average SR-IR	1.125	1.000	1.000
Average IR-SR	1.111	1.000	1.111

Question 5: Eat**Table 3.22: Average Score on Question 5 by Treatment Group.**

TX Group	Visit 1	Visit 2	Visit 3
Average – All	1.000	1.000	1.000
Average SR-IR	1.000	1.000	1.000
Average IR-SR	1.000	1.000	1.000

Question 6: Stand up**Table 3.23: Average Score on Question 6 by Treatment Group.**

Tx Group	Visit 1	Visit 2	Visit 3
Average - All	1.529	1.176	1.117
Average SR-IR	1.500	1.000	1.000
Average IR-SR	1.555	1.555	1.222

Question 7: Walk**Table 3.24: Average Score on Question 7 by Treatment Group.**

Tx Group	Visit 1	Visit 2	Visit 3
Average – All	1.235	1.058	1.176
Average SR-IR	1.375	1.125	1.250
Average IR-SR	1.111	1.000	1.111

Question 8: Climb Stairs**Table 3.25: Average Score on Question 8 by Treatment Group.**

Tx Group	Visit 1	Visit 2	Visit 3
Average – All	1.588	1.647	1.294
Average SR-IR	1.625	1.750	1.125
Average IR-SR	1.555	1.555	1.444

Question 9: Clean House or do everyday chores

Table 3.26: Average Score on Question 9 by Treatment Group.

Tx Group	Visit 1	Visit 2	Visit 3
Average – All	1.235	1.235	1.235
Average SR-IR	1.250	1.125	1.125
Average IR-SR	1.222	1.333	1.333

Two things were clear to the investigator about these questions and are related to observations made in the recruitment section of this paper. Both are personal observations and cannot be supported or refuted by the data collected. The first observation was that the presence or absence of a second person during the interview might have affected the patient's answer to the disability questions. The second person (usually the patient's spouse) tended to result in the patient reporting less disability than if the patient was interviewed alone. This is not surprising as the generation of veterans who participated in this study were raised to "act like a man" and not admit weakness or disability. Unfortunately, records of other people present at the interviews were not kept for inclusion in the analysis.

The second observation was that even when alone, the patients tended to underestimate the effect that the disease has on their abilities. An example is the answer to question 8 about climbing the stairs. Most patients stated that they seldom needed help from another person to climb stairs, yet almost all patients requested to use the elevator when going from the recruitment area of the clinic, downstairs to the pharmacy one floor below. Several patients were later to admit that they "seldom needed help from another person" to climb stairs because they just didn't do it at all. This may be a function of individual pride or a fault in the way that the questions were

written. As mentioned previously, the generation from which this population was drawn was taught as young men not to admit disability. As for the faulty questions, future recruiters may consider either evaluating the disability themselves or developing more specific questions for evaluation of disability and not relying on just patient reported information.

Question 5 did not yield any information relative to this study. In retrospect, it is easy to see why osteoarthritis of the knee did not have significant impact on the eating habits of the enrolled patients.

Medication Efficacy and Side Effects

As before, data analysis was performed only on the 17 patients completing the study. Data were examined first for overall changes in average score for all 17 patients, then by treatment group. Those patients receiving the SR treatment as their first treatment will be designated as treatment group SR-IR (n=8). Likewise those patients receiving the IR treatment as their first treatment will be designated as treatment group IR-SR (n=9).

Question 10: The pain medication that I have been taking for the last 4 weeks relieves my pain:

Patients were asked to rate pain relief provided by the medication taken for the last 4 weeks as 1=seldom, 2=sometimes, or 3=often.

Table 3.27: Average Score on Question 10 by Treatment Group.

Tx Group	Visit 1	Visit 2	Visit 3
Average – All	1.705	2.235	2.441
Average SR-IR	1.625	2.213	2.750
Average IR-SR	1.777	2.333	2.166

This question was included to help determine if the medication (acetaminophen) was effective in relieving the pain. The increase in the average rating could be the result of two separate effects. One may be the result of a decrease in the pain because of chronic administration of the medication rather than "as needed" use. The second may be the result of withdrawal of patients for whom the drug did not work effectively. By the third evaluation, it is possible that only drug "responders" remained in the study and that all drug "non-responders" had withdrawn from the study due to lack of efficacy.

Question 11: The pain relief lasts for the entire time between doses:

Patients were asked to rank the duration of pain relief provided by the medication taken for the last 4 weeks as 1= seldom, 2=sometimes, or 3=often.

Table 3.28: Average Score on Question 11 by Treatment Group.

Tx Group	Visit 1	Visit 2	Visit 3
Average – All	1.588	2.000	2.235
Average SR-IR	1.250	1.875	2.375
Average IR-SR	1.888	2.111	2.111

The baseline value for this question was 1.588 ± 0.79 (n=17). Verbally, this indicates that patients often have breakthrough pain between doses of their baseline medication. With regular dosing of the study medication, pain relief duration increases to 2.000 ± 0.71 (n=17). By evaluation 3, the average had increased to 2.235 ± 0.83 (n=17). The same arguments can be used for this question as were used for Question 10. The increase in pain relief could be due to either chronic medication dosing or withdrawal of medication non-responders.

Question 12: In the last four weeks, have you had any side effects or bad reactions to the medication?

This questions was extensively examined earlier in the paper with all side effects reported by all enrolled patients examined. For the 17 patients completing the study the percentage and type of side effects were as follows:

Table 3.29: Percentage of Side Effects Occurring by Treatment

Side Effect	# pt on IR Tx	% pt on IR Tx	# pt on SR Tx	% pt on SR Tx
Drowsiness	2	5.8%	2	5.8%
Headache	1	2.9%	1	2.9%
Nausea/GI upset	1	2.9%	1	2.9%
Diarrhea	0	0	1	2.9%

Time to Walk 50 Feet:

This test was designed to determine if pain relief could improve the knee's functional status. Patients were asked to walk a total of 50 feet while being timed. Patients would walk down a hallway 25 feet, pivot and return the same distance. Time to walk 50 feet measurements were taken at each evaluation visit. As before, data analysis was performed only on the 17 patients completing the study. Data were examined first for overall changes in average score for all 17 patients, then by treatment group. Those patients receiving the SR treatment as their first treatment will be designated as treatment group SR-IR (n=8). Likewise those patients receiving the IR treatment as their first treatment will be designated as treatment group IR-SR (n=9).

Table 3.30: Average Time to Walk 50 Feet by Treatment

Tx Group	Visit 1	Visit 2	Visit 3
Average - All	17.00	15.68	14.88
Average SR-IR	15.70	15.31	14.40
Average IR-SR	18.00	16.02	15.29

STATISTICAL ANALYSIS

Comparing the sustained release acetaminophen treatment to the immediate release acetaminophen treatment:

The first and primary goal of this investigation was to determine if the sustained release acetaminophen formulation described in chapters 1 and 2 was as effective in relieving osteoarthritis pain as the immediate release product. Each question asked in the pain and disability questionnaire had three discrete answers. It was therefore decided that the discreteness of the data violated the assumption of normality. Nonparametric analysis techniques were chosen to analyze the data. The Signed Rank Test was performed on all questions to address the differences between the SR and the IR acetaminophen treatments.

Table 3.31: Results of the Signed Rank Test Comparing the Immediate Release Acetaminophen Treatment to the Sustained Release Treatment.

QUESTION	#PREFER SR	#PREFER IR	#TIE D	P-VALUE*
1	5	5	7	1.00
2	4	7	5	1.00
3	2	2	13	1.00
4	0	1	16	1.00
5	0	0	17	-----
6	1	0	16	1.00
7	1	1	15	1.00
8	3	5	9	0.73
9	2	0	15	1.00
10	1	7	9	0.07
11	4	6	7	0.75

* p-values are two-sided and obtained from multiplying the cumulative binomial probability by two.

Interpreting the results of the sustained release acetaminophen treatment to the immediate release acetaminophen treatment:

The p-values calculated above showed no difference in the sustained release acetaminophen treatment and the immediate release treatment in all but one question. Question 5 did not provide any information to this study. As previously discussed, in retrospect it is easy to see why osteoarthritis of the knee does not affect the ability of the patient to eat. In Question 10, patients preferred the immediate release acetaminophen treatment over the sustained release acetaminophen for the pain relief.

It is possible that patients were expecting pain relief immediately after taking the tablets. If so, because of the higher peak of the immediate release formulation patients may have perceived the immediate release acetaminophen as relieving pain better than the sustained release acetaminophen. All other questions including the duration of pain relief and effect on disability questions showed that 2.6grams/day of sustained release acetaminophen was as effective as 4grams/day of immediate release acetaminophen in this population.

This is an exciting conclusion because, while the two treatments utilize the same drug, the dose and frequency of administration are significantly less for the sustained release formulation. Using only 2.6 grams of sustained release acetaminophen was as effective as using 4 grams of immediate release acetaminophen per day in reducing disability and improving the duration of pain relief. The lower amount of drug required could potentially reduce some of the risks of liver toxicity and other side effects in patients such as these that require chronic pain management with acetaminophen. The twelve hour dosing frequency that the sustained release

product provides improves the convenience of the medication and could increase compliance with the medication regimen.

Comparing the sustained release acetaminophen treatment to the baseline treatment:

The previous analysis of the questionnaire showed that the immediate release acetaminophen treatment was the same as the sustained release acetaminophen treatment in treating disability and pain relief duration. While important to this study, it is also necessary to determine if either the immediate release or the sustained release acetaminophen formulations were effective at all. It is possible that the results simply indicate that both treatments are equally poor at treating pain and improving disability in osteoarthritis patients.

To test whether or not the acetaminophen treatments were effective, the analysis described above must be repeated. This time the sustained release formulation will be compared to the baseline medication values for each questionnaire question. The baseline measurements represent a collection of different medications and treatment regimens that were currently in use by the patients before they were recruited for the study. Treatment ranged from no medication at all, to intermittent dosing with anti-inflammatory drugs and immediate release acetaminophen, to scheduled dosing with anti-inflammatory drugs, to intermittent narcotic analgesic dosing.

Table 3.32: Results of the Signed Rank Test Comparing the Sustained Release Acetaminophen Treatment to the Baseline Treatment

QUESTION	#PREFER SR	#PREFER BASELINE	TIED	P-VALUE*
1	9	1	7	0.02
2	8	3	6	0.23
3	8	4	5	0.39
4	2	1	14	1.00
5	0	0	17	-----
6	6	0	11	0.03
7	2	1	14	1.00
8	5	4	8	1.00
9	1	0	16	1.00
10	9	3	5	0.15
11	9	1	7	0.02

* p-values are two-sided and obtained from multiplying the cumulative binomial probability by two.

Interpreting the results of the sustained release acetaminophen treatment to the baseline treatment:

For the pain evaluation questions (questions 1-3) the results were encouraging. All three questions suggested that the sustained release acetaminophen treatment was a significant improvement over the baseline treatments. Patients rated their pain as being less severe on the sustained release acetaminophen treatment. The average pain score dropped from 2.20 (between level 2 = moderate and level 3 = severe) to 1.65 (between level 1 = mild to level 2 = moderate). During the four week treatment, patients described their pain as better and as occurring less often.

For the disability questions, only one of the questions showed a statistical difference between the sustained release acetaminophen treatment and the baseline treatments. This was Question 6. Recall this question evaluated how much help the

patients required to stand. The average answer after the baseline treatment was 1.53. After the sustained release treatment the score dropped to 1.12. Although both treatments fall between “I seldom need help” (level =1) and “!sometimes need help” (level =2), the improving score is encouraging. These patients often experience pain in their knees and have difficulty standing up because of the physical changes occurring secondary to the disease state. If the sustained release acetaminophen treatment can relieve at least part of the discomfort associated with the activity of standing, it can be considered successful.

The most encouraging portion of the analysis was the statistically significant improvement in the medication efficacy and duration of action questions. In both of these questions, a statistically larger number of patients felt that the sustained release acetaminophen treatments both relieved their pain and relieved the pain for a longer period of time than the baseline treatments.

Although no statistical analysis was performed on the time to walk 50 feet data, the average time after the sustained release acetaminophen treatment was 1.65 seconds less than the average time after the baseline treatments. Perhaps the reduction in time is representative of improvement that occurred because of the reduction in pain and improved duration of action of the sustained release treatment.

CONCLUSIONS

Thirty men between the ages of 44 and 76 were recruited for a double blind crossover study comparing two different acetaminophen formulations. Seventeen patients completed the study. In those seventeen patients, the estimated trough acetaminophen concentrations were 1.34mg/L and 5.11mg/L for the immediate release and sustained release formulations respectively. Estimated plasma concentrations for the sustained release formulation met and exceeded the target multiple dose plasma concentration of 5mg/L. Patients were adequately compliant with the study protocols and used appropriate amounts of the ibuprofen rescue analgesic. Twelve questions designed to evaluate pain, disability, and medication efficacy were asked at three different occasions throughout the study. Time to walk 50 feet measurements were also taken at these intervals. Signed Rank tests performed on these questions in the two formulations showed only one statistical difference between the two treatment groups regardless of the large difference in total daily dose (2.6grams/day for the SR group vs. 4 grams/day for the IR group. Patients preferred the immediate release treatment over the sustained release treatment for pain relief. Additional Signed Rank tests performed on the baseline treatments and the SR treatments showed statistically significant improvements in the patients average overall rating of their pain levels, the ability of these patients to stand without help from another person, and in the duration of pain relief that these patients received from their treatment medication. Unchanged throughout this study is the fact that these patients live with moderate to severe pain that occurs at least daily in all of these

patients. The SR treatment did manage to slightly reduce the disability due to this pain and increase the duration of pain relief that these patients experience while reducing the total acetaminophen dose to 2.6 grams per day. Follow up studies are necessary to validate these findings due to the small sample size in this study. However, preliminary results in these patients are promising.

Overall, the SR formulation succeeded in meeting the formulation goals described in Chapter 1. Improvements in duration of pain relief and steady state plasma levels of 5mg/L were achieved as a result of careful design and testing of the preparation. Incorporation of pharmacodynamic information into the pharmaceutical design process has the potential to change the development techniques of the future. The current drawback to this technique is the lack of information about the minimum effective plasma concentrations for most drugs. Whenever available, this information could be used to prepare target formulations that improve efficacy and reduce side effects in patients by allowing administration of the minimum effective amount of medication.

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CONCLUSIONS

In the past the formulation of tablets has been approached in a haphazardly or trial-and error approach. The idea of using the desired pharmacodynamic properties of the medication to formulate the tablet product has not received the attention that it deserves. This thesis successfully used the suggested minimum plasma concentrations for acetaminophen to simulate, design and formulate a sustained release acetaminophen product. Other information that contributed to the positive outcome of this thesis included knowledge of patient compliance habits and characteristics of the target disease.

Although encouraging, the results of the Phase II clinical trial described in this thesis cannot be considered conclusive without additional trials in a significantly larger number of patients. In addition, more accurate and quantitative measures of pain and disability would be desirable in the larger studies to reduce the dependence of the investigator on subjective, "hearsay" information from the patient. More quantitative measures of pain and disability would also reduce some of the statistical error in the analysis.

Future studies are also needed to examine the role of the placebo effect in the sustained release acetaminophen product. It is possible that once the placebo doses that were used in this study are eliminated, the product might "lose" some of its effectiveness because of a perceived difference in effect between the four doses per day used in this study and the two doses per day that actually contain drug. A crossover study could be developed that compared immediate release acetaminophen

1000mg four times a day, with the sustained release acetaminophen 1300mg twice a day, with and without placebo controls. That should expose any placebo effects that are confounding the data.

Sustained release acetaminophen may also have applications in other chronic disease states as well. Although primarily an inflammatory disease, rheumatoid arthritis patients may also benefit from additional pure analgesic medication. Other chronic pain disorders such as fibromyalgia, trigeminal neuralgia, chronic back pain, and chronic fatigue syndrome may also find uses for sustained release acetaminophen.

Lastly, sustained release acetaminophen has the potential to reduce the severity of acetaminophen overdoses. Most hospitals admit an average of 1-2 patients per week with some type of accidental or intentional acetaminophen overdose. Products with slower release give rescuers more time after ingestion to remove the tablets from the system and to administer the appropriate antidote. New nomograms for overdose treatment would need to be developed for these new products since the peak drug release would be delayed when compared to the immediate release products.

