ELSEVIER

International Journal of Pharmaceutics 133 (1996) 223–235

international journal of pharmaceutics

Relative bioavailability of a novel sustained-release acetaminophen molded tablet[1]

Mohammad Hossain[2]*, James W. Ayres

College of Pharmacy, Oregon State University, Corvallis, OR 97331, USA

Received 17 April 1995; revised 6 November 1995; accepted 4 January 1996

Abstract

An experimental easily swallowable oral sustained-release dosage form of acetaminophen (APAP) that can be administered to patients every 12 hours was formulated and evaluated in 8 healthy, adult volunteers. The test product was compared to a well-characterized, commercially available immediate-release acetaminophen caplet. Multiple doses of these two products were administered to 8 healthy human subjects in a two-way cross-over design. Saliva samples were collected over a period of 24–48 h depending upon the administered treatment. The time course of acetaminophen concentrations in saliva was analyzed using non-compartmental methods. Results indicate that it is possible to maintain the desired therapeutic concentration over a 12-h dosing interval using the molded tablet dosage form.

Keywords: Acetaminophen molded tablet; Multiple dose pharmacokinetics; Non-invasive sample collection; HPLC assay; Relative bioavailability; Sustained release

1. Introduction

Formulation of a new sustained-action acetaminophen (APAP) molded tablet proposed to maintain an average minimum plasma acetaminophen concentration (C_{min}) of 5 μg/ml for 12 h in order to produce maximum analgesic-antipyretic effects for the entire dosing interval has been reported (Hossain and Ayres, 1992). Maximum antipyresis for APAP has been reported to be associated with an average minimum plasma level of 4–6 μg/ml (Wilson et al., 1982; Wilson, 1985).

APAP is a widely used non-prescription, non-narcotic analgesic and antipyretic. Concerns about Reye's syndrome being associated with salicylate use have resulted in APAP becoming one of the safest and most widely used analgesic-antipyretics in children (Temple, 1983; Walson et al., 1989; Yaffe, 1981; Lovejoy, 1978; Tarlin et al., 1972). It is rapidly absorbed from the gastrointes-

[1] The views expressed are personal opinions of the authors and not those of the U.S. Food and Drug Administration.

[2] Current Address: Division of Pharmaceutical Evaluation I, Office of Clinical Pharmacology and Biopharmaceutics, Center for Drug Evaluation and Research, FDA, Rockville, MD 20857 (U.S.A.).

* Corresponding author. 3208 Weeping Willow Court # 33, Silver Spring, MD 20906. Tel.: + 301 594 0488 (work).

PII S0378-5173(96)04445-6

tinal tract with peak plasma concentrations occurring between 0.5 and 2 h post-dosing. However, it is incompletely available to the systemic circulation after oral administration since a variable proportion, depending upon the amount administered, is lost through first-pass metabolism (Chiou, 1975; Perucca and Richens, 1979; Rawlins et al., 1977; Ameer et al., 1983). APAP is extensively metabolized (primarily in the liver) and eliminated in the urine as glucuronide and sulfate conjugates with only 2–5% of a therapeutic dose being excreted unchanged (Cummings et al., 1967). Mean terminal elimination phase half-life values for APAP are in the range of 2–3 h (Forrest et al., 1982; Ahmed and Enever, 1981).

Sustained-release formulations tend to reduce peaks while increasing troughs compared to the more frequent administration of standard formulations (Quiding et al., 1984; Welling, 1983; Baker, 1987). Such a formulation of APAP could provide convenience to patients receiving long-term therapy, and may also suppress pain and fever during a whole night following a single dose at bedtime. Suppositories of APAP produce much flatter plasma concentration curves compared to tablets, and thus mimic the expected plasma concentrations after an oral sustained-release formulation (Seymour and Rawlins, 1981). A marked prolonged antipyretic effect is evident after administration of suppositories of APAP (Maron and Ickes, 1976; Keinanen et al., 1977), and the antipyretic effect does not depend on a high initial plasma concentration peak. Pharmacodynamic-pharmacokinetic considerations across studies have shown that prolonged maximum antipyretic and analgesic effects are expected so long as the average plasma concentrations of APAP are maintained above 5 μg/ml (Hossain and Ayres, 1992). Thus, controlling and prolonging release of therapeutic concentrations of APAP should extend antipyresis and analgesia, thereby decreasing the required frequency of administration.