Rational drug formulation design has exciting implications in the field of Biopharmaceutics. Drug development often takes years. The use of pharmacodynamic information could result in drug products that are more disease state oriented. Both patients and drug companies could benefit from additional studies in this area.

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Appendix 2A

**Copy of the Approved Application for Human Trials
to the Oregon State University Committee for the
Protection of Human Subjects**

571.5

Copy of Approved Investigational Research Board Proposal from Oregon State University.

RESEARCH PROPOSAL INVOLVING HUMAN TEST SUBJECTS

This is a preliminary investigation conducted by Oregon State University College of Pharmacy Department of Pharmaceutics to evaluate a sustained released formulation of acetaminophen (Tylenol®). The information collected will be used to establish an *in vitro - in vivo* correlation for the development of a new acetaminophen formulation. An *in vitro - in vivo* correlation will allow the *in vitro* behavior of future formulations to predict *in vivo* behavior. New formulations can then be developed with a minimum of human testing.

Acetaminophen is a widely used, over-the-counter medication for analgesia and fever. It has been available to the general public for over 30 years. Acetaminophen is currently given either as an immediate release product (650-1000mg every 4-6 hours) or as an extended release product (1300mg every 8 hours). A new sustained release formulation developed in our laboratory would provide 1300mg every 12 hours. The sustained release tablets are manufactured using well known procedures and are made from Food and Drug Administration (FDA) approved ingredients.

Participants will be involved in several one (1) day test periods with a seven (7) days wash out period between them. Participants will be asked to fast for 2 hours prior to receiving a dose of acetaminophen. At specified time intervals after dosing, participants will be asked to chew a one inch square of Parafilm® for 1 minute to stimulate saliva production and to collect a saliva sample. It has been well documented in

the literature that saliva acetaminophen concentrations are directly correlated with blood acetaminophen concentrations. All operators handling samples will wear gloves in compliance with federal "universal precaution" recommendations. All operators are aware of the risks of handling bio-hazardous materials including the potential for contracting hepatitis and/or the HIV virus.

Justification: Currently available formulations of acetaminophen must be taken every 4 to 8 hours to maintain adequate drug concentrations in the blood to provide pain relief. The development of a sustained release formulation would provide extended relief from pain while minimizing the dose, and thereby the side effects of the drug. Twelve hour dosing intervals have also been shown to increase the compliance of patients. This is especially important in patients who require pain relief on a long term basis (arthritis).

Although simulation and calculations may be performed to predict the behavior of new drug formulations, there are often factors in the body that cannot be foreseen. The ultimate test of a formulation measures the change in drug concentrations in the body over the dosing interval. As acetaminophen saliva concentrations can be directly correlated with plasma concentrations, saliva data can be used as a non-invasive method of evaluating the performance of new acetaminophen formulations.

Figure 1 is a comparison of *in vitro* release rates of 3 acetaminophen formulations. The diamonds represent the dissolution of 1000mg (2 x 500mg) acetaminophen (Tylenol Extra Strength®) tablets. The filled circles show a similar curve for 1300mg (2 x 650mg) acetaminophen extended release (Tylenol ER®) caplets. Note that both of these products are completely released by 3 hours. The triangles represent the *in vitro*

dissolution profile of the sustained release formulation developed in our laboratory. Note that with this product complete release is not obtained until twelve hours.

Side-Effects: Few side effects have been reported with the use of acetaminophen in therapeutic doses (4 grams a day or less). Reported side effects of acetaminophen are dose dependant and unlikely, but can include skin rash, hives, itching, bloody or cloudy urine, difficulty in urination, sudden decrease in urine output, unexplained sore throat or fever, unusual bleeding or bruising, or unusual tiredness or weakness (see attached United States Pharmacopeia Drug Information sheet. Other symptoms may occur in overdose situations but are not expected during this study as the dosage given is below the maximum daily dose of acetaminophen (4 grams per day).

Exclusions: All test participants will be healthy, normal people with no known medical problems. Pregnant women will be excluded, even though acetaminophen is the drug of choice for analgesia in these patients, because of the inadvisability of taking any medication while pregnant if not absolutely necessary. Test subjects will be excluded from this study if any of the following are true:

1. They have shown any previous hypersensitivity to acetaminophen or to acetaminophen combination products.
2. They have renal abnormalities or known renal dysfunction.
3. They have liver abnormalities or known liver dysfunction.
4. They are currently taking any prescription or non-prescription form of acetaminophen or acetaminophen containing product.
5. They are currently taking any medication that might effect the elimination of acetaminophen (i.e. phenobarbital, phenytoin)

6. They are or expect to become pregnant during the duration of the study.
7. Persons who have ever had hepatitis B or C, who have tested positive for HIV or any AIDS virus, who have AIDS, or who are at risk for getting and spreading any AIDS virus. You are at risk if:
 - you are a man who has had sex with another man since 1977, even one time.
 - you have shared a needle, even one time, to inject drugs or medication.
 - you have taken clotting factor concentrates for a bleeding disorder such as hemophilia.
 - you have ever had a positive test for any AIDS virus or hepatitis B or C or any AIDS antibody.
 - you have had sex with any person described above.
 - you have had sex with a male or female prostitute since 1977.

Test Subjects: Test participants will be 20 healthy, normal volunteers drawn from the Oregon State University faculty, staff, and student population. Written consent of each participant will be obtained after verbal and written information is presented by a registered pharmacist.

Anonymity: All records will be kept confidential. The identity of the research participants will not be released through either oral or written transmission to any member not directly involved in the research group. Records from each subject shall be retained in the project file for three years beyond the end date of the project.

MATERIALS AND METHODS

Materials: Acetaminophen NF/USP, lot #JE321 was obtained from Spectrum Chemical Mfg Corp. Gardena, CA, magnesium stearate NF/USP, lot #KC502 was obtained from Spectrum Chemical Mfg Corp. Gardena, CA, hydroxypropylmethylcellulose (Methocel® K100M PREM CR) lot #MM92101105K was obtained from Dow Chemical Co. Midland, MI, and polyvinylpyrrolidone NF/USP from Spectrum Chemical Mfg Corp. Gardena, CA. All water used was distilled de-ionized water.

Tablets: Each tablet contains 89.0% acetaminophen, 5.0% hydroxypropylmethylcellulose (HPMC), 5.0% polyvinylpyrrolidone (PVP), and 1.0% magnesium stearate by weight. The PVP is dissolved in 0.5ml of water per tablet. The HPMC and the acetaminophen are premixed and then slowly added to the PVP solution. The resulting thick paste is extruded into noodles and dried. The dried noodles can then be broken into granules. Magnesium stearate is added to the granules and mixed to thoroughly coat the granules. Tablets are made by placing loading granules into a single punch tableting machine. Desired tablet weight is 730.0mg.

Subjects: Test participants are normal, healthy volunteers who are not currently taking any prescription or non-prescription forms of acetaminophen and have previously fasted for 2 hours or greater prior to the dose. Fasting must continue for two hours after

taking the dose. Subjects will not be allowed to eat or drink anything 5 minutes before each sample.

Design: A cross-over design will be used. Subjects are randomly assigned to one of the three formulations. After a one week wash out period, a second formulation will be given. Finally, after a second week long wash out period, the third formulation will be given.

Sampling: Saliva samples will be collected at times 0.0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 9.0, 12.0 and 24.0 hours. Each participant will chew a 1 inch square of Parafilm® for 1 minute during each sample collection to initiate adequate saliva flow. Saliva produced during the minute of chewing will then be collected for each time point and frozen for later analysis.

Solutions:

1. Acetaminophen standards of 0.4, 1.0, 2.0, 4.0, 6.0, 8.0, 10.0, and 16.0 µg/ml in water will be used. All standards were made by aliquot dilution of a 1000 µg/ml stock solution.
2. Internal standard solution of 40 µg/ml 7-beta- hydroxyethyl- theophylline.
3. Mobile phase of 30% methanol and 70% water.

Assay: All saliva samples will be frozen prior to use (-20°C). Aliquots of saliva will be centrifuged at 14,000 rpm for 2 minutes to pelletize particulates. One hundred fifty µl of supernatant will be then pipetted into a micro centrifuge tube. One hundred

fifty μ l of the internal standard (7-beta-hydroxyethyl theophylline) will be added and the mixture vortexed for 30 seconds.

Chromatography: Samples will be injected onto the High Pressure Liquid Chromatograph (HPLC) using an automatic sampler (WISP 712; Waters Assoc.) Separations of components is obtained by using a C18-Reverse Phase column. The mobile phase of 30% methanol/70% water will be delivered at a rate of 0.8ml/min (M-6000A Solvent Delivery System) and samples will be monitored at 254nm with a model 440 absorbance detector. Injection volume will be set at 20 μ l.

Quantitation: Standard curves are run daily. Quantitation of the sample curves is based on peak height ratios using the internal standard peak as the divisor. The resulting calibration curve is fitted using PSI-PLOT® to a least-squared linear regression line. The equation is then used to convert peak ratios into corresponding concentrations.

CONSENT FORM

This study is a research project conducted by the Department of Pharmaceutics, College of Pharmacy, Oregon State University. The purpose of this study is to evaluate a sustained release formulation of the drug acetaminophen. Acetaminophen (Tylenol®) is a non-prescription medication that is used to treat mild pain and fever. Currently the medication must be taken 3-4 times a day. The new formulation that you will take is designed to release slowly over a 12 hours period.

Your participation will involve one (1) day per week for three (3) weeks (3 days total with a 7 day wash out period between doses). You will be asked not to eat for at least 2 hours prior to the study and after the dose, and to refrain from eating or drinking for 5 minutes before each sample time. After dosing, you will be given a time sheet for recording sample times, tubes in which to collect saliva samples, and 1 inch squares of Parafilm®. You must chew the square of Parafilm® for 1 minute during each sample collection to stimulate saliva production. A total of 12 saliva samples will be collected over the 24 hour period.

Side Effects: If you have previous taken Tylenol® or Tylenol Extra Strength® with no untoward effects, you should not experience any difficulty with this product. On rare occasions, people taking acetaminophen develop a rash or drowsiness. Any possible side effects or abnormal symptoms that you experience should be reported to the study investigator immediately.

Exclusions: You are excluded from this study if you are not a normal, healthy adult free of known liver or kidney damage or if you are pregnant or plan to become pregnant during the study period. You are also excluded if you have ever shown any sensitivity to acetaminophen or acetaminophen containing products. Subjects should not be taking any medications that might effect the elimination of acetaminophen (i.e. phenobarbital, phenytoin, etc.)

Anonymity: All records will be kept confidential. The identity of the research participants will not be released through either oral or written transmission to any member outside of the research group.

Confidentiality: I have been informed that because this study involves articles regulated by the FDA (Food and Drug Administration), the FDA may choose to inspect records identifying me as a subject in this investigation.

Withdrawal: Participation in this study is voluntary, you may withdraw at any time. There is no penalty if you withdraw from the study for any reason: exclusion, competing commitments, drug reaction, loss of interest. No loss of benefits, standing, or relationship with the research group or Oregon State University will result. Questions about the research, your rights, or research related injuries should be directed to James Ayres, Ph. D., at 737-5787, or Carol Keller at 737-5771.

I have read the consent form above and I understand the information presented. I understand that the University does not provide a research subject with compensation or medical treatment in the event that the subject is injured as a result of participation in the research project. My participation is voluntary, and refusal to participate will involve no penalty or loss or benefits to which I am otherwise entitled, and that I may discontinue participation at any time without penalty or loss of benefits to which I am otherwise entitled.

Signature _____ Date _____

DATA SHEET

Please record the time of each sample collection to the nearest 5 minutes.

Time the dose was taken: _____

Hours after dose

Time sample was taken

0.0

0.5

1.0

1.5

2.0

3.0

4.0

5.0

6.0

9.0

12.0

24.0

Signature: _____ Date: _____

SUBJECT DATA SHEET

Data for Subject: _____ Identifier: _____

Formulation: _____

<u>Hours after dose</u>	<u>Actual time</u>	<u>Concentration</u>
-------------------------	--------------------	----------------------

0.0

0.5

1.0

1.5

2.0

3.0

4.0

5.0

6.0

9.0

12.0

24.0

Signature: _____ Date: _____

Appendix 2B:

**Raw Saliva Concentration vs. Time Data for Four Test Formulations in
10 Healthy Human Subjects**

Figure 2B.1: Raw Saliva Concentration Vs Time Data for 10 Subjects Taking 1000mg of Tylenol Extra Strength

TIME (hr)	SUBJECT 1	SUBJECT 2	SUBJECT 3	SUBJECT 4	SUBJECT 5
0.5	5.91	12.21	6.64	1.64	7.35
1.0	15.22	10.95	7.61	10.61	6.41
1.5	11.95	10.13	6.89	9.02	5.11
2.0	10.38	9.57	5.82	6.46	-----
3.0	3.45	6.43	5.11	4.59	3.40
4.0	1.39	4.08	3.39	2.86	2.89
5.0	1.34	2.91	-----	1.72	1.72
6.0	0.49	2.26	4.00	0.89	0.82
9.0	0.13	0.76	3.01	0.35	0.42
12.0	0.05	0.23	2.71	0.17	0.38
24.0	0.01	-----	1.24	0.13	0.25

TIME (hr)	SUBJECT 6	SUBJECT 7	SUBJECT 8	SUBJECT 9	SUBJECT 10
0.5	15.88	16.45	7.55	16.66	-----
1.0	11.78	14.64	6.91	14.74	11.59
1.5	9.20	11.74	6.30	13.65	-----
2.0	7.05	11.19	4.34	12.59	7.54
3.0	5.43	7.78	2.22	10.54	6.61
4.0	4.21	3.84	2.12	8.46	4.18
5.0	3.94	3.76	1.87	7.15	3.69
6.0	2.65	1.99	1.41	5.14	3.50
9.0	2.20	1.53	0.60	3.92	1.928
12.0	1.26	0.72	0.42	2.99	1.48
24.0	0.70	0.03	0.37	1.50	0.82

---- Line indicates missing data points. Time zero data points were not used in the fitting because of program constraints.

Figure 2B.2: Raw Saliva Concentration Vs Time Data for 10 Subjects Taking 1300mg of Tylenol Extended Relief

TIME (hr)	SUBJECT 1	SUBJECT 2	SUBJECT 3	SUBJECT 4	SUBJECT 5
0.5	1.12	8.199	8.29	1.22	10.76
1.0	8.33	10.23	9.075	13.61	9.47
1.5	14.34	14.04	7.46	-----	8.54
2.0	10.06	11.78	4.61	15.16	6.91
3.0	8.01	9.84	3.6	8.89	4.04
4.0	6.56	8.44	2.55	7.33	2.97
5.0	4.54	7.32	1.89	4.54	2.56
6.0	3.49	5.36	1.14	2.6	1.64
9.0	0.54	3.56	0.47	1.84	0.94
12.0	0.31	0.68	0.1	1.25	0.86
24.0	0	037	0.03	1.15	0.37

TIME (hr)	SUBJECT 6	SUBJECT 7	SUBJECT 8	SUBJECT 9	SUBJECT 10
0.5	8.43	8.36	14.64	6.25	-----
1.0	8.82	15.11	14.88	14.7	10.67
1.5	13.25	14.85	14.81	13.85	-----
2.0	2.04	14.69	14.63	11.21	9.87
3.0	10.56	12.66	9.83	9.61	7.05
4.0	8.02	6.96	8.29	7.42	3.25
5.0	5.32	6.17	5.45	7.09	3.13
6.0	5.18	4.16	3.12	7.09	2.56
9.0	2.4	-----	2.39	3.44	1.326
12.0	0.61	3.011	0.81	1.12	-----
24.0	-----	2.32	0.45	0.02	0.01

---- Line indicates missing data points. Time zero data points were not used in the fitting because of program constraints.

Figure 2B.3: Raw Saliva Concentration Vs Time Data for 10 Subjects Taking 1300mg of the 5% HPMC Sustained Release Acetaminophen Formulation.

TIME (hr)	SUBJECT 1	SUBJECT 2	SUBJECT 3	SUBJECT 4	SUBJECT 5
0.5	1.45	1.36	0.62	0.47	1.44
1.0	3.36	2.54	1.55	1.53	2.49
1.5	4.45	3.88	2.64	2.63	2.69
2.0	5.03	5.36	2.67	3.14	2.75
3.0	5.52	7.11	5.39	7.96	6.33
4.0	6.69	9.43	5.52	10.41	5.03
5.0	4.97	5.87	3.82	11.32	2.92
6.0	4.37	4.04	3.74	6.05	2.11
9.0	3.52	3.46	3.12	3.99	0.77
12.0	3.34	2.31	2.48	1.76	0.44
24.0	1.39	1.64	2.07	1.46	-----

TIME (hr)	SUBJECT 6	SUBJECT 7	SUBJECT 8	SUBJECT 9	SUBJECT 10
0.5	2.40	1.65	0.31	2.13	2.00
1.0	5.95	3.00	1.75	2.22	2.46
1.5	6.15	3.71	2.34	3.73	4.30
2.0	6.28	4.37	2.69	4.27	5.37
3.0	7.87	6.14	3.13	4.90	6.63
4.0	6.39	8.29	3.69	4.89	5.63
5.0	6.21	5.88	5.56	4.69	4.18
6.0	4.00	4.44	3.96	4.59	3.42
9.0	3.58	-----	0.75	3.89	2.67
12.0	3.31	-----	0.60	3.65	-----
24.0	1.88	0.2	0.16	1.93	0.01

---- Line indicates missing data points. Time zero data points were not used in the fitting because of program constraints.

Figure 2B.4: Raw Saliva Concentration Vs Time Data for 10 Subjects Taking 1300mg of the 7.5% HPMC Sustained Release Acetaminophen Formulation.

TIME (hr)	SUBJECT 1	SUBJECT 2	SUBJECT 3	SUBJECT 4	SUBJECT 5
0.5	0.74	2.43	0.81	0.13	0.83
1.0	1.02	3.32	1.12	0.22	1.21
1.5	1.23	3.56	1.17	0.34	1.60
2.0	1.60	4.02	1.30	0.53	2.94
3.0	1.82	4.08	1.45	0.76	1.39
4.0	1.33	2.78	1.61	1.53	0.88
5.0	1.30	2.50	1.64	2.66	0.84
6.0	1.26	1.94	1.65	2.03	0.65
9.0	0.69	1.85	1.75	0.86	0.61
12.0	0.51	1.0	1.60	0.00	0.60
24.0	0.40	0.46	1.24	-----	0.44

TIME (hr)	SUBJECT 6	SUBJECT 7	SUBJECT 8	SUBJECT 9	SUBJECT 10
0.5	0.40	-----	0.31	1.03	2.71
1.0	1.07	1.59	1.14	1.23	2.79
1.5	1.22	2.27	2.95	1.53	2.85
2.0	2.42	2.95	4.11	2.01	3.15
3.0	3.57	3.20	3.73	4.11	3.60
4.0	3.97	3.11	3.43	2.70	4.48
5.0	3.41	-----	3.13	2.49	4.10
6.0	3.19	2.68	-----	1.78	-----
9.0	2.78	2.49	2.99	1.71	2.89
12.0	2.20	2.21	2.08	1.50	2.74
24.0	1.02	1.11	0.54	0.39	1.18

---- Line indicates missing data points. Time zero data points were not used in the fitting because of program constraints.

APPENDIX 3A:

Copy of the Application to the OSU Investigational Research

Board for the Protection of Human Subjects.

Comparison of Immediate and Sustained Release Acetaminophen for Symptomatic Relief of Pain in Osteoarthritis Patients

Significance: This is a phase II clinical trial of a new sustained release formulation of acetaminophen. Phase I consisted of testing the new formulation in healthy volunteers and has been completed. Phase II involves limited testing of the new formulation in patients with the disease state that the drug was designed to treat. In this case, that includes patients with osteoarthritis of the knee. Preliminary studies suggest that the chronic pain due to osteoarthritis can be adequately relieved by this new sustained release acetaminophen dosage form as well or better than the conventional immediate release acetaminophen formulations.

Acetaminophen is a widely used, over-the-counter medication for analgesia and fever. It has been available to the general public for over 30 years without a prescription. Acetaminophen is currently given either as an immediate release product (650-1000mg every 4-6 hours) or as an extended release product (1300mg every 8 hours). A new sustained release formulation developed in our laboratory would provide 1300mg every 12 hours. The sustained release tablets are manufactured using well known procedures and are made from Food and Drug Administration (FDA) approved ingredients. Acetaminophen has been shown to be effective in relieving pain due to osteoarthritis, however the current dosing interval is inconvenient for patients who require pain relief on a chronic basis. The new 12 hour formulation would relieve pain while minimizing the overall daily dose and maximizing convenience.

Patients will be enrolled in this study to compare a new long acting formulation of acetaminophen to the original immediate release form for relief of pain in people with osteoarthritis. Each participant will be asked to take both medications. The participants will take one medication for four weeks, have a one week acetaminophen-free period, and then take the other medication for four weeks. Ibuprofen tablets are provided to the patients as a rescue analgesic. They may take 400mg of ibuprofen every 6 hours for pain not relieved by the current treatment and during the acetaminophen-free period. The order of the medications will be randomly assigned. One medication is the currently available form of acetaminophen. It is taken as two 500mg tablets every six hours. The second medication is a new long acting form that only needs to be taken every twelve hours. Tablets that appear similar to the long acting form but contain no drug (placebos) are provided for two additional doses. The placebo tablets allow both treatments to appear to be identical. Neither the investigator nor the participant will know which medication is being taken.

During the first visit, participants will be asked to answer a questionnaire that will provide information about themselves (age, weight, height) and the pain that they have. They will also be asked to walk 50 feet. The time it takes to walk 50 feet will be used to help measure pain. At this first visit, participants will also receive their first packet of medication. They will receive four identical cards of medication, one for each week. Participants will be asked to take two tablets of the study medication four times a day.

After four weeks of the first medication, participants will be asked to return to the clinic. The questions about pain and the time to walk 50 feet will be repeated. Participants will be provided with the second packet of medication. Participants will be

asked to wait for one week and repeat the four week trial, again taking the medication four times a day. Participants will also be asked to spit into a small tube so that the level of drug can be measured in the body.

At the completion of the second four week period, participants will be asked to return to the clinic for a third and last evaluation. The questions about pain and the walking test will be repeated. Participants will be asked to spit into a small tube again to measure the level of the drug in the body.

Justification: Currently available formulations of acetaminophen must be taken every 6 to 8 hours to maintain adequate drug concentrations in the blood to provide pain relief. The development of a sustained release formulation would provide extended relief from pain while minimizing the dose, and thereby the side effects of the drug. Twelve hour dosing intervals have also been shown to increase the compliance of patients. This is especially important in patients who require pain relief on a long term basis (arthritis).

Side-Effects: Few side effects have been reported with the use of acetaminophen in therapeutic doses (4 grams a day or less). Reported side effects of acetaminophen are dose dependant and unlikely, but can include skin rash, hives, itching, bloody or cloudy urine, difficulty in urination, sudden decrease in urine output, unexplained sore throat or fever, unusual bleeding or bruising, or unusual tiredness or weakness (see attached United States Pharmacopeia Drug Information sheet. Other symptoms may occur in overdose situations but are not expected during this study as the dosage given is below the maximum daily dose of acetaminophen (4 grams per day).

Benefits: Participants may benefit from their participation in this study in that the pain due to their osteoarthritis may be reduced or eliminated. It is also possible that the pain will not be controlled by the use of this medication, and it will then be necessary to take the ibuprofen provided for additional pain control.

Alternative Treatments: If participants do not choose to participate in this study, other drugs are available for the treatment of osteoarthritis. They include non-steroidal-anti-inflammatory medications such as ibuprofen, aspirin, naprosyn and narcotic pain relievers such as Darvocet N-100®, Vicodin®, and Tylenol #3®.

Exclusion/Inclusion Criteria

Inclusion criteria includes:

Participants in this study should:

1. Be age 40-75, inclusive.
2. Be able to walk 50 feet without assistive devices (canes, walkers, etc.)
3. Have previously diagnosed (history > 3 months) osteoarthritis of the knee and a history of pain due to the disease.

Exclusion criteria includes:

1. Trauma to or intra-articular injections in the affected joint(s) in the last three months.
2. Previous history of sensitivity to acetaminophen or acetaminophen containing products.
3. Previous history of sensitivity to ibuprofen or ibuprofen containing products.

4. Previous history of angina pectoris, congestive heart failure, chronic obstructive pulmonary disease, peripheral vascular disease, fibromyalgia, bursitis, inflammatory arthritis, or any other musculoskeletal condition that could cause concomitant leg pain.

5. Previous history of hepatic insufficiency.

6. Previous history of renal insufficiency.

7. Patients with history of gastric ulceration or who are presently receiving thrombolytic therapy.

8. Pregnancy.

9. Persons who have ever had hepatitis B or C, who have tested positive for HIV or any AIDS virus, who have AIDS, or who are at risk for getting and spreading any AIDS virus. You are at risk if:

- you are a man who has had sex with another man since 1977, even one time.

- you have shared a needle, even one time, to inject drugs or medication.

- you have taken clotting factor concentrates for a bleeding disorder such as hemophilia.

- you have ever had a positive test for any AIDS virus or hepatitis B or C or any AIDS antibody.

- you have had sex with any person described above.

- you have had sex with a male or female prostitute since 1977.

Test Subjects: Participants will be recruited from the Veterans Administration Hospital in Portland, OR in conjunction with Dr. Theresa Bianco Pharm. D. and Dr. Minot Cleveland M.D.. Potential patients will be identified by chart review and will be approached regarding their participation in person.

Anonymity: All records will be kept confidential. The identity of the research participants will not be released to any member not directly involved in the research group. Each participant will be assigned a subject number and all references to participants will be by subject number. Subjects will be advised that because the study involves an investigational new drug, all records are subject to review by the Food and Drug Administration. Records from each subject will be retained in the project file at the Veterans Administration Hospital for three years beyond the end date of the project.

Consent Form: A copy of the proposed consent form is included in Appendix A. This form is in the Veterans Administration Hospital format and is currently being reviewed by the Investigational Research Board of that institution. Any changes required to obtain approval at the VA institution will be reported and will be subject to secondary approval by Oregon State University.

MATERIALS AND METHODS

Manufacture of Sustained Release Tablets:

Ingredients and Excipients: A licensed pharmacist at the pharmaceuticals laboratory at Oregon State University will undertake production of the sustained release tablets. The following materials will be used in the production of the tablets. They include acetaminophen NF/USP (Spectrum Chemical MFG. Corp., Gardena, CA) Lot JE321, polyvinylpyrrolidone K-30 NF/USP (Spectrum Chemical MFG. Corp., Gardena, CA) Lot KD186 as a tablet binder, magnesium stearate NF/USP (Spectrum Chemical MFG. Corp., Gardena, CA) Lot KC502 as a tableting lubricant/glidant, and Methocel®

K100M PREM CR brand of hydroxypropylmethylcellulose (Dow Chemical Co. Midland, MI) Lot MM92101105K as a sustained release matrix substrate. Avicel® microcrystalline cellulose NF/USP (FMC Corporation, Philadelphia, PA) Lot X129 is used in place of the acetaminophen in the placebo tablets. Water used during the granulation process is distilled and then passed through a de-ionization system.

Cleaning: All surfaces are cleaned prior to each production run. All equipment and the surrounding area will be cleaned with Alconox®, rinsed with distilled, deionized water, and swabbed with 95% ethanol. All surfaces will be free of soap residue or films. The process will be attended at all times.

Manufacturing Process: Each tablet contains 89.0% acetaminophen, 5.0% hydroxypropylmethylcellulose (HPMC), 5.0% polyvinylpyrrolidone (PVP), and 1.0% magnesium stearate by weight. The desired amount of PVP is dissolved in 0.75ml water per tablet. The HPMC and the acetaminophen are premixed and slowly added to the PVP solution. The resulting thick paste is extruded into noodles onto a flat, plastic wrap covered surface and allowed to dry overnight at room temperature. The dried noodles are mechanically broken up into granules using a mortar and pestle and sieved through a succession of sieves. Granules that pass through a 14 mesh sieve but are retained on a 60 mesh sieve are used. Granules not within the prescribed range are discarded. Magnesium stearate is then added to the granules and mixed to thoroughly coat the granules. Tablets are made from the granules by loading the mixture into a single punch tableting machine (Chemical and Pharmaceutical Industry Co., New York, NY, Model TPK-12). Ejected

tablets are 12mm in diameter with a 4mm belly band and curved faces. One face of the tablet is scored across the middle and bears the imprint 427 OPD. Desired tablet weight is 730mg. Each batch produced will be assigned sequential lot numbers.

Placebo tablets are made by replacing the acetaminophen in the tablets with Avicel®. Granulation of the placebo tablets is not necessary as the Avicel® is already granular. The four ingredients are dry mixed and loaded into the single punch tableting machine to produce tablets that are identical to the study medication in appearance and weight.

Labeling: Finished tablets will be stored at room temperature in amber vials until packaging. Each vial will bear the following label:

INVESTIGATIONAL DRUG
Acetaminophen Sustained Release Tablets
650mg
Date
Lot

To help assess compliance, the treatment medications will be placed in unit dose cards. Each card holds a single week's worth of medication. Each treatment will last 4 weeks. All four cards will be dispensed at once. The medication will be placed in REDI-PAK® compliance cards and will be labeled for use.

OREGON STATE UNIVERSITY
COLLEGE OF PHARMACY
INVESTIGATIONAL ACETAMINOPHEN STUDY

PATIENT NUMBER 1
TREATMENT 1
WEEK 1

	DOSE 1	DOSE 2	DOSE 3	DOSE 4
S				
U				
N				
M				
O				
N				
T				
U				
E				
S				
W				
E				
D				
T				
H				
U				
R				
F				
R				
I				
S				
A				
T				

Patients will be randomly assigned in a crossover fashion to one of two treatments. Each treatment involves the patient taking 2 tablets four times a day for four weeks. After a week washout period each patient is crossed over to the second treatment. For one treatment the dose packets will contain 2 X 500mg immediate release tablets. For the other treatment the dose packets will contain two doses of the sustained release formulation (Dose 1 and Dose 3) and two doses of placebo tablets (Dose 2 and Dose 4). Neither the patient nor the investigator will know which treatment the patient is currently taking.

Tablet Characterization: Each batch of tablets produced will be evaluated for hardness and friability. Tablet hardness will be measured using a Strong-Cobb hardness tester. Tablets with hardness values of less than 4kg will be considered unacceptable and will be discarded. Friability will be tested using a Roche Friabilator. Five tablets from each batch will be tested for 100 rotations. Tablet samples that lose greater than 1% of their weight will be considered to be unacceptable and will be discarded. Each tablet batch will also be weighed and an average tablet weight recorded.

Tablet Dissolution: Six tablets from each batch will be evaluated using a USP dissolution (Paddle Method) test. For the first two hours each tablet will be exposed to 900ml of enzyme-free simulated gastric fluid (pH = 1.4). Samples will be taken from the vessels with replacement at 20 minutes, 40 minutes, 1 hour, 1 hour and 20 minutes, 1 hour and 40 minutes, and 2 hours. After two hours the fluid is filtered through No. 1 filter paper and the particles retained. The particles and the filter paper will then be exposed to 900ml of enzyme-free simulated intestinal fluid (pH = 7.4) for the remaining 22 hour period. Samples will be taken with replacement at 3 hours, 4 hours, 6 hours, 9 hours, 12 hours, and 24 hours. Samples will be diluted 1:100 with distilled, deionized water and analyzed at 244nm in a Hewlett Packard variable wavelength UV-VIS spectrophotometer equipped with a sipper cell. Standard solutions of acetaminophen in distilled, deionized water will be used to correlate absorbance to concentration. Previous experience has indicated that interference from polymers and or other excipients that may be present in the dissolution medium is negligible.

Dissolution will also be performed on the commercial acetaminophen products for comparison purposes. By design, the immediate release commercial formulation should rapidly dissolve in the gastric fluid. Samples will therefore be taken in gastric fluid only, unless dissolution is incomplete in the first two hours. Samples will be taken with replacement at 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 40 minutes, 60 minutes, 75 minutes, 90 minutes, 105 minutes and 120 minutes.

Procedure: After signed consent is obtained and inclusion/exclusion criteria are met, patients will undergo an initial evaluation. A history and disease characterization will be performed including height, weight, and age. An initial evaluation of the type and duration of pain in the patient will be assessed using modified Stanford Health Assessment Questionnaire (HAQ) pain scores (Appendix B) and time to walk 50 feet.