A significant limitation in oral controlled-release dosage form design is the size of the dose to be administered in order to elicit therapeutic response. This is especially important for a relatively large dose drug like acetaminophen (1000 mg every 6 h), when the half-life is short (2–3 h). Currently, a long-acting dosage form of APAP is not available commercially. An easily swallowable, sustained-release oral dosage form of APAP is desirable. Polymer film coating technology has been used to produce controlled-release (sustained action) acetaminophen beads that can be molded into an easily swallowable, rapidly disintegrating tablet (Hossain and Ayres, 1992).

The purpose of this study is to evaluate the bioavailability of a new, oral controlled-release acetaminophen molded tablet relative to a commercially available product (Extra-Strength Tylenol® caplet). The new tablet is designed and intended to 'melt' (rapidly disintegrate) in the mouth and release individual beads which are then swallowed without chewing or crushing. Relative bioavailability is important in evaluating dosage forms as lower bioavailability means that the dosage form may not be functioning optimally. Hence, a patient may not absorb an effective amount of the dose. The molded tablet contains polymer-coated APAP loaded beads which is designed to prolong or delay absorption in order to sustain therapeutic effect. However, polymer coatings often interfere significantly with absorption resulting in poor bioavailability. This study is needed to show that the sustained-release (SR) molded tablet does allow complete absorption of the active ingredient.

2. Materials and methods

2.1. Molded tablet dosage form production

Production of polymer coated acetaminophen beads using fluid-bed coating technology has already been reported by Hossain and Ayres (1992). Each molded tablet contained a combination of sustained release and immediate release acetaminophen (Table 1). The ingredients listed in Table 1 were individually combined by geometric dilution. The mixed ingredients were moistened with water. All ingredients used in the production of this test tablet meet United States Pharmacopeia guidelines and are common, non-toxic ingredients used routinely in tablet manufacture. The custom made hand molding apparatus used

for making the molded tablets consists of two plates made from plastics (Fig. 1). The mold plate contains 24 polished perforations. The other plate is fitted with a corresponding number of punches which fit the perforations in the mold plate. The mold plate is placed over the plate with the corresponding pegs and the wet mass for each tablet is then gently forced into the perforations and the exposed surface smoothened with a spatula. The mold apparatus was placed in an air-dried oven at 55°C for about 10 min and then removed. As hand pressure was applied to the plates, the pegs forced the tablet out of the mold as shown in Fig. 1. The ejected tablets were placed on individual glass petri-dishes and dried in the oven for an additional 50 min.

2.2. In vitro dissolution

In vitro dissolution was performed in at least triplicate using the USP dissolution apparatus II (Paddle) at 37 ± 0.5°C and 50 rpm. Dissolution media for the first 2 h was 900 ml of enzyme-free simulated gastric fluid (pH = 1.4 ± 0.1), which was then changed by an equivalent volume to enzyme-free simulated intestinal fluid (pH = 7.4 ± 0.1). Samples were collected at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0 h (in gastric fluid) and 3, 4, 5, 6, 8, 12, 24, 30, 36 and 48 h with replacement by an equivalent volume of temperature equilibrated media. Assay of released drug was conducted spectrophotometrically at 244 nm.

Table 1
Composition of molded tablet for acetaminophen pellets

Ingredient	Weight (mg)
Uncoated immediate release beads (200 mg APAP)	268
2.5% Aquacoat coated beads (750 mg APAP)	966
4% Aquacoat coated beads (250 mg APAP)	380
Mannitol[a]	736
Ac-di-sol[b]	150
Total Weight	2500

[a] Mannitol powder, J.T. Baker Chemical Co., Phillipsburg, NJ 08865.
[b] Modified cellulose gum, FMC Corp., Philadelphia, PA 19103.

2.3. Content uniformity

Molded tablets oven-dried for 1.5 h at 55–60°C were ground into a fine powder. All powder was transferred into a 1-l dissolution flask and stirred in 900 ml deionized water at 37 ± 0.5°C for 4 h. Then 3 ml samples were collected, filtered and assayed using a spectrophotometer (Model 34, Beckman Instruments, Inc., Fullerton, California) at 244 nm to determine their acetaminophen content. At least three replicate determinations were performed.

2.4. Ageing study for molded tablet

Molded tablets produced using the formulation listed in Table 1 were placed in small air-tight glass bottles and stored in an air-dried oven at 37°C. In vitro acetaminophen dissolution from these molded tablets was determined after 1 day, 1 week and 1 month. The unmolded formulation was used as control.

2.5. Bioavailability study design

Eight healthy volunteers (6 male and 2 female) participated in this study after written informed consent was obtained from each of the volunteers prior to the study. Average age and weight were 28.8 years and 66.5 kg respectively (Table 2). The study was approved by the Oregon State University Protection of Human Subjects Committee. All participants were taking no medications (including oral contraceptives) or alcohol for at least 3 days prior to and throughout the study period, and had no history of chronic disease. Subjects who smoke regularly, who were allergic to acetaminophen or who received therapy with an enzyme-inducing agent within the previous 30 days were excluded from participation. One treatment consisted of two molded tablets containing uncoated immediate release beads and coated sustained release acetaminophen beads as shown in Table 1, given once every 12 h for a total of three doses. The control treatment consisted of two 500 mg Extra-Strength Tylenol® Caplets, Control No. FCA969 (McNeil Consumer Products Co., Fort Washington, PA) as immediate release product,

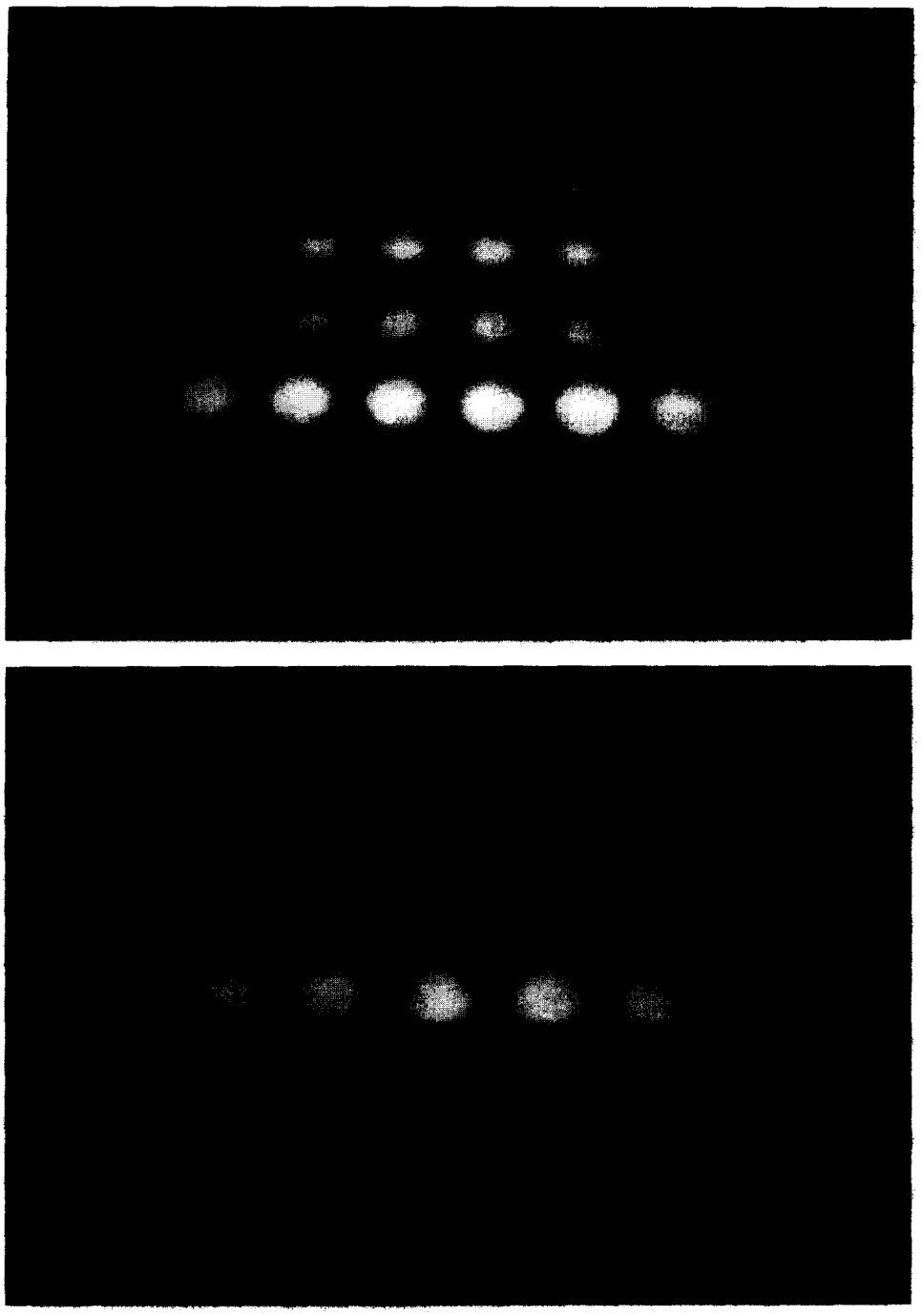

Fig. 1. Hand molding apparatus used for making molded tablets.

given once every 6 h for a total of three doses. Half-lives determined during each treatment suggested that near steady-state conditions prevailed during the third dosing interval for each regimen. Also, the three doses for the dosing intervals selected in this study were more acceptable to the

Table 2
Vital statistics of subjects

Subject No.	Sex	Age (years)	Weight (kg)	Height (cm)
1	F	30	53.6	162.56
2	F	24	54.0	170.18
3	M	30	59.1	169.93
4	M	31	62.3	175.26
5	M	30	95.5	182.88
6	M	27	86.0	176.53
7	M	29	70.5	177.80
8	M	29	51.0	165.10
Mean		28.8	66.5	172.53
S.D.		2.1	15.3	6.82
Range		27–31	51–95.5	162.6–183

volunteers because it allowed convenient sampling schemes.

The molded tablet has been designed to disintegrate into individual beads in the presence of saliva in 30–40 seconds. If needed, small amounts of water can be taken to facilitate disintegration. The individual beads are to be swallowed intact, without chewing. Children and the elderly, and some healthy adults may have swallowing difficulties when given solid oral dosage forms (tablets or capsules), especially drug delivery systems containing a large dose of active ingredient like acetaminophen. The rapidly disintegrating molded tablet dosage form allows easy swallowing of the beads without crushing. If the coated beads are chewed or crushed, all sustained-release properties are lost.