Enrolled patients will be randomly assigned to one of two groups. Each group will be asked to take two tablets four times a day. Group 1 will take two 500mg acetaminophen tablets four times a day. Group 2 will take two 650mg sustained release tablets twice a day alternating with 2 identical placebo tablets for the remaining two doses per day. Doses will be unit dosed to help assess compliance. Patients will be asked to continue the dosing regimen for four weeks. Compliance will be assessed by tablet count. Ibuprofen 200mg tablets will be provided to patients as a rescue analgesic. Patients will be asked to record their usage of the rescue analgesic. A maximum of 400mg of ibuprofen may be taken every 6 hours. At the end of the four week study period, patients will be asked to repeat the initial evaluation of their pain. Patients will also be asked to provide a saliva sample at the time of reassessment just prior to the final dose of the

medication to assess compliance and to evaluate the relationship of saliva acetaminophen concentrations to pain control. After a 7 day washout period, patients will be crossed over to the second treatment. After a 4 week period, the patients will return for a third and final evaluation.

Laboratory analysis: Saliva samples will be collected in 10ml plastic sample tubes and immediately frozen at 4°C until analysis. Samples are then thawed, centrifuged at 3000 rpm for 10 minutes, and the supernatant refrozen. Samples are re-thawed, re-centrifuged, and 150µl of the supernatant is transferred to a microcentrifuge tube. A 150µl aliquot of 7-beta-hydroxyethyl-theophylline is then added as an internal standard. The samples are centrifuged a third time and transferred to 1ml high pressure liquid chromatography (HPLC) tubes for analysis. Samples will be run in duplicate to verify acetaminophen concentrations.

Data Analysis: Data collected on pain control will be analyzed using analysis of variance. Data will be analyzed as a randomized block design with factors included in the model for treatment order and carryover effects. Correlation between saliva acetaminophen concentrations and pain control will also be analyzed using an analysis of variance.

Initial Demographic Information**Visit 1****To be administered by the Investigator**

Name _____

Age _____

Sex _____

Height _____

Weight _____ lbs.
_____ kg.How long have you been diagnosed with osteoarthritis? _____
_____Which joint(s) are affected by the osteoarthritis? _____

_____Do you usually have pain associated with your illness? _____

_____What medication do you normally take to relieve this pain? _____

_____Does this product adequately relieve your pain? _____

_____Have you taken Tylenol® or Tylenol® containing products in the
last 7 days? _____

Have you ever had any problems or side effects while taking Tylenol® or Tylenol® containing products? YES NO

If so, what? _____

Have you ever had any problems or side effects while taking Advil®, Motrin®, or ibuprofen containing products? YES NO

If so, what? _____

What medications have you taken in the past for your osteoarthritis? _____

What prescription medications do you currently take? _____

What non-prescription medication do you take. Include vitamin preparations. _____

Inclusion/Exclusion Criteria

Do you have a history of:

- | | | |
|--|-----|----|
| 1. Trauma to the affected joint in the last 3 months | YES | NO |
| 2. Corticosteroid injections in the last 3 months | YES | NO |
| 3. Angina | YES | NO |
| 4. Congestive Heart Failure | YES | NO |
| 5. Chronic Obstructive Pulmonary Disease | YES | NO |
| 6. Peripheral Vascular Disease | YES | NO |
| 7. Fibromyalgia | YES | NO |
| 8. Bursitis | YES | NO |
| 9. Rheumatoid Arthritis | YES | NO |
| 10. Kidney Problems | YES | NO |
| 11. Ulcers | YES | NO |

Pain Evaluation Visit 1 2 3

Subject _____

Treatment _____

How would you rate your overall pain during the last 4 weeks?

1	2	3
mild	mod	severe

How would you describe the change in your pain in the last 4 weeks?

1	2	3
better	no change	worse

My pain is best described as:

1	2	3
periodic	daily	constant

I need help from another person to do the following things:

	Seldom	Sometimes	Often
Dress	1	2	3
Eat	1	2	3
Stand up	1	2	3
Walk	1	2	3
Climb stairs	1	2	3
Clean House	1	2	3

The pain medication that I have been taking for the last 4 weeks relieves my pain -

Seldom	Sometimes	Often
1	2	3

The pain relief lasts for the entire time between doses

Seldom	Sometimes	Often
1	2	3

List any side effects or problems with the medication that you have been taking for the last 4 weeks.

Time to walk 50 feet _____

Other Approvals:

1. Investigation New Drug Application was filed December 5, 1995. Approval is pending. The review and approval process is being hindered by the governmental shutdown. Unspecified changes have been requested. Details are expected Jan 15, 1996.
2. Investigational Review Board Application with the Veterans Administration Hospital was filed Dec 23, 1995. Approval is pending. Review is scheduled for the first Wed of January, but may also be effected by the governmental shutdown.

APPENDIX 3B:

Copy of the Investigation Review Board application to the Veterans

Administration Hospital Human Studies Committees

Purpose: You have been asked to participate in a research study to determine if a new long acting formulation of acetaminophen (Tylenol®) can control your osteoarthritis (joint) pain. You have been asked to participate in this study because you have been diagnosed with osteoarthritis and have had pain because of this disease. Acetaminophen has been previously shown to be effective in treating pain due to osteoarthritis but it has to be taken four times a day. A new longer acting form of the drug would allow it to be taken only two times a day. This study is important because it will help evaluate new form of the drug and how well it works. This study will last for 10 weeks and will require three 1-hour visits.

Procedures: If you agree to participate in this study, we will contact your doctor to obtain permission. Once permission from your doctor is obtained, you will be asked to stop taking your usual pain medication for the duration of this study. One week after stopping your usual pain medication, you will come to the clinics at the Veterans Administration Hospital. Ibuprofen tablets (200mg) will be provided for pain during this time. You will be asked to keep track of how many ibuprofen tablets that you use. A maximum of two ibuprofen tablets three times a day will be allowed. You will be asked not to take the ibuprofen for 12 hours before each visit.

At the first visit, you will be asked to complete a questionnaire about yourself and the type of pain that you have. In addition, you will be asked to walk 50 feet to evaluate how well you can move. You will then be given a study medication packet. For four weeks, you will be asked to take 2 tablets of your study medication four times a day. You will be taking either two short-acting acetaminophen tablets (500mg each) four times a

day, or two long acting acetaminophen tablets (650mg each) alternating with two placebo tablets. A placebo is a tablet that contains no active drug. Neither you nor the investigators will know which study medication you receive. Ibuprofen tablets (200mg) will be provided for pain not relieved by the study medication. You will be asked to keep track of how many ibuprofen tablets that you use. A maximum of two ibuprofen tablets three times a day will be allowed. After the four week period you will be asked to return to the center and repeat the questionnaire and walking test. In addition, you will be asked to provide a saliva sample. The saliva samples will tell us how much medication is in the blood without having to actually draw blood. At this visit, you will be provided with the other type of medication to take for a second four week period. You must wait a week for the effects of the first medication to wear off before you begin taking the second medication. Ibuprofen will be provided for pain relief during the week between medications. Again, at the end of the four week period you will be asked to repeat the questionnaire and walking test.

Expected Discomfort or Inconvenience: Care has been taken to make this study as easy as possible for you. However, you will be expected to make three total visits to the clinic to pick up your study medication and to fill out your questionnaires. The visits may represent an inconvenience to some people. In addition, the walking test may cause some discomfort in those people who are not use to walking that distance. The discomfort will be short-lived and we expect any discomfort to be relieved by the medication that is provided.

Risks and Discomforts: There may be adverse reactions involved in participating in this study. The most common reaction is sleepiness. Very rarely, acetaminophen can result in a rash or hives. This means that you are allergic to the medication. You should stop taking the medication and immediately inform one of the study investigators. Your symptoms will be treated and the study will be stopped. Acetaminophen can cause liver problems, nausea, vomiting, and kidney problems. The doses in this study are much less than the doses that cause these problems, but if nausea or vomiting develop, you may be unusually sensitive to the medication and the study will be stopped.

The most common side effect of the ibuprofen is stomach upset. It can also cause a rash or hives. This means that you are allergic to the medication. You should stop taking the medication and immediately inform one of the study investigators. Ibuprofen can also cause ulcers, bleeding problems, and kidney problems, especially if taken in doses higher than recommended. The risk of adverse reactions with either acetaminophen or ibuprofen is increased by the use of alcohol.

Benefits: You may benefit from your participation in this study in that the pain due to your osteoarthritis may be reduced or eliminated. It is also possible that your pain will not be controlled by the use of this medication, and it will then be necessary to take the ibuprofen that has been provided for additional pain control.

Alternative Treatments: If you do not choose to participate in this study, other drugs are available for the treatment of osteoarthritis. They include non-steroidal-anti-

inflammatory medication like ibuprofen, aspirin, naproxen, and narcotic pain relievers such as Vicodin® and Tylenol #3®.

Exclusions: You should not participate in this study if you have shown previous side effects from Tylenol® or other acetaminophen containing combinations. You should not participate in this study if you have shown previous side effects to Motrin®, Advil®, or other forms of ibuprofen. You should not participate in this study if you have had recent (last 3 months) trauma to the affected joint or injections into the joint. Pregnant women will not be allowed to participate in this study. Although the medication will not harm the child, it is not a good idea to be taking any unneeded medication if you are pregnant. You should be able to walk 50 feet without assistance or assistive devices (canes, walkers, etc.) You should not take the study medication if you have liver or kidney disease. You should not participate in this study if you have had an active ulcer in the last 12 months or if you consume greater than 2 alcohol containing beverages per day. You will not be allowed to participate if you have a documented history of alcoholism because you are at increased risk for adverse side effects.

Withdrawal from the Study: Your participation in this study is voluntary, and you may withdraw from this study at any time without prejudice to yourself or to any future medical care with this institution or with the Department of Veterans Affairs(VA).

You may be removed from the study without your consent if your doctor decides that this is in your best interest, or if you fail to follow the study schedule (such as not taking

your assigned medication). Follow-up visits may still be recommended after your withdrawal.

Costs and Compensation: The investigators will pay any medication costs involved in this study. You will not be charged for your participation in this study. Your participation in this study is free of charge. You will receive no money for participating in this study.

Liability: Every reasonable effort to prevent any injury that could result from this study will be taken. In the event of physical injury resulting from the study, medical care and treatment will be available at this institution. For eligible veterans, compensation damages may be payable under 38 USC 251 or, in some circumstances, under Federal Tort Claims Act. For non-eligible veterans and non-veterans, compensation would be limited to situations where negligence occurred and would be controlled by the provisions of the Federal Tort Claims Act. For clarification of these laws, contact District Counsel at (503)326-2441. You have not waived any legal rights or released the hospital or its agents from liability for negligence by signing this form.

Any patient participating in a study at the Department of Veterans Affairs Medical Center, Portland Oregon is encouraged to contact Dr. Dennis Mazur, Chairman, Subcommittee on Human Subjects, to discuss any issues related to their research participation. Dr. Mazur can be reached through the Research Service (503) 220-8262 extension 6620.

Your signature below indicates that you understand that the Department of Veterans Affairs Medical Center, your investigators, and the sponsors of this research study bear no responsibility for any costs you may incur at other hospitals, clinics, or care institutions related to this study or to any of your medical conditions.

Signature: _____ Date: _____

Confidentiality: The results of your participation in this study may be used for publication or for scientific purposes, but your identity will not be disclosed unless you give separate, specific consent to this, or unless required by law. I have been informed that because this study involves articles regulated by the FDA (Food and Drug Administration), the FDA may choose to inspect records identifying me as a subject in this investigation.

Other: Registered Pharmacists Theresa Bianco, Pharm. D. (273-5398), and Carol Keller, R. Ph. (737-7776) have offered to answer any questions that you may have. You will receive a copy of this consent form. Your signature below indicates that you have read the foregoing and agree to participate in the study.

OREGON STATE UNIVERSITY
INVESTIGATIONAL ACETAMINOPHEN PROTOCOL SUMMARY

Objective: The specific aim of this study is to compare the effectiveness of a new sustained release formulation of acetaminophen with currently available acetaminophen products for the relief of pain due to osteoarthritis.

Research Plan: This study is a randomized, double blind, placebo controlled cross-over study. The study population will consist of patients with previously diagnosed osteoarthritis of the knee.

Methodology: After signed consent is obtained and inclusion/exclusion criteria are met, patients will undergo an initial evaluation. A history and disease characterization will be performed including height, weight, and age. An initial evaluation of the type and duration of pain in the patient will be assessed after a one week washout period using modified Stanford Health Assessment Questionnaire (HAQ) pain scores and time to walk 50 feet. Enrolled patients will be randomly assigned to one of two groups. Each group will be asked to take two tablets four times a day. Group 1 will take two 500mg acetaminophen tablets four times a day. Group 2 will take two 650mg sustained release tablets twice a day with 2 identical placebo tablets for the remaining two doses. Doses will be individually packaged to help assess compliance. Patients will be asked to continue the dosing regimen for four weeks. Compliance will be assessed by tablet count. Ibuprofen 200mg tablets will be provided to patients as a rescue analgesic. Patients will be asked to record their usage of the rescue analgesic. A maximum of 400mg of ibuprofen two times a day may be taken. At the

end of the four week study period, patients will be asked to repeat the initial evaluation of their pain. Patients will also be asked to provide a saliva sample at the time of reassessment just prior to the final dose of the medication to assess compliance and to evaluate the relationship of saliva acetaminophen concentrations to pain control. After a 7 day washout period, patients will then be crossed over to the other treatment for an additional 4 weeks. Reassessment will be repeated after the second four-week period.

Laboratory Analysis: Saliva samples will be collected in 4ml plastic sample tubes and immediately frozen at 4°C until analysis. Samples are then thawed, centrifuged at 3000 rpm for 10 minutes, and the supernatant refrozen. Samples are re-thawed, re-centrifuged, and 150µl of the supernatant is transferred to a microcentrifuge tube. A 150µl aliquot of 7-beta-hydroxyethyl-theophylline 40µg/ml is added as an internal standard. Samples will be analyzed in duplicate using high pressure liquid chromatography to determine acetaminophen concentrations.

Results to Date: None.

EVALUATION OF A CONTROLLED RELEASE ACETAMINOPHEN TABLET FOR ANALGESIA IN OSTEOARTHRITIS PATIENTS

A PILOT STUDY

Principal Investigators

Theresa M. Bianco, Pharm. D.

Carol A. Keller, R. Ph.

Introduction: An estimated 40.5 million adults in the United States suffer from some form of osteoarthritis (OA)¹. With a steadily aging population, that number is expected to increase in the coming years. The disease is age associated and the prevalence ranges from 4% in people age 18-24 years old to 85% in patients 75-79 years old.^{1,2} The incidence of OA is higher in women and in some racial types.^{1,3} The specific aim of this study is to assess the effectiveness of a novel sustained release formulation of acetaminophen in relieving pain in these patients.

The symptoms of osteoarthritis vary with the duration of the disease and the number of joints that are involved. The predominant symptom is a localized deep, aching pain in the affected joint(s). Early in the course of the disease, the pain is present when the affected joint is first used and is relieved when the joint is at rest or when weight is removed from the joint. As the disease progresses, the pain can become present with minimal movement and at rest. In addition to pain, patients may experience loss of range-of-motion (ROM), stiffness, and physical deformities.¹

No cure exists for OA. Treatment is aimed at reducing pain, maintaining mobility, and minimizing disability.⁴ Historically, OA has been treated much like rheumatoid arthritis, with non-steroidal-anti-inflammatory medications (NSAIDs).⁵⁻⁷ Although effective, these medications present several problems in the elderly population with OA. The NSAIDs cause significant gastric distress and ulceration, increase

prothrombin time, and have uricosuric activity.⁵ Recently, it has been shown that since OA does not involve an inflammatory component, that pure analgesic medication, such as acetaminophen, are equally effective as NSAIDS in the relief of the pain and stiffness these patients experience without some of the side effects.^{5,8-12}

Acetaminophen has been safely used for over 30 years as an over-the-counter analgesic. In therapeutic doses of less than 4 grams per day, it does not cause gastric distress, changes in prothrombin times, or uricosuric activity. The major problem with using acetaminophen for chronic pain relief has been the fact that traditional immediate release formulation must be taken every 4-6 hours to maintain analgesic effect. The immediate release preparations do not provide lasting relief for these patients and the potential exists for patients to take excessive doses in an effort to maintain analgesia for a longer period of time. Chronic ingestion of greater than 4 grams per day primarily manifests as hepatic necrosis that is characterized by nausea, vomiting, and abdominal pain that can progress to methemoglobinemia, vascular collapse, hepatic coma and death if left untreated.^{1,13-16} In addition, chronic abuse can also result in renal papillary necrosis and interstitial nephritis. Oliguria, hematuria, and renal insufficiency can result if left untreated.^{13,16,17} There is a great need for a longer lasting product that would maintain sufficient blood levels of the drug for analgesia, while minimizing the overall daily dose and maximizing convenience to the patient. Studies have shown the efficacy of immediate release acetaminophen in osteoarthritis patients.^{18-20,11} This study was designed to evaluate a novel sustained release formulation of acetaminophen for chronic pain relief in osteoarthritis patients.