The two treatments were administered randomly as a two-way cross-over design on two occasions with a minimum of a 4-day washout period between treatments (Ahmed and Enever, 1981). Acetaminophen absorption depends on the rate of gastric emptying (Heading et al., 1973) and is delayed with a full stomach (Nimmo, 1976). Increasing amounts of carbohydrate in the gut appear to delay acetaminophen absorption (Jaffe et al., 1971; McGilveray and Mattock, 1972). Therefore, subjects were fasted 12 h prior to and 2 h after the first dose beginning each treatment phase. They were also required to fast 2 h prior and 2 h after the second and third dose. During the fasting periods no food or beverage other than water was allowed.

Treatments were administered by volunteers either at home or in the Pharmaceutics laboratory with 180 ml of water. Immediately after swallowing the dosage form and water, the individual's mouth was rinsed with 20 ml of Scope® mouthwash (Proctor and Gamble, Cincinnati, OH) followed by a water rinse to eliminate any residual drug from the oral cavity, thus avoiding contamination of the first postdose saliva sample.

2.6. Saliva sample collection

Drug excretion in saliva has been reported in man (Borzelleca and Cherrick, 1965; Danhof and Breimer, 1978) and saliva concentrations of acetaminophen have been reported to be proportional to plasma concentrations (Ahmed and Enever, 1981; Adithan and Thangam, 1982; Glynn and Bastain, 1973; Kamali et al., 1987). However, definitive individual correlations have not been established. To gain an initial approximation of the systemic availability of APAP from this SR formulation, collection and measurement of acetaminophen in saliva was preferred because it presents a non-invasive method of obtaining information about acetaminophen plasma concentrations. It also allowed the participants to collect their own samples without the discomfort, possible hazards, and necessary attendance of medical staff required for repeated venipunctures.

Saliva samples were collected by each subject in 12-ml glass centrifuge tubes over a 1-min period

by chewing on Parafilm (American Can Co., Greenwich, CT) squares (2.5 cm X 2.5 cm) to induce saliva production. Subjects were also required to refrain from drinking beverages, juice, water or brushing teeth to prevent artificial dilution of acetaminophen in the saliva sample, and not to ingest food immediately preceding saliva collection to avoid excessive accumulation of particulate matter in samples. Samples were collected according to the following schedule: 0 h (just prior to first dose, second dose, and third dose with each treatment), and then 10, 20, 30, 45 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 h after the third dose for the commercial Tylenol® caplet treatment and additional samples at 16, and 24 h after the third dose for the molded tablet. Samples were covered with Parafilm and refrigerated immediately after collection.

All saliva samples were returned to the laboratory at the end of each treatment. Samples were frozen at −20°C, thawed and centrifuged (Beckman Model TJ-6 Centrifuge, Palo Alto, CA) at 3000 rpm for 30 min to remove mucous and particulate matter. Salivary supernatant was removed and transferred to 2.5-ml polypropylene Cryo-Stor screw-cap vials (Perfector Scientific, Inc., Atascadero, CA) and stored at −20°C until analyzed. These were again centrifuged prior to HPLC analysis.

2.7. Standard acetaminophen solutions

Stock solutions containing 20, 50, 100, 200, 300, 400, 500, 600, 800, 1000, 1200 and 1500 μg/ml of acetaminophen (Sigma Chemical Co., St. Louis, MO) were prepared in distilled, deionized water. An 80 μg/ml solution of 2-acetamidophenol (Sigma Chemical Co., St. Louis, MO) in distilled water was used as the internal standard. Standards were prepared by spiking 500 μl of blank saliva with 25 μl of the above stock solutions. One hundred microliters of standard or unknown was mixed with 100 μl of internal standard solution in a 250 μl polyethylene centrifuge tube and vortexed for 20 seconds, prior to injection into a high pressure liquid chromatograph (HPLC).

2.8. Acetaminophen HPLC assay

Acetaminophen concentration in saliva was determined by an HPLC system consisting of a delivery pump (M-6000A, Waters Associates, Milford, MA), an automatic sample injector (WISP 712B, Waters Associates, Milford, MA), a C-1308 guard column with Perisorb® RP-18 packing material (Upchurch Scientific, Inc., Oak Harbor, WA), a 4.6 mm X 25 cm reverse phase Zorbax Pro-10 C8 analytical column (Part No. 884988-902, Du Pont Company, Wilmington, DE), a fixed wavelength UV detector (Model 440, Waters Associates, Milford, MA) set at 254 nm, and an integrator (C-R3A Chromatopac, Shimadzu Corp., Kyoto, Japan).

Saliva acetaminophen concentrations were determined using a modification of an HPLC procedure used by Borin and Ayres (1989). Mobile phase consisted of 10% (v/v) methanol in distilled water at a flow rate of 2.5 ml/min. Injections of 10 μl were made with the UV absorbance detector set at 0.005 AUFS sensitivity. Integrator attenuation and chart speed were 5 and 6 mm/min. Retention times were 2.6 min for acetaminophen and 3.4 min for 2-acetamidophenol (Fig. 2).

Standard curves were generated using the peak area ratios of acetaminophen:internal standard versus known acetaminophen concentration fit to a line via linear regression. A typical standard curve is shown in Fig. 3. Standard curves were run daily and had coefficients of determination, $R^2 \geq 0.994$. The linear range of the standard curve was found to be from 0.95 to 71.4 μg/ml. The coefficient of variation varied from 4.7 to 8.32% over the range of 0.95 to 47.62 μg/ml of acetaminophen. The sensitivity of the assay was approximately 1 μg/ml. Replicate analysis of the high and low concentrations revealed only a slight variation for the lower concentration. Additional standard samples were run at the middle and at the end of the HPLC assay as control. Concentrations above the range of the linear standard curve were reassayed after dilution and concentrations below the range of the linear standard curve were reported to be below the limit of quantitation (LOQ). A coefficient of variation (CV) of not more than ± 15% (except for LOQ, where it

should not exceed ± 20%) was considered to be acceptable for both accuracy and precision.

2.9. Noncompartmental analysis

Bioavailability parameters were calculated from saliva acetaminophen concentration-time curves for the last (third) dose with model-independent calculations for both Extra-Strength Tylenol® and the sustained-action molded tablet. The peak saliva concentration (C_{max}), time to peak concentration (T_{max}) and lag time (T_{lag}) were obtained from individual concentration-time profiles for each of the administered products. Terminal elimination rate constants (K) were estimated by least squares regression of concentration-time data points lying in the terminal log-linear region of the curves. Area under the concentration-time curve (AUC) and area under the moment curve (AUMC) were calculated for the third dose (assuming steady-state has been reached for both treatments) using the linear trapezoidal rule. Ratio of AUMC to AUC gave mean residence time (MRT). MRT has been defined as the mean time for intact drug molecules to transit through the body (Riegelman and Collier, 1980). Relative bioavailability (F_{rel}) for the molded tablet was calculated as the ratio of AUC_{24-36} for the third dose of the molded tablet divided by AUC_{12-18} for Extra-Strength Tylenol® third dose for each subject. AUC_{12-18} adjusted to a 2400 mg dose were made for the third dose of Extra-Strength Tylenol® prior to calculation of F_{rel}.