Results to Date: Preliminary pharmacokinetic calculations were performed using published parameters.²¹ The pharmacokinetics goal is to maintain $C_p > 5.0\text{mg/L}$ for the full 12 hours. Initial *in vitro* evaluation of the drug product were completed and release factors were optimized. Pharmacokinetic *in vivo* evaluation is currently underway and the release characteristics of the formulation will be finalized based on the correlation developed between the *in vitro* and *in vivo* results.

Initial formulation studies in human subjects were conducted at Oregon State University. Ten healthy volunteers were given four acetaminophen formulations in a single dose study. The four formulation consisted of Tylenol Extra strength tablets (2x500mg), Tylenol Extended Release tablets (2x650mg), and two sustained release formulations containing 7.5 and 5.0% of the controlling matrix (2x650mg). The four formulations were administered in a four way crossover fashion with at least 7 days separating each single dose study. Subjects were asked to fast overnight before taking the dose and refrain from eating for two hours after the dose. Saliva samples were collected in 4ml plastic test tubes at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 9.0, 12.0, and 24.0 hours after the dose. To collect each sample, subjects were asked to chew an one inch square of Parafilm to stimulate saliva and to collect all saliva produced in a one minute period of chewing. Collected saliva samples were frozen and stored until analysis.

Samples were analyzed using high pressure liquid chromatography. Samples were centrifuged at 3,000 rpm for 20 minutes and the supernatant decanted to remove extraneous proteins. The supernatant was refrozen for at least 24 hours after being decanted. Samples were then re-thawed and re-centrifuged at 3,000 rpm for 15 minutes prior to final sample preparation. An sample aliquot of 150 μl in mixed with a 150 μl

aliquot of 7-beta-hydroxyethyl theophylline vortexed to ensure mixing. The 7-beta hydroxyethyl theophylline solution (40 μ g/ml) is added as an internal standard. External standard solutions of acetaminophen ranging from 0.4-16 μ m/ml were run with each set of samples. Absorbance was monitored at 254nm, the mobile phase consisted of 20:80 MeOH/water solution infused at 0.8ml/min.

Data was analyzed using peak height ratios between the acetaminophen and the 7-beta hydroxyethyl theophylline. The enclosed graph is the average saliva concentrations in the 10 subjects over twenty four hours for the four formulations. The graph demonstrates by twelve hour after the dose, both the Tylenol Extra Strength and the Tylenol Extended Release have decayed to a level of about 1mg/L in the saliva. In contrast, the 5% sustained release formulation still maintains a saliva concentration of about 2.5mg/L. The 7.5% sustained release formulation was eliminated because of low bioavailability. Upon multiple dosing, the 5% sustained release tablets appear to meet the 5mg/L target saliva concentration.

Research Design:

Goal: To evaluate the effectiveness of a novel sustained release preparation of acetaminophen in the relief of pain in osteoarthritis patients.

Study Design: This is a randomized, double blind, placebo controlled study in a crossover design.

Subject Recruitment: Subjects will be recruited from the outpatient clinics. Patients who meet preliminary criteria will be approached concerning their interest in

participating in the study. If interested, permission of the primary care physician will be obtained before informed consent is signed.

Inclusion criteria: Patients with chronic mechanical-type knee pain and previous diagnosis of osteoarthritis of the knee. Age is 40-75 years inclusive. Lack of trauma to the affected joint(s) or intra-articular corticosteroid injections in the last three months.

Exclusion criteria: Previous history of sensitivity to acetaminophen or acetaminophen containing products. Previous history of sensitivity to ibuprofen. History of trauma or intra-articular corticosteroid injections in the affected joint(s) in the last 3 months. Patients with any other medical condition which would limit ability to walk 50 feet including but not limited to, angina pectoris, congestive heart failure, chronic obstructive pulmonary disease, peripheral vascular disease, fibromyalgia, bursitis, inflammatory arthritis, or other musculoskeletal conditions of the leg which could cause concomitant leg pain. Patients must be able to walk 50 feet without assistance or assistive devices. Patients with liver disease, renal insufficiencies, gastric ulceration, or any medical condition in which non-steroidal anti-inflammatory medications would be contraindicated will also be excluded from this study. Patients who have previously not responded to acetaminophen therapy will also be excluded. Pregnant women will not be allowed to participate in the study. Pregnancy testing on the study population will be done on all women of child bearing age who do not have documented history of hysterectomy, sterility, or menopause. Patient with a documented history of alcoholism or who consume greater than two alcohol containing beverages per day will also be excluded.

Sample Size Justification: Sample size calculations were performed using data published by Bradley et al¹¹. Bradley compared two treatments for osteoarthritis in a parallel design using a modified HAQ test and time to walk 50 feet. Using his published data, within-subject estimates of treatment differences and standard deviations were calculated. After adjusting for the crossover design and setting $\alpha = 0.1$ and power = 80% a sample size of 40 was calculated.

Methods and Procedures: After signed consent is obtained and inclusion/exclusion criteria are met, patients will undergo an initial evaluation. A history and disease characterization will be performed including height, weight, and age. Patients will be asked to stop their current analgesic medication one week prior to the initial evaluation. Ibuprofen 200mg tablets will be provided to patients throughout the study as a rescue analgesic. Patients will be asked to record their usage of the rescue analgesic and to refrain from taking the ibuprofen for 12 hours prior to each walking test. A maximum of 400mg of ibuprofen may be taken three times a day. An initial evaluation of the type and duration of pain in the patient will be assessed using modified Stanford Health Assessment Questionnaire (HAQ)²² pain scores (Appendix A) and time to walk 50 feet.

Enrolled patients will randomly assigned to one of two groups. Each group will be asked to take two tablets four times a day. Group 1 will take two 500mg acetaminophen tablets four times a day. Group 2 will take two 650mg sustained release tablets twice a day alternating with 2 identical placebo tablets for the remaining two doses per day. The tablets will be packaged in unit of use bubble packing to assist patients in taking the appropriate formulation and to help assess compliance. Patients will be asked to continue the dosing regimen for four weeks. Compliance will be assessed by tablet

count. At the end of the four week study period, patients will be asked to repeat the initial evaluation of their pain. Patients will also be asked to provide a saliva sample at the time of reassessment just prior to the final dose of the medication to assess compliance and to evaluate the relationship of saliva acetaminophen concentrations to pain control.^{21,23} After a 7 day washout period, patients will be crossed over to the second treatment. After a 4 week period, the patients will return for a third and final evaluation.

Laboratory analysis: Saliva samples will be collected in 4ml plastic sample tubes and immediately frozen at 4°C until analysis. Samples are then thawed, centrifuged at 3000 rpm for 10 minutes, and the supernatant refrozen. Samples are re-thawed, re-centrifuged, and 150µl of the supernatant is transferred to a microcentrifuge tube. A 150µl aliquot of 7-beta-hydroxyethyl-theophylline is then added as an internal standard. The samples are centrifuged a third time and transferred to 1ml high pressure liquid chromatography (HPLC) tubes for analysis. Samples will be run in duplicate to verify acetaminophen concentrations.

Data Analysis: Data collected on pain control will be analyzed using analysis of variance. Data will be analyzed as a randomized block design with factors included in the model for treatment order and carryover effects. Other factors will be included in the model if found to be significant (i.e. age, sex, use of breakthrough analgesic). Correlation between saliva acetaminophen concentrations and pain control will also be analyzed using an analysis of variance.

Initial Demographic Information

Visit 1

To be administered by the Investigator

Name _____

Age _____

Sex _____

Height _____

Weight _____ lbs.
 _____ kg.

How long have you been diagnosed with osteoarthritis? _____

Which joint(s) are affected by the osteoarthritis? _____

Do you usually have pain associated with your illness? _____

What medication do you normally take to relieve this pain? _____

Does this product adequately relieve your pain? _____

Have you taken Tylenol® or Tylenol® containing products (as shown in the attached list) in the last 7 days? _____

Have you ever had any problems or side effects while taking Tylenol® or Tylenol® containing products? YES NO

If so, what? _____

Have you ever had any problems or side effects while taking Advil®, Motrin®, Nuprin®, or ibuprofen containing products? YES NO

If so, what? _____

What medications have you taken in the past for your osteoarthritis? _____

What prescription medications do you currently take? _____

What nonprescription medication do you take. Include vitamin preparations. _____

Inclusion/Exclusion Criteria

Do you have a history of:

- 1. Trauma to the affected joint in the last 3 months YES NO
- 2. Corticosteroid injections in the last 3 months YES NO
- 3. Angina YES NO

- | | | |
|--|-----|----|
| 4. Congestive Heart Failure | YES | NO |
| 5. Chronic Obstructive Pulmonary Disease | YES | NO |
| 6. Peripheral Vascular Disease | YES | NO |
| 7. Fibromyalgia | YES | NO |
| 8. Bursitis | YES | NO |
| 9. Rheumatoid Arthritis | YES | NO |
| 10. Kidney Problems | YES | NO |
| 11. Ulcers | YES | NO |
| 12. Alcoholism | YES | NO |

13. How often do you drink alcoholic
beverages? _____

Pain Evaluation Visit 1 2 3
 Subject _____
 Treatment _____

How would you rate your overall pain during the last 4 weeks?

1 2 3
 mild mod severe

How would you describe the change in your pain in the last 4 weeks?

1 2 3
 better no change worse

My pain is best described as:

1 2 3
 periodic daily constant

I need help from another person to do the following things:

	Seldom	Sometimes	Often
Dress	1	2	3
Eat	1	2	3
Stand Up	1	2	3
Walk	1	2	3
Climb stairs	1	2	3
Clean House	1	2	3

The pain medication that I have been taking for the last 4 weeks relieves my pain -

Seldom Sometimes Often
 1 2 3

The pain relief lasts for the entire time between doses

Seldom Sometimes Often
 1 2 3

List any side effects or problems with the medication that you have been taking for the last 4 weeks. _____

Time to walk 50 feet _____

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APPENDIX 3C:

Copy of IND Sent to the FDA

December 5, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5600 Fishers Lane, HFD-120
Rockville, Maryland 20852

Dear Madam/Sir,

I have enclosed three copies of an Investigational New Drug Application seeking permission to administer acetaminophen to consenting adult, human volunteers using a sustained release oral tablet. This will be a Phase II study conducted at Veterans Hospital in Portland, Oregon. The Investigator for this project is Carol Keller R. Ph. The Sponsor of this project is Dr. James Ayres. The mailing address for both the Investigator and the Sponsor is:

Dr. James Ayres
Pharmacy Bld. 231
Oregon State University
Corvallis, OR 97331-3507

Phone:(503) 737-5787
FAX: (503) 737-3999
e-mail: ayresj@ccmail.orst.edu

Enclosed with this packet is a copy of the Certificates of Analysis for each of the components used in the manufacture of the sustained release tablets. All chemicals used are National Formulary/United States Pharmacopeia grade.

Also enclosed is a copy of the proposed Investigational Research Proposal from the Veterans Hospital and the approved copy of the Investigational Research Proposal from Oregon State University.

Thank you for your assistance.
Sincerely,

James Ayres, Ph. D., R. Ph.
Professor of Biopharmaceutics and Pharmacokinetics
Oregon State University

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Form 1571

Form 1572

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**1571.5 Investigational Research Board Protocol Approved by
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1571.8 Certificates of Analysis

1571.1

Description of Acetaminophen

Acetaminophen: N-(4-hydroxyphenyl)acetamide

4'-hydroxyacetanilide

p-hydroxyacetanilide

p-acetamidophenol

p-acetaminophenol

p-acetylaminophenol

N-acetyl-*p*-aminophenol

paracetamol

Abensanil®

Acamol®

Acetalgin®

Alpiny®

Amadil®

Anafon®

Anhiba®

Apamide®

APAP®

Ben-u-ron®

Bickie-mol®

Calpol®

Captin®

Cetadol®

Dafalgan®

Datril®

Dial-a-gesic®

Dirox®

Disprol®

Doliprane®

Dolprone®

Dymadon®

Enelfa®

Eneril®

Eu-Med®

Exdol®

Febrilix®

Finimal®

Gelocatil®

Hedox®

Homoolan®

Korum®

Lyteca®

Momentum®

Naprinol®

Nobedon®

Ortensan®

Pacemo®

Paldesic®

Panadol®

Panaleve®

Panasorb®

Panets®

Panex®

Panofen®

Parelan®

Paraspen®

Parmol®

Pasolind®

Salzone®

Tabalgin®

Tapar®

Temlo®

Tempra®

Tralgon®

Tylenol®

Valadol®

Method of Administration: Acetaminophen will be administered in a double blind crossover study that compares two formulations of acetaminophen. The products tested will include acetaminophen immediate release tablets,(2 x 500mg) and a sustained release acetaminophen preparation (2 x 650mg). Doses of 1000mg every 6 hours or 1300mg every 12 hours will be given for 4 weeks as two separate studies separated by a 7 day "wash-out" (drug free) interval between each study. Patients age 40-75 years of age with previously diagnosed osteoarthritis of the knee will be asked to participate.

1571.2**Chemical Manufacturer**

All chemicals used in the production of the sustained release product are of National Formulary/United States Pharmacopeia grade. Copies of the Certificates of Analysis for each ingredient are included with this packet. They include acetaminophen NF/USP (Spectrum Chemical MFG. Corp., Gardena, CA) Lot JE321, polyvinylpyrrolidone K-30 NF/USP (Spectrum Chemical MFG. Corp., Gardena, CA) Lot KD186, magnesium stearate NF/USP (Spectrum Chemical MFG. Corp., Gardena, CA) Lot KC502, and Methocel® K100M PREM CR brand of hydroxypropylmethylcellulose (Dow Chemical Co. Midland, MI) Lot MM92101105K. Avicel® microcrystalline cellulose NF/USP (FMC Corporation, Philadelphia, PA) Lot X129 is used in place of the acetaminophen in the placebo tablets.

The tablets will be prepared as described in section 1571.4.

Immediate release acetaminophen tablets (500mg) will be purchased at a local retail outlet and dispensed as received. Lot numbers, retailer information, and expiration dates will be recorded.

Ibuprofen 200mg tablets will be used as a rescue analgesic during the study. These tablets will also be purchased at a local retail outlet and dispensed as received. Lot numbers, retailer information, and expiration dates will be recorded.

1571.3

Department of Pharmaceutics Manufacturing Laboratory: College of Pharmacy, Oregon State University, Corvallis, Oregon

The pharmaceutical manufacturing laboratory at the College of Pharmacy has been previously used to produce melatonin products and other sustained release acetaminophen formulations which have been evaluated in human subjects. Several USP dissolution apparatus are available for in vitro evaluation of oral dosage forms. A friabulator and USP hardness tester are available to evaluate tablet parameters. A single punch tableting machine is available for tablet production. High Pressure Liquid Chromatographic (HPLC) systems equipped with a variety of columns and detectors are available in the laboratory. UV-VIS spectrophotometry, Franz cell diffusion systems, Perkin-Elmer DSC, gas chromatography, scintillation and gamma counters, and a laboratory scale spray coater are available for use within the College of Pharmacy. The handling of radioactive substances is not permitted in the manufacturing laboratory and is not part of this investigation.

Veterans Administration Hospital: Portland, Oregon

The Hospital has provided service to thousands of U.S. Veterans throughout the years. It continues to serve patients by providing excellent medical care and by sponsoring medical research into prevalent conditions and afflictions. See form 1572.

1571.4

Manufacture of Sustained Release Tablets

Ingredients and Excipients: A licensed pharmacist at the pharmaceuticals laboratory at Oregon State University will undertake production of the sustained release tablets. The following materials will be used in the tablets. They include acetaminophen NF/USP (Spectrum Chemical MFG. Corp., Gardena, CA) Lot JE321, polyvinylpyrrolidone K-30 NF/USP (Spectrum Chemical MFG. Corp., Gardena, CA) Lot KD186 as a tablet binder, magnesium stearate NF/USP (Spectrum Chemical MFG. Corp., Gardena, CA) Lot KC502 as a tableting lubricant/glidant, and Methocel® K100M PREM CR brand of hydroxypropylmethylcellulose (Dow Chemical Co. Midland, MI) Lot MM92101105K as a sustained release matrix substrate. Avicel® microcrystalline cellulose NF/USP (FMC Corporation, Philadelphia, PA) Lot X129 is used in place of the acetaminophen in the placebo tablets. Water used during the granulation process is distilled and then passed through a de-ionization system.

Cleaning: All surfaces are cleaned prior to each production run. All equipment and the surrounding area will be cleaned with Alconox®, rinsed with distilled, deionized water, and swabbed with 95% ethanol. All surfaces will be free of soap residue or films. The process will be attended at all times.

Manufacturing Process: Each tablet contains 89.0% acetaminophen, 5.0% hydroxypropylmethylcellulose (HPMC), 5.0% polyvinylpyrrolidone (PVP), and 1.0% magnesium stearate by weight. The desired amount of PVP is dissolved in 0.75ml water per tablet. The HPMC and the acetaminophen are premixed and slowly added to the PVP solution. The resulting thick paste is extruded into noodles onto a flat, plastic wrap covered surface and allowed to dry overnight at room temperature. The dried noodles are mechanically broken up into granules using a mortar and pestle and sieved through a succession of sieves. Granules that pass through a 14 mesh sieve but are retained on a 60 mesh sieve are used. Granules not within the prescribed range are discarded. Magnesium stearate is then added to the granules and mixed to thoroughly coat the granules. Tablets are made from the granules by loading the mixture into a single punch tableting machine (Chemical and Pharmaceutical Industry Co., New York, NY, Model TPK-12). Ejected tablets are 12mm in diameter with a 4mm belly band and curved faces. One face of the tablet is scored across the middle and bears the imprint 427 OPD. Desired tablet weight is 730mg. Each batch produced will be assigned sequential lot numbers.

Placebo tablets are made by replacing the acetaminophen in the tablets with Avicel®. Granulation of the placebo tablets is not necessary as the Avicel® is already granular. The four ingredients are dry mixed and loaded into the single punch tableting machine to produce tablets that are identical to the study medication in appearance and weight.

Labeling: Finished tablets will be stored at room temperature in amber vials until packaging. Each vial will bear the following label:

INVESTIGATIONAL DRUG
Acetaminophen Sustained Release Tablets
650mg
Date
Lot

To help assess compliance the treatment medications will be placed in unit dose cards. Each card holds a single weeks worth of medication. Each treatment will last 4 weeks. All four cards will be dispensed at once. The medication will be placed in REDI-PAK® compliance cards and will be labeled for use.

OREGON STATE UNIVERSITY
COLLEGE OF PHARMACY
INVESTIGATIONAL ACETAMINOPHEN STUDY

PATIENT NUMBER 1
TREATMENT 1
WEEK 1

	DOSE 1	DOSE 2	DOSE 3	DOSE 4
S				
U				
N				
M				
O				
N				
T				
U				
E				
S				
W				
E				
D				
T				
H				
U				
R				
R				
F				
R				
I				
S				
A				
T				

Patients will be randomly assigned in a crossover fashion to one of two treatments. Each treatment involves the patient taking 2 tablets four times a day for four weeks. After a week wash out period each patient is crossed over to the second treatment. For one treatment the dose packets will contain 2 X 500mg immediate release tablets. For the other treatment the dose packets will contain two doses of the sustained release formulation (Dose 1 and Dose 3) and two doses of placebo tablets (Dose 2 and Dose 4). Neither the patient nor the investigator will know which treatment the patient is currently taking.

FDA: Administration of Oral, Sustained Release Acetaminophen Delivery to Human Subjects.

Tablet Characterization: Each batch of tablets produced will be evaluated for hardness and friability. Tablet hardness will be measured using a Strong-Cobb hardness tester. Tablets with hardness values of less than 4kg will be considered unacceptable and will be discarded. Friability will be tested using a Roche Friabilator. Five tablets from each batch will be tested for 100 rotations. Tablet samples that lose greater than 1% of their weight will be considered to be unacceptable and will be discarded.

Each tablet batch will also be weighed and an average tablet weight recorded.

In Vitro Characterization of the Release of Acetaminophen from the Sustained Release Dosage Form

Six tablets from each batch will be evaluated using a USP dissolution (Paddle Method) test. For the first two hours each tablet will be exposed to 900ml of enzyme-free simulated gastric fluid (Ph = 1.4). Samples will be taken from the vessels with replacement at 20 minutes, 40 minutes, 1 hour, 1 hour and 20 minutes, 1 hour and 40 minutes, and 2 hours. After two hours the fluid is filtered through No. 1 filter paper and the particles retained. The particles and the filter paper will then be exposed to 900ml of enzyme-free simulated intestinal fluid (Ph = 7.4) for the remaining 22 hour period. Samples will be taken with replacement at 3 hours, 4 hours, 6 hours, 9 hours, 12 hours, and 24 hours. Samples will be diluted 1:100 with distilled, deionized water and analyzed at 244nm in a Hewlett Packard variable wavelength UV-VIS spectrophotometer equipped with a sipper cell. Standard solutions of acetaminophen in distilled, deionized water will

be used to correlate absorbance to concentration. Previous experience has indicated that interference from polymers and or other excipients that may be present in the dissolution medium is negligible.

Dissolution will also be performed on the commercial acetaminophen products for comparison purposes. By design, the immediate release commercial formulation should rapidly dissolve in the gastric fluid. Samples will therefore be taken in gastric fluid only, unless dissolution is incomplete in the first two hours. Samples will be taken with replacement at 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 40 minutes 60 minutes, 75 minutes, 90 minutes, 105 minutes and 120 minutes.

Figure 1 is a graph of the drug release from the immediate release acetaminophen product (2 x 500mg) to be used in this study. Note that dissolution is essentially complete by the 5 minutes sample time. Figure 2 is a graph of the drug release from the sustained release acetaminophen tablet (2 x 650mg) to be used in this study.

Section 1571.5

Approved Investigational Research Protocol from Oregon State University.

571.5

Copy of Approved Investigational Research Board Proposal from Oregon State University.

RESEARCH PROPOSAL INVOLVING HUMAN TEST SUBJECTS

This is a preliminary investigation conducted by Oregon State University College of Pharmacy Department of Pharmaceutics to evaluate a sustained released formulation of acetaminophen (Tylenol®). The information collected will be used to establish an *in*

vitro - *in vivo* correlation for the development of a new acetaminophen formulation. An *in vitro* - *in vivo* correlation will allow the *in vitro* behavior of future formulations to predict *in vivo* behavior. New formulations can then be developed with a minimum of human testing.

Acetaminophen is a widely used, over-the-counter medication for analgesia and fever. It has been available to the general public for over 30 years. Acetaminophen is currently given either as an immediate release product (650-1000mg every 4-6 hours) or as an extended release product (1300mg every 8 hours). A new sustained release formulation developed in our laboratory would provide 1300mg every 12 hours. The sustained release tablets are manufactured using well known procedures and are made from Food and Drug Administration (FDA) approved ingredients.

Participants will be involved in several one (1) day test periods with a seven (7) days wash out period between them. Participants will be asked to fast for 2 hours prior to receiving a dose of acetaminophen. At specified time intervals after dosing, participants will be asked to chew a one inch square of Parafilm® for 1 minute to stimulate saliva production and to collect a saliva sample. It has been well documented in the literature that saliva acetaminophen concentrations are directly correlated with blood acetaminophen concentrations. All operators handling samples will wear gloves in compliance with federal "universal precaution" recommendations. All operators are aware of the risks of handling bio-hazardous materials including the potential for contracting hepatitis and/or the HIV virus.

Justification: Currently available formulations of acetaminophen must be taken every 4 to 8 hours to maintain adequate drug concentrations in the blood to provide pain relief. The development of a sustained release formulation would provide extended relief from pain while minimizing the dose, and thereby the side effects of the drug. Twelve hour dosing intervals have also been shown to increase the compliance of patients. This is especially important in patients who require pain relief on a long term basis (arthritis).

Although simulation and calculations may be performed to predict the behavior of new drug formulations, there are often factors in the body that cannot be foreseen. The ultimate test of a formulation measures the change in drug concentrations in the body over the dosing interval. As acetaminophen saliva concentrations can be directly correlated with plasma concentrations, saliva data can be used as a non-invasive method of evaluating the performance of new acetaminophen formulations.

Figure 1 is a comparison of *in vitro* release rates of 3 acetaminophen formulations. The diamonds represent the dissolution of 1000mg (2 x 500mg) acetaminophen (Tylenol Extra Strength®) tablets. The filled circles show a similar curve for 1300mg (2 x 650mg) acetaminophen extended release (Tylenol ER®) caplets. Note that both of these products are completely released by 3 hours. The triangles represent the *in vitro* dissolution profile of the sustained release formulation developed in our laboratory. Note that with this product complete release is not obtained until twelve hours.

Side-Effects: Few side effects have been reported with the use of acetaminophen in therapeutic doses (4 grams a day or less). Reported side effects of acetaminophen are dose dependant and unlikely, but can include skin rash, hives, itching,

bloody or cloudy urine, difficulty in urination, sudden decrease in urine output, unexplained sore throat or fever, unusual bleeding or bruising, or unusual tiredness or weakness (see attached United States Pharmacopeia Drug Information sheet. Other symptoms may occur in overdose situations but are not expected during this study as the dosage given is below the maximum daily dose of acetaminophen (4 grams per day).

Exclusions: All test participants will be healthy, normal people with no known medical problems. Pregnant women will be excluded, even though acetaminophen is the drug of choice for analgesia in these patients, because of the inadvisability of taking any medication while pregnant if not absolutely necessary. Test subjects will be excluded from this study if any of the following are true:

1. They have shown any previous hypersensitivity to acetaminophen or to acetaminophen combination products.
2. They have renal abnormalities or known renal dysfunction.
3. They have liver abnormalities or known liver dysfunction.
4. They are currently taking any prescription or non-prescription form of acetaminophen or acetaminophen containing product.
5. They are currently taking any medication that might effect the elimination of acetaminophen (i.e. phenobarbital, phenytoin)
6. They are or expect to become pregnant during the duration of the study.
7. Persons who have ever had hepatitis B or C, who have tested positive for HIV or any AIDS virus, who have AIDS, or who are at risk for getting and spreading any AIDS virus. You are at risk if:
 - you are a man who has had sex with another man since 1977, even one time.
 - you have shared a needle, even one time, to inject drugs or medication.

- you have taken clotting factor concentrates for a bleeding disorder such as hemophilia.
- you have ever had a positive test for any AIDS virus or hepatitis B or C or any AIDS antibody.
- you have had sex with any person described above.
- you have had sex with a male or female prostitute since 1977.

Test Subjects: Test participants will be 20 healthy, normal volunteers drawn from the Oregon State University faculty, staff, and student population. Written consent of each participant will be obtained after verbal and written information is presented by a registered pharmacist.

Anonymity: All records will be kept confidential. The identity of the research participants will not be released through either oral or written transmission to any member not directly involved in the research group. Records from each subject shall be retained in the project file for three years beyond the end date of the project.

MATERIALS AND METHODS

Materials: Acetaminophen NF/USP, lot #JE321 was obtained from Spectrum Chemical Mfg Corp. Gardena, CA, magnesium stearate NF/USP, lot #KC502 was obtained from Spectrum Chemical Mfg Corp. Gardena, CA, hydroxypropylmethylcellulose (Methocel® K100M PREM CR) lot #MM92101105K was obtained from Dow Chemical Co. Midland, MI, and polyvinylpyrrolidone NF/USP from

Spectrum Chemical Mfg Corp. Gardena, CA. All water used was distilled de-ionized water.

Tablets: Each tablet contains 89.0% acetaminophen, 5.0% hydroxypropylmethylcellulose (HPMC), 5.0% polyvinylpyrrolidone (PVP), and 1.0% magnesium stearate by weight. The PVP is dissolved in 0.5ml of water per tablet. The HPMC and the acetaminophen are premixed and then slowly added to the PVP solution. The resulting thick paste is extruded into noodles and dried. The dried noodles can then be broken into granules. Magnesium stearate is added to the granules and mixed to thoroughly coat the granules. Tablets are made by placing loading granules into a single punch tableting machine. Desired tablet weight is 730.0mg.

Subjects: Test participants are normal, healthy volunteers who are not currently taking any prescription or non-prescription forms of acetaminophen and have previously fasted for 2 hours or greater prior to the dose. Fasting must continue for two hours after taking the dose. Subjects will not be allowed to eat or drink anything 5 minutes before each sample.

Design: A cross-over design will be used. Subjects are randomly assigned to one of the three formulations. After a one week wash out period, a second formulation will be given. Finally, after a second week long wash out period, the third formulation will be given.

Sampling: Saliva samples will be collected at times 0.0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 9.0, 12.0 and 24.0 hours. Each participant will chew a 1 inch square of Parafilm® for 1 minute during each sample collection to initiate adequate saliva flow. Saliva produced during the minute of chewing will then be collected for each time point and frozen for later analysis.

Solutions:

1. Acetaminophen standards of 0.4, 1.0, 2.0, 4.0, 6.0, 8.0, 10.0, and 16.0 µg/ml in water will be used. All standards were made by aliquot dilution of a 1000 µg/ml stock solution.
2. Internal standard solution of 40 µg/ml 7-beta-hydroxyethyl-theophylline.
3. Mobile phase of 30% methanol and 70% water.

Assay: All saliva samples will be frozen prior to use (-20°C). Aliquots of saliva will be centrifuged at 14,000 rpm for 2 minutes to pelletize particulates. One hundred fifty µl of supernatant will be then pipetted into a micro centrifuge tube. One hundred fifty µl of the internal standard (7-beta-hydroxyethyl theophylline) will be added and the mixture vortexed for 30 seconds.

Chromatography: Samples will be injected onto the High Pressure Liquid Chromatograph (HPLC) using an automatic sampler (WISP 712; Waters Assoc.) Separations of components is obtained by using a C18-Reverse Phase column. The mobile phase of 30% methanol/70% water will be delivered at a rate of 0.8ml/min (M-6000A Solvent Delivery System) and samples will be monitored at 254nm with a model 440 absorbance detector. Injection volume will be set at 20 µl.

Quantitation: Standard curves are run daily. Quantitation of the sample curves is based on peak height ratios using the internal standard peak as the divisor. The resulting calibration curve is fitted using PSI-PLOT® to a least-squared linear regression line. The equation is then used to convert peak ratios into corresponding concentrations.

CONSENT FORM

This study is a research project conducted by the Department of Pharmaceutics, College of Pharmacy, Oregon State University. The purpose of this study is to evaluate a sustained release formulation of the drug acetaminophen. Acetaminophen (Tylenol®) is a non-prescription medication that is used to treat mild pain and fever. Currently the medication must be taken 3-4 times a day. The new formulation that you will take is designed to release slowly over a 12 hours period.

Your participation will involve one (1) day per week for three (3) weeks (3 days total with a 7 day wash out period between doses). You will be asked not to eat for at least 2 hours prior to the study and after the dose, and to refrain from eating or drinking for 5 minutes before each sample time. After dosing, you will be given a time sheet for recording sample times, tubes in which to collect saliva samples, and 1 inch squares of Parafilm®. You must chew the square of Parafilm® for 1 minute during each sample collection to stimulate saliva production. A total of 12 saliva samples will be collected over the 24 hour period.

Side Effects: If you have previous taken Tylenol® or Tylenol Extra Strength® with no untoward effects, you should not experience any difficulty with this product. On

rare occasions, people taking acetaminophen develop a rash or drowsiness. Any possible side effects or abnormal symptoms that you experience should be reported to the study investigator immediately.

Exclusions: You are excluded from this study if you are not a normal, healthy adult free of known liver or kidney damage or if you are pregnant or plan to become pregnant during the study period. You are also excluded if you have ever shown any sensitivity to acetaminophen or acetaminophen containing products. Subjects should not be taking any medications that might effect the elimination of acetaminophen (i.e. phenobarbital, phenytoin, etc.)