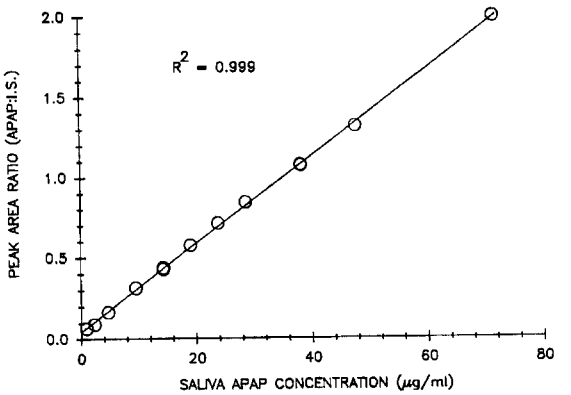

Fig. 3. Plot of peak area ratios of acetaminophen (APAP):internal standard (I.S.) versus known acetaminophen concentration.

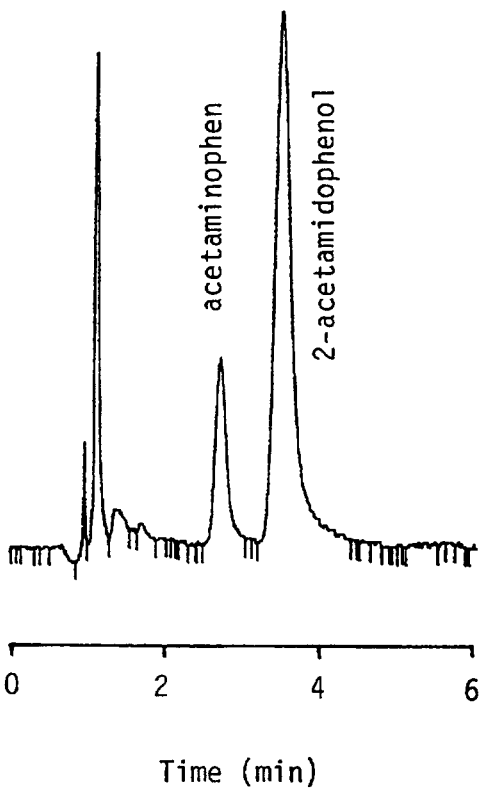

Fig. 2. Typical chromatogram for acetaminophen and 2-acetamidophenol.

2.10. Statistical analysis

Statistical analysis of selected bioavailability parameters and dose-corrected parameters was performed using analysis of variance (ANOVA). Calculations were performed using STATGRAPHICS (STATGRAPHICS User's Guide, 1987) software (STSC Inc., 1987). Statistical significance among treatments, period/days and subjects was evaluated using a three-way ANOVA.

3. Results and discussion

3.1. In vitro dissolution data

Dissolution from molded tablets produced using the formulation listed in Table 1 appears to be slightly faster than the unmolded formulation as shown in Fig. 4a. The slight increase in dissolution rate from about 6.5% per h to about 7.3% per h (Fig. 4b) maybe due to the tablet molding process, which involves moistening of the pellets with water and mixing with a spatula. Content uniformity from ground molded tablets ($n = 3$) revealed the percent APAP content to be 109% ± 2.6% and is consistent with the percent of APAP released from the molded tablets (Fig. 4a). Drug dissolution from the unmolded pellet formulation shows some APAP is still retained in the beads for the duration of the dissolution study.

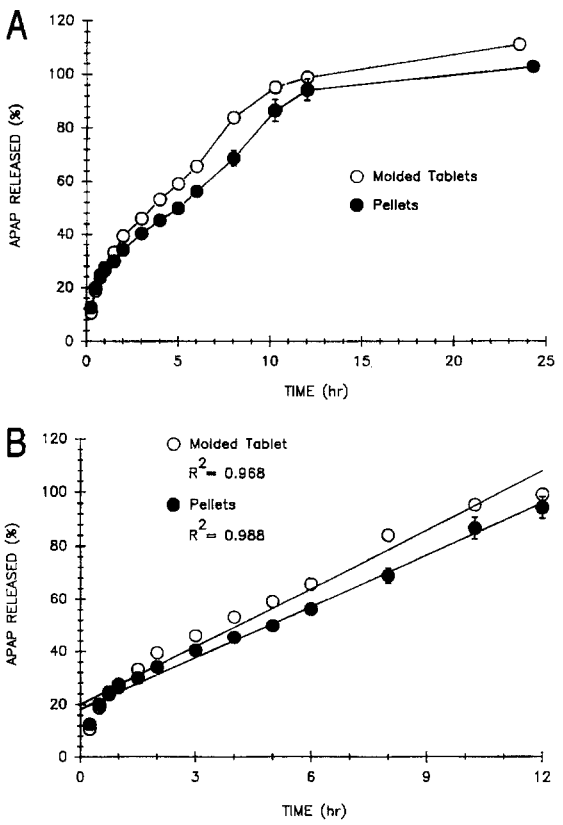

Fig. 4. (a) Dissolution profile of molded tablet and unmolded pellets (formulation listed in Table 1). (b) Simple linear regression of dissolution data of molded tablet and unmolded pellets (formulation listed in Table 1).

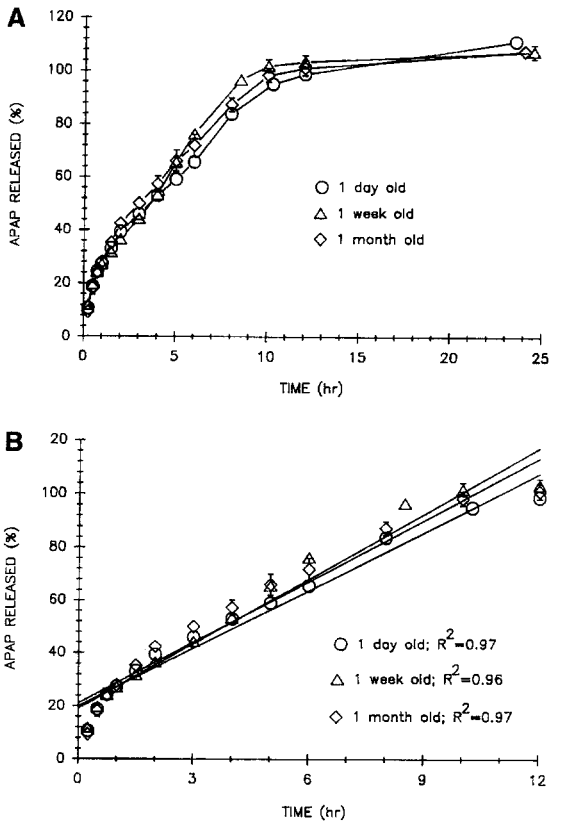

Fig. 5. (a) Dissolution profile of molded tablets aged 1 day, 1 week and 1 month (formulation listed in Table 1). (b) Simple linear regression of dissolution data of molded tablets aged 1 day, 1 week and 1 month (formulation listed in Table 1).

Molded tablets produced using the ingredients listed in Table 1 and aged 1 day, 1 week, and 1 month possess similar dissolution profiles (Fig. 5a). The data can be approximated by straight lines whose slopes range from 7.3% per h to 8.2% per h (Fig. 5b) and are sufficiently close to the desired sustained zero-order release rate of 8.3% per h over 12 h.

3.2. In vivo acetaminophen data

Noncompartmental bioavailability parameters calculated from saliva acetaminophen concentration-time data for each of the administered products are presented in Table 3 and Table 4.