Anonymity: All records will be kept confidential. The identity of the research participants will not be released through either oral or written transmission to any member outside of the research group.

Confidentiality: I have been informed that because this study involves articles regulated by the FDA (Food and Drug Administration), the FDA may choose to inspect records identifying me as a subject in this investigation.

Withdrawal: Participation in this study is voluntary, you may withdraw at any time. There is no penalty if you withdraw from the study for any reason: exclusion, competing commitments, drug reaction, loss of interest. No loss of benefits, standing, or relationship with the research group or Oregon State University will result.

Questions about the research, your rights, or research related injuries should be directed to James Ayres, Ph. D., at 737-5787, or Carol Keller at 737-5771.

I have read the consent form above and I understand the information presented. I understand that the University does not provide a research subject with compensation or medical treatment in the event that the subject is injured as a result of participation in the research project. My participation is voluntary, and refusal to participate will involve no penalty or loss or benefits to which I am otherwise entitled, and that I may discontinue participation at any time without penalty or loss of benefits to which I am otherwise entitled.

Signature _____ Date _____

DATA SHEET

Please record the time of each sample collection to the nearest 5 minutes.

Time the dose was taken: _____

<u>Hours after dose</u>	<u>Time sample was taken</u>
0.0	
0.5	
1.0	
1.5	
2.0	
3.0	
4.0	
5.0	
6.0	
9.0	
12.0	
24.0	

Signature: _____ Date: _____

SUBJECT DATA SHEET

Data for Subject: _____ Identifier: _____

Formulation: _____

<u>Hours after dose</u>	<u>Actual time</u>	<u>Concentration</u>
-------------------------	--------------------	----------------------

0.0

0.5

1.0

1.5

2.0

3.0

4.0

5.0

6.0

9.0

12.0

24.0

Signature: _____ Date: _____

Section 1571.6**Proposed Research Protocol for the Veterans Administration Hospital****Copy of Proposed Investigational Research Protocol for the Veterans Administration Hospital.****VA RESEARCH CONSENT FORM 10-9012
DESCRIPTION OF RESEARCH BY INVESTIGATOR**

Purpose: You have been asked to participate in a research study to determine if a new long acting formulation of acetaminophen (Tylenol®) can control your osteoarthritis (joint) pain. You have been asked to participate in this study because you have been diagnosed with osteoarthritis and have had pain because of this disease. Acetaminophen has been previously shown to be effective in treating pain due to osteoarthritis but it has to be taken four times a day. A new longer acting form of the drug would allow it to be taken only two times a day. This study is important because it will help evaluate new form of the drug and how well it works. This study will last for 9 weeks and will require three 1-hour visits.

Procedures: If you agree to participate in this study, you will be asked to come to the clinics at the Veterans Administration Hospital. You will be asked to complete a questionnaire about yourself and the type of pain that you have. In addition, you will be asked to walk 50 feet to evaluate how well you can move.

At the first visit you will be given a study medication packet. For 4 weeks, you will be asked to take 2 tablets of your study medication four times a day. You will be taking either two short-acting acetaminophen tablets (500mg each) four times a day, or

two long acting acetaminophen tablets (650mg each) alternating with two placebo tablets. A placebo is a tablet that contains no active drug. Neither you nor the investigators will know which study medication you receive. Ibuprofen tablets (200mg) will be provided for pain not relieved by the study medication. You will be asked to keep track of how many ibuprofen tablets that you use. A maximum of 2 ibuprofen tablets twice a day will be allowed.

After the four week period you will be asked to return to the center and repeat the questionnaire and walking test. In addition, you will be asked to provide a saliva sample. The saliva samples will tell us how much medication is in the blood without having to actually draw blood. At this visit, you will be provided with the other type of medication to take for a second four week period. You must wait a week for the effects of the first medication to wear off before you begin taking the second medication. Ibuprofen will be provided for pain relief during the week between medications. Again, at the end of the four week period you will be asked to repeat the questionnaire and walking test.

Risks and Discomforts: There may be adverse reactions involved in participating in this study. The most common reaction is sleepiness. Very rarely, acetaminophen can result in a rash or hives. This means that you are allergic to the medication. You should stop taking the medication and immediately inform one of the study investigators. Your symptoms will be treated and the study will be stopped. Acetaminophen can cause liver problems, nausea, vomiting, and kidney problems. The doses in this study are much less than the doses that cause these problems doses, but if

nausea or vomiting develop, you may be unusually sensitive to the medication and the study will be stopped.

Benefits: You may benefit from your participation in this study in that the pain due to your osteoarthritis may be reduced or eliminated. It is also possible that your pain will not be controlled by the use of this medication, and it will then be necessary to take the ibuprofen which has been provided for additional pain control.

Alternative Treatments: If you do not choose to participate in this study, other drugs are available for the treatment of osteoarthritis. They include non-steroidal-anti-inflammatory medication like ibuprofen, aspirin, naprosyn and narcotic pain relievers such as Darvocet N-100®, Vicodin®, and Tylenol #3®.

Exclusions: You should not participate in this study if you have shown previous side effects from Tylenol® or other acetaminophen containing combinations. You should not participate in this study if you have shown previous side effects to Motrin®, Advil®, or other forms of ibuprofen. You should not participate in this study if you have had recent (last 3 months) trauma to the affected joint or injections into the joint. Pregnant women will not be allowed to participate in this study. Although the medication will not harm the child, it is not a good idea to be taking any un-needed medication if you are pregnant. You should be able to walk 50 feet without assistance or assistive devices (canes, walkers, etc.)

Your participation in this study is voluntary, and you may withdraw from this study at any time without prejudice to yourself or to any future medical care with this institution or with the Department of Veterans Affairs(VA).

You may be removed from the study without your consent if your doctor decides that this is in your best interest, or if you fail to follow the study schedule (such as not taking your assigned medication). Follow-up visits may still be recommended after your withdrawal.

Costs: The investigators will pay any medication costs involved in this study. You will not be charged for your participation in this study.

Compensation: Your participation in this study is free of charge. You will receive no money for participating in this study.

Liability: Every reasonable effort to prevent any injury that could result from this study will be taken. In the event of physical injury resulting from the study, medical care and treatment will be available at this institution. For eligible veterans, compensation damages may be payable under 38 USC 251 or, in some circumstances, under Federal Tort Claims Act. For non-eligible veterans and non-veterans, compensation would be limited to situations where negligence occurred and would be controlled by the provisions of the Federal Tort Claims Act. For clarification of these laws, contact District Counsel at (503)326-2441. You have not waived any legal rights or released the hospital or its agents from liability for negligence by signing this form.

Confidentiality: The results of your participation in this study may be used for publication or for scientific purposes, but your identity will not be disclosed unless you give separate, specific consent to this, or unless required by law.

Other: Registered Pharmacists Theresa Bianco, Pharm. D. (273-5398) and Carol Keller, R. Ph. (737-7776) have offered to answer any questions that you may have.

You will receive a copy of this consent form. Your signature below indicates that you have read the foregoing and agree to participate in the study.

Name _____ Date _____

RDIS ABSTRACT VA FORM 10-1436

Objective: The specific aim of this study is to compare the effectiveness of a new sustained release formulation of acetaminophen with currently available acetaminophen products for the relief of pain due to osteoarthritis.

Research Plan: This study is a randomized, double blind, placebo controlled cross-over study. The study population will consist of patients with previously diagnosed osteoarthritis of the knee.

Methodology: After signed consent is obtained and inclusion/exclusion criteria are met, patients will undergo an initial evaluation. A history and disease characterization will be performed including height, weight, and age. An initial evaluation of the type and duration of pain in the patient will be assessed using modified Stanford Health Assessment Questionnaire (HAQ) pain scores and time to walk 50 feet.

Enrolled patients will be randomly assigned to one of two groups. Each group will be asked to take two tablets four times a day. Group 1 will take two 500mg acetaminophen tablets four times a day. Group 2 will take two 650mg sustained release tablets twice a day with 2 identical placebo tablets for the remaining two doses. Doses will be individually packaged to help assess compliance. Patients will be asked to continue the dosing regimen for four weeks. Compliance will be assessed by tablet count. Ibuprofen 200mg tablets will be provided to patients as a rescue analgesic. Patients will be asked to record their usage of the rescue analgesic. A maximum of 400mg of ibuprofen every 6 hours may be taken. At the end of the four week study period, patients

will be asked to repeat the initial evaluation of their pain. Patients will also be asked to provide a saliva sample at the time of reassessment just prior to the final dose of the medication to assess compliance and to evaluate the relationship of saliva acetaminophen concentrations to pain control. After a 7 day washout period, patients will then be crossed over to the other treatment for an additional 4 weeks. Reassessment will be repeated after the second four-week period.

Laboratory Analysis: Saliva samples will be collected in 10ml plastic sample tubes and immediately frozen at 4°C until analysis. Samples are then thawed, centrifuged at 3000 rpm for 10 minutes, and the supernatant refrozen. Samples are re-thawed, re-centrifuged, and 150µl of the supernatant is transferred to a microcentrifuge tube. A 150µl aliquot of 7-beta-hydroxyethyl-theophylline 40µg/ml is added as an internal standard. Samples will be analyzed in duplicate using high pressure liquid chromatography to determine acetaminophen concentrations.

EVALUATION OF A CONTROLLED RELEASE ACETAMINOPHEN TABLET FOR ANALGESIA IN OSTEOARTHRITIS PATIENTS

A PILOT STUDY

Principal Investigators
Theresa M. Bianco, Pharm. D.
Carol A. Keller, R. Ph.

Introduction: An estimated 40.5 million adults in the United States suffer from some form of osteoarthritis (OA)¹. With a steadily aging population, that number is expected to increase in the coming years. The disease is age associated and the prevalence ranges from 4% in people age 18-24 years old to 85% in patients 75-79 years old.^{1,2} The incidence of OA is higher in women and in some racial types.^{1,3} The specific aim of this study is to assess the effectiveness of a novel sustained release formulation of acetaminophen in relieving pain in these patients.

The symptoms of osteoarthritis vary with the duration of the disease and the number of joints that are involved. The predominant symptom is a localized deep, aching pain in the affected joint(s). Early in the course of the disease, the pain is present when the affected joint is first used and is relieved when the joint is at rest or when weight is removed from the joint. As the disease progresses, the pain can become present with minimal movement and at rest. In addition to pain, patients may experience loss of range-of-motion (ROM), stiffness, and physical deformities.¹

No cure exists for OA. Treatment is aimed at reducing pain, maintaining mobility, and minimizing disability.⁴ Historically, OA has been treated much like rheumatoid arthritis, with non-steroidal-anti-inflammatory medications (NSAIDs).⁵⁻⁷ Although effective, these medications present several problems in the elderly population

with OA. The NSAIDS cause significant gastric distress and ulceration, increase prothrombin time, and have uricosuric activity.⁵ Recently, it has been shown that since OA does not involve an inflammatory component, that pure analgesic medication, such as acetaminophen, are equally effective as NSAIDS in the relief of the pain and stiffness these patients experience without some of the side effects.^{5,8-12}

Acetaminophen has been safely used for over 30 years as an over-the-counter analgesic. In therapeutic doses of less than 4 grams per day, it does not cause gastric distress, changes in prothrombin times, or uricosuric activity. The major problem with using acetaminophen for chronic pain relief has been the fact that traditional immediate release formulation must be taken every 4-6 hours to maintain analgesic effect. The immediate release preparations do not provide lasting relief for these patients and the potential exists for patients to take excessive doses in an effort to maintain analgesia for a longer period of time. Chronic ingestion of greater than 4 grams per day primarily manifests as hepatic necrosis that is characterized by nausea, vomiting, and abdominal pain that can progress to methemoglobinemia, vascular collapse, hepatic coma and death if left untreated.^{1,13-16} In addition, chronic abuse can also result in renal papillary necrosis and interstitial nephritis. Oliguria, hematuria, and renal insufficiency can result if left untreated.^{13,16,17} There is a great need for a longer lasting product that would maintain sufficient blood levels of the drug for analgesia, while minimizing the overall daily dose and maximizing convenience to the patient. Studies have shown the efficacy of immediate release acetaminophen in osteoarthritis patients.^{18-20,11} This study was designed to evaluate a novel sustained release formulation of acetaminophen for chronic pain relief in osteoarthritis patients.

Results to Date: Preliminary pharmacokinetic calculations were performed using published parameters.²¹ The pharmacokinetics goal is to maintain $C_p > 5.0\text{mg/L}$ for the full 12 hours. Initial *in vitro* evaluation of the drug product were completed and release factors were optimized. Pharmacokinetic *in vivo* evaluation is currently underway and the release characteristics of the formulation will be finalized based on the correlation developed between the *in vitro* and *in vivo* results.

Research Design

Goal: To evaluate the effectiveness of a novel sustained release preparation of acetaminophen in the relief of pain in osteoarthritis patients.

Study Design: This is a randomized, double blind, placebo controlled study in a crossover design.

Inclusion criteria: Patients with chronic mechanical-type knee pain and previous diagnosis of osteoarthritis of the knee. Age is 18-75 years inclusive. Lack of trauma to the affected joint(s) or intra-articular corticosteroid injections in the last three months.

Exclusion criteria: Previous history of sensitivity to acetaminophen or acetaminophen combination products. Previous history of sensitivity to ibuprofen. History of trauma or intra-articular corticosteroid injections in the affected joint(s) in the last 3 months. Patients with any other medical condition which would limit ability to walk 50 feet including but not limited to, angina pectoris, congestive heart failure, chronic obstructive pulmonary disease, peripheral vascular disease, fibromyalgia, bursitis,

inflammatory arthritis, or other musculoskeletal conditions of the leg which could cause concomitant leg pain. Patients must be able to walk 50 feet without assistance or assistive devices. Patient with renal insufficiencies, gastric ulceration, undergoing thrombolytic therapy, or any medical condition in which non-steroidal anti-inflammatory medications would be contra-indicated will also be excluded from this study.

Sample size justification: Sample size calculations were performed using data published by Bradley et al¹¹. Bradley compared two treatments for osteoarthritis in a parallel design using a modified HAQ test and time to walk 50 feet. Using his published data, within-subject estimates of treatment differences and standard deviations were calculated. After adjusting for the crossover design and setting $\alpha = 0.1$ and power = 80% a sample size of 40 was calculated.

Methods and Procedures: After signed consent is obtained and inclusion/exclusion criteria are met, patients will undergo an initial evaluation. A history and disease characterization will be performed including height, weight, and age. An initial evaluation of the type and duration of pain in the patient will be assessed using modified Stanford Health Assessment Questionnaire (HAQ)²² pain scores (Appendix A) and time to walk 50 feet.

Enrolled patients will randomly assigned to one of two groups. Each group will be asked to take two tablets four times a day. Group 1 will take two 500mg acetaminophen tablets four times a day. Group 2 will take two 650mg sustained release tablets twice a day alternating with 2 identical placebo tablets for the remaining two doses per day. Doses will be unit dosed to help assess compliance. Patients will be asked to

continue the dosing regimen for four weeks. Compliance will be assessed by tablet count. Ibuprofen 200mg tablets will be provided to patients as a rescue analgesic. Patients will be asked to record their usage of the rescue analgesic. A maximum of 400mg of ibuprofen may be taken every 6 hours. At the end of the four week study period, patients will be asked to repeat the initial evaluation of their pain. Patients will also be asked to provide a saliva sample at the time of reassessment just prior to the final dose of the medication to assess compliance and to evaluate the relationship of saliva acetaminophen concentrations to pain control.^{21,23} After a 7 day washout period, patients will be crossed over to the second treatment. After a 4 week period, the patients will return for a third and final evaluation.

Laboratory analysis: Saliva samples will be collected in 10ml plastic sample tubes and immediately frozen at 4°C until analysis. Samples are then thawed, centrifuged at 3000 rpm for 10 minutes, and the supernatant refrozen. Samples are re-thawed, re-centrifuged, and 150µl of the supernatant is transferred to a microcentrifuge tube. A 150µl aliquot of 7-beta-hydroxyethyl-theophylline is then added as an internal standard. The samples are centrifuged a third time and transferred to 1ml high pressure liquid chromatography (HPLC) tubes for analysis. Samples will be run in duplicate to verify acetaminophen concentrations.

Data Analysis: Data collected on pain control will be analyzed using analysis of variance. Data will be analyzed as a randomized block design with factors included in the model for treatment order and carryover effects. Correlation between saliva acetaminophen concentrations and pain control will also be analyzed using an analysis of variance.

Appendix A

Initial Demographic Information

Visit 1

To be administered by the Investigator

Name _____

Age _____

Sex _____

Height _____

Weight _____ lbs.

How long have you been diagnosed with osteoarthritis? _____

Which joint(s) are affected by the osteoarthritis? _____

Do you usually have pain associated with your illness? _____

What medication do you normally take to relieve this pain? _____

Does this product adequately relieve your pain? _____

Have you taken Tylenol® or Tylenol® containing products in the last 7 days? _____

Have you ever had any problems or side effects while taking Tylenol® or Tylenol® containing products? YES NO

If so, what? _____

Have you ever had any problems or side effects while taking Advil®, Motrin®, or ibuprofen containing products? YES NO

If so, what? _____

What medications have you taken in the past for your osteoarthritis? _____

What prescription medications do you currently take? _____

What non-prescription medication do you take. Include vitamin preparations. _____

Inclusion/Exclusion Criteria

Do you have a history of:

- | | | |
|--|-----|----|
| 1. Trauma to the affected joint in the last 3 months | YES | NO |
| 2. Corticosteroid injections in the last 3 months | YES | NO |
| 3. Angina | YES | NO |
| 4. Congestive Heart Failure | YES | NO |
| 5. Chronic Obstructive Pulmonary Disease | YES | NO |
| 6. Peripheral Vascular Disease | YES | NO |
| 7. Fibromyalgia | YES | NO |
| 8. Bursitis | YES | NO |
| 9. Rheumatoid Arthritis | YES | NO |
| 10. Kidney Problems | YES | NO |
| 11. Ulcers | YES | NO |

Pain Evaluation Visit 1 2 3

Subject _____

Treatment _____

How would you rate your overall pain during the last 4 weeks?

1	2	3
mild	mod	severe

How would you describe the change in your pain in the last 4 weeks?

1	2	3
better	no change	worse

My pain is best described as:

1	2	3
periodic	daily	constant

I need help from another person to do the following things:

	Seldom	Sometimes	Often
Dress	1	2	3
Eat	1	2	3
Stand up	1	2	3
Walk	1	2	3
Climb stairs	1	2	3
Clean House	1	2	3

The pain medication that I have been taking for the last 4 weeks relieves my pain -

Seldom	Sometimes	Often
1	2	3

The pain relief lasts for the entire time between doses

Seldom	Sometimes	Often
1	2	3

List any side effects or problems with the medication that you have been taking for the last 4 weeks. _____

Time to walk 50 feet _____

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APPENDIX 3D:
Raw Data From Questionnaires

Question 1: Overall Pain Rating

Patient #	Baseline Evaluation	Tx #1	Evaluation After Tx 1	Tx #2	Evaluation After Tx 2
1	2	IR	1	SR	1
2	2	SR	1	IR	2.5
3	3	SR	3	IR	1
4	3	IR	2	SR	1
5	2.5	SR	3	IR	2
6	3	IR	2.5	SR	3
7	3	IR	3	SR	1
8	2	IR	1	SR	1
9	2.5	SR	1	IR	-----
10	1	SR	-----	IR	-----
11	1	IR	1	SR	1
12	1	SR	-----	IR	-----
13	2	SR	2	IR	1
14	1	IR	1	SR	1
15	2	SR	-----	IR	-----
16	2.5	SR	2	IR	2
17	1.5	SR	-----	IR	-----
18	2	SR	2	IR	2
19	3	SR	-----	IR	-----
20	2	SR	-----	IR	-----
21	2	IR	-----	SR	-----
22	1	IR	-----	SR	-----
23	1	IR	-----	SR	-----
24	2.5	IR	2	SR	2
25	3	IR	2	SR	1
26	3	IR	1	SR	2
27	1	SR	1	IR	2
28	2	IR	1	SR	-----
29	-----	SR	-----	IR	-----
30	3	SR	-----	IR	-----

Question 2: Change in Pain

Patient #	Baseline Evaluation	Tx #1	Evaluation After Tx 1	Tx #2	Evaluation After Tx 2
1	2	IR	1	SR	1
2	2	SR	1	IR	2
3	1	SR	2	IR	2
4	2	IR	2	SR	1
5	2	SR	2	IR	1
6	3	IR	2	SR	3
7	2	IR	3	SR	1
8	3	IR	2	SR	1
9	2	SR	1	IR	-----
10	2	SR	-----	IR	-----
11	2	IR	2	SR	2
12	2	SR	-----	IR	-----
13	3	SR	2	IR	1
14	2	IR	1	SR	2
15	2	SR	-----	IR	-----
16	2	SR	1	IR	1
17	2	SR	-----	IR	-----
18	2	SR	3	IR	2
19	2	SR	-----	IR	-----
20	2	SR	-----	IR	-----
21	2	IR	-----	SR	-----
22	2	IR	-----	SR	-----
23	2	IR	-----	SR	-----
24	2	IR	1	SR	1
25	2	IR	1	SR	2
26	2	IR	2	SR	3
27	1	SR	1	IR	1
28	2	IR	-----	SR	-----
29	-----	SR	-----	IR	-----
30	1	SR	-----	IR	-----

Question 3: Description of Pain

Patient #	Baseline Evaluation	Tx #1	Evaluation After Tx 1	Tx #2	Evaluation After Tx 2
1	3	IR	3	SR	3
2	2	SR	1	IR	1
3	1	SR	3	IR	3
4	3	IR	1	SR	2
5	3	SR	1	IR	3
6	3	IR	3	SR	3
7	3	IR	3	SR	3
8	3	IR	3	SR	2
9	1	SR	1	IR	-----
10	1	SR	-----	IR	-----
11	2	IR	1	SR	1
12	3	SR	-----	IR	-----
13	3	SR	2	IR	2
14	1	IR	1	SR	1
15	2	SR	-----	IR	-----
16	3	SR	3	IR	3
17	3	SR	-----	IR	-----
18	2	SR	3	IR	2
19	3	SR	-----	IR	-----
20	3	SR	-----	IR	-----
21	1	IR	-----	SR	-----
22	1	IR	-----	SR	-----
23	1	IR	-----	SR	-----
24	2	IR	1	SR	1
25	2	IR	3	SR	3
26	2	IR	1	SR	1
27	1	SR	3	IR	3
28	3	IR	-----	SR	-----
29	-----	SR	-----	IR	-----
30	3	SR	-----	IR	-----

Question 4: Disability – Dressing

Patient #	Baseline Evaluation	Tx #1	Evaluation After Tx 1	Tx #2	Evaluation After Tx 2
1	1	IR	1	SR	1
2	1	SR	1	IR	1
3	1	SR	1	IR	1
4	1	IR	1	SR	1
5	2	SR	1	IR	1
6	1	IR	1	SR	1
7	2	IR	1	SR	1
8	1	IR	1	SR	1
9	1	SR	1	IR	-----
10	1	SR	-----	IR	-----
11	1	IR	1	SR	1
12	1	SR	-----	IR	-----
13	1	SR	1	IR	1
14	1	IR	1	SR	1
15	1	SR	-----	IR	-----
16	1	SR	1	IR	1
17	1	SR	-----	IR	-----
18	1	SR	1	IR	1
19	1	SR	-----	IR	-----
20	1	SR	-----	IR	-----
21	1	IR	-----	SR	-----
22	1	IR	-----	SR	-----
23	1	IR	-----	SR	-----
24	1	IR	1	SR	2
25	1	IR	1	SR	1
26	1	IR	1	SR	1
27	1	SR	1	IR	1
28	1	IR	-----	SR	-----
29	-----	SR	-----	IR	-----
30	1	SR	-----	IR	-----

Question 5: Disability – Eating

Patient #	Baseline Evaluation	Tx #1	Evaluation After Tx 1	Tx #2	Evaluation After Tx 2
1	1	IR	1	SR	1
2	1	SR	1	IR	1
3	1	SR	1	IR	1
4	1	IR	1	SR	1
5	1	SR	1	IR	1
6	1	IR	1	SR	1
7	1	IR	1	SR	1
8	1	IR	1	SR	1
9	1	SR	1	IR	-----
10	1	SR	-----	IR	-----
11	1	IR	1	SR	1
12	1	SR	-----	IR	-----
13	1	SR	1	IR	1
14	1	IR	1	SR	1
15	1	SR	-----	IR	-----
16	1	SR	1	IR	1
17	1	SR	-----	IR	-----
18	1	SR	1	IR	1
19	1	SR	-----	IR	-----
20	1	SR	-----	IR	-----
21	1	IR	-----	SR	-----
22	1	IR	-----	SR	-----
23	1	IR	-----	SR	-----
24	1	IR	1	SR	1
25	1	IR	1	SR	1
26	1	IR	1	SR	1
27	1	SR	1	IR	1
28	1	IR	-----	SR	-----
29	-----	SR	-----	IR	-----
30	1	SR	-----	IR	-----

Question 6: Disability - Stand Up

Patient #	Baseline Evaluation	Tx #1	Evaluation After Tx 1	Tx #2	Evaluation After Tx 2
1	1	IR	1	SR	1
2	1	SR	1	IR	1
3	2	SR	1	IR	1
4	2	IR	1	SR	1
5	2	SR	1	IR	1
6	2	IR	1	SR	1
7	1	IR	1	SR	1
8	1	IR	1	SR	1
9	1	SR	1	IR	-----
10	2	SR	-----	IR	-----
11	1	IR	1	SR	1
12	1	SR	-----	IR	-----
13	2	SR	1	IR	1
14	1	IR	1	SR	1
15	1	SR	-----	IR	-----
16	1	SR	1	IR	1
17	1	SR	-----	IR	-----
18	1	SR	1	IR	1
19	2	SR	-----	IR	-----
20	1	SR	-----	IR	-----
21	1	IR	-----	SR	-----
22	1	IR	-----	SR	-----
23	1	IR	-----	SR	-----
24	3	IR	3	SR	2
25	1	IR	1	SR	1
26	1	IR	1	SR	1
27	2	SR	2	IR	2
28	2	IR	-----	SR	-----
29	-----	SR	-----	IR	-----
30	1	SR	-----	IR	-----

Question 7: Disability – Walking

Patient #	Baseline Evaluation	Tx #1	Evaluation After Tx 1	Tx #2	Evaluation After Tx 2
1	1	IR	1	SR	1
2	1	SR	1	IR	1
3	2	SR	1	IR	1
4	1	IR	1	SR	1
5	1	SR	1	IR	2
6	1	IR	1	SR	1
7	1	IR	1	SR	1
8	1	IR	1	SR	1
9	1	SR	1	IR	-----
10	1	SR	-----	IR	-----
11	1	IR	1	SR	1
12	1	SR	-----	IR	-----
13	2	SR	1	IR	1
14	1	IR	1	SR	1
15	1	SR	-----	IR	-----
16	2	SR	2	IR	2
17	1	SR	-----	IR	-----
18	1	SR	1	IR	1
19	1	SR	-----	IR	-----
20	1	SR	-----	IR	-----
21	1	IR	-----	SR	-----
22	1	IR	-----	SR	-----
23	1	IR	-----	SR	-----
24	1	IR	1	SR	2
25	1	IR	1	SR	1
26	1	IR	1	SR	1
27	1	SR	1	IR	1
28	2	IR	-----	SR	-----
29	-----	SR	-----	IR	-----
30	2	SR	-----	IR	-----

Question 8: Disability - Climbing Stairs

Patient #	Baseline Evaluation	Tx #1	Evaluation After Tx 1	Tx #2	Evaluation After Tx 2
1	1	IR	1	SR	2
2	1	SR	2	IR	1
3	1	SR	1	IR	1
4	1	IR	2	SR	1
5	2	SR	1	IR	1
6	1	IR	1	SR	2
7	3	IR	3	SR	1
8	2	IR	2	SR	1
9	1	SR	1	IR	-----
10	1	SR	-----	IR	-----
11	1	IR	1	SR	1
12	1	SR	-----	IR	-----
13	3	SR	2	IR	1
14	1	IR	1	SR	1
15	1	SR	-----	IR	-----
16	3	SR	2	IR	2
17	1	SR	-----	IR	-----
18	1	SR	1	IR	1
19	2	SR	-----	IR	-----
20	3	SR	-----	IR	-----
21	1	IR	-----	SR	-----
22	1	IR	-----	SR	-----
23	1	IR	-----	SR	-----
24	3	IR	3	SR	3
25	1	IR	1	SR	1
26	1	IR	1	SR	1
27	1	SR	2	IR	1
28	1	IR	-----	SR	-----
29	-----	SR	-----	IR	-----
30	2	SR	-----	IR	-----

Question 9: Disability - Clean House/Everyday Chores

Patient #	Baseline Evaluation	Tx #1	Evaluation After Tx 1	Tx #2	Evaluation After Tx 2
1	1	IR	1	SR	1
2	1	SR	1	IR	1
3	1	SR	1	IR	1
4	1	IR	1	SR	1
5	1	SR	1	IR	1
6	1	IR	2	SR	1
7	1	IR	1	SR	1
8	1	IR	1	SR	1
9	1	SR	1	IR	-----
10	1	SR	-----	IR	-----
11	1	IR	1	SR	1
12	1	SR	-----	IR	-----
13	2	SR	1	IR	1
14	1	IR	1	SR	1
15	1	SR	-----	IR	-----
16	2	SR	2	IR	2
17	1	SR	-----	IR	-----
18	1	SR	1	IR	1
19	1	SR	-----	IR	-----
20	1	SR	-----	IR	-----
21	1	IR	-----	SR	-----
22	1	IR	-----	SR	-----
23	1	IR	-----	SR	-----
24	3	IR	3	SR	3
25	1	IR	1	SR	1
26	1	IR	1	SR	1
27	1	SR	1	IR	2
28	1	IR	-----	SR	-----
29	-----	SR	-----	IR	-----
30	1	SR	-----	IR	-----

Question 10: Pain Relief from Medication

Patient #	Baseline Evaluation	Tx #1	Evaluation After Tx 1	Tx #2	Evaluation After Tx 2
1	2	IR	3	SR	2
2	2	SR	3	IR	3
3	2	SR	1	IR	2
4	1	IR	1	SR	2.5
5	1	SR	1	IR	3
6	1	IR	1	SR	1
7	3	IR	2	SR	2
8	1	IR	3	SR	3
9	2	SR	3	IR	-----
10	3	SR	-----	IR	-----
11	2	IR	2	SR	1
12	-----	SR	-----	IR	-----
13	1	SR	2	IR	3
14	-----	IR	3	SR	3
15	3	SR	-----	IR	-----
16	2	SR	3	IR	3
17	2	SR	-----	IR	-----
18	1	SR	1	IR	2
19	1	SR	-----	IR	-----
20	3	SR	-----	IR	-----
21	2	IR	-----	SR	-----
22	3	IR	-----	SR	-----
23	3	IR	-----	SR	-----
24	1	IR	3	SR	2
25	2	IR	3	SR	3
26	3	IR	3	SR	3
27	2	SR	3	IR	3
28	3	IR	-----	SR	-----
29	-----	SR	-----	IR	-----
30	3	SR	-----	IR	-----

Question 11: Pain Relief Duration

Patient #	Baseline Evaluation	Tx #1	Evaluation After Tx 1	Tx #2	Evaluation After Tx 2
1	2	IR	3	SR	3
2	2	SR	2	IR	3
3	1	SR	1	IR	1
4	3	IR	2	SR	3
5	1	SR	1	IR	2
6	1	IR	2	SR	1
7	3	IR	3	SR	2
8	1	IR	2	SR	2
9	2	SR	2	IR	-----
10	3	SR	-----	IR	-----
11	1	IR	2	SR	1
12	-----	SR	-----	IR	-----
13	1	SR	3	IR	3
14	-----	IR	2	SR	3
15	3	SR	-----	IR	-----
16	1	SR	2	IR	3
17	1	SR	-----	IR	-----
18	1	SR	1	IR	1
19	1	SR	-----	IR	-----
20	3	SR	-----	IR	-----
21	2	IR	-----	SR	-----
22	2	IR	-----	SR	-----
23	3	IR	-----	SR	-----
24	1	IR	1	SR	2
25	2	IR	2	SR	3
26	1	IR	3	SR	3
27	1	SR	2	IR	2
28	3	IR	-----	SR	-----
29	-----	SR	-----	IR	-----
30	1	SR	-----	IR	-----