Table 3
Non-compartmental pharmacokinetic parameters (steady state 12–18 h) for acetaminophen following multiple oral administration of 2 X 500 mg Extra-Strength Tylenol® Caplets (1000-mg dose)

Parameters	Subject Number								Mean	C.V.(%)[a]
	1	2	3	4	5	6	7	8		
K (h^{-1})[b]	0.344	0.246	0.328	0.334	0.189	0.398	0.249	0.271	0.295	22.9
$T_{1/2}$ (h)[c]	2.02	2.82	2.11	2.08	3.66	1.74	2.78	2.56	2.47	25.0
AUC (μg.h/ml)[d]	92.27	86.12	60.34	39.25	41.44	39.15	36.25	75.98	58.85	39.3
AUMC (μg.h^2/ml)[e]	188.3	184.9	127.5	106.1	111.8	100.7	106.5	235.2	145.1	34.9
MRT (h)[f]	2.04	2.15	2.11	2.70	2.70	2.57	2.94	3.10	2.54	15.7
C_{max} (μg/ml)[g]	35.4	36.3	22.5	11.8	15.3	11.9	11.1	22.4	20.8	49.4
T_{max} (h)[h]	0.5	0.5	0.75	2.0	1.5	1.5	1.5	1.5	1.22	45.7
AUC_D (μg/ml)[i]	221.4	206.7	144.8	94.2	99.5	94.0	87.0	182.4	141.3	39.3
C_{maxD} (μg/ml)[j]	84.9	87.1	54.1	28.3	36.7	28.5	26.7	53.8	50.0	49.4

[a] Coefficient of variation.
[b] Slope of the terminal log-linear region of saliva acetaminophen concentration-time curve calculated by least squares regression.
[c] Half-life = 0.693/K.
[d] AUC for the third dose (12–18 h).
[e] AUMC for the third dose (12–18 h).
[f] MRT = AUMC/AUC.
[g] Maximum observed concentration.
[h] Time to maximum observed concentration.
[i] Area under the curve adjusted to a 2400-mg dose.
[j] Maximum observed concentration adjusted to a 2400-mg dose.

Following administration of 1000 mg acetaminophen from Extra-Strength Tylenol® caplets, average maximum saliva acetaminophen concentration (C_{max}) and average time to maximum concentration (T_{max}) at steady state (third dose) were 20.8 μg/ml and 1.22 h, respectively, indicating relatively rapid absorption. For all the concentration-time curves there was a lag time (T_{lag}) between administration of the Extra-Strength Tylenol® caplet and onset of absorption. Mean lag time was found to be 0.35 h (CV = 50%).

The mean saliva acetaminophen concentrations for all subjects and for each acetaminophen product are shown in Fig. 6. Average minimum saliva acetaminophen concentrations of 5 μg/ml or greater correlate with therapeutic efficacy. Following administration of two 1200 mg molded tablets given once every 12 h for a total of three doses, the average saliva acetaminophen concentration-time curve is consistent with rapid achievement of therapeutic concentration and maintenance of that concentration over the dosing period of 12 h. Average maximum saliva acetaminophen concentration of 22.4 μg/ml was achieved at 2.13 h (Table 4). Decline of saliva acetaminophen concentration was slower than for the immediate release product (Extra-Strength Tylenol® caplet), as would be expected from a sustained-release dosage from. There is a minimal lag time, if any, from the molded tablet compared to the Extra-Strength Tylenol® caplets (Fig. 6). This may be due to the fact that the molded tablet contains multiple units of coated and uncoated acetaminophen beads which provide a larger surface area for drug dissolution and absorption compared to the single unit Extra-Strength Tylenol® caplets. Hence, more rapid absorption may occur following administration of the molded tablet. Recently, it has been reported that under fasted conditions, saliva APAP profile shows rapid absorption from Tylenol® tablets but absorption is slower and incomplete from sustained-release acetaminophen matrix tablets (Phuapradit and Bolton, 1991).

Table 4
Non-compartmental pharmacokinetic parameters (steady state 24–36 h) for acetaminophen following multiple oral administration of 2 X 1200 mg Molded Tablets (2400-mg dose)

Parameters	Subject Number								Mean	C.V.(%)[a]
	1	2	3	4	5	6	7	8		
K (h^{-1})[b]	0.118	0.135	0.162	0.119	0.113	0.309	0.143	0.136	0.154	42
$T_{1/2}$ (h)[c]	5.88	5.14	4.29	5.85	6.15	2.24	4.84	5.08	4.93	25.4
AUC (μg.h/ml)[d]	195.3	174.8	114.6	107.8	97.5	56.9	120.2	275.4	142.8	48.3
AUMC (μg.h^2/ml)[e]	947.3	818.4	570.9	559.3	533.8	290.0	470.7	1279	683.7	46
MRT (h)[f]	4.85	4.68	4.98	5.19	5.48	5.10	3.91	4.64	4.85	9.7
C_{max} (μg/ml)[g]	35.5	25.5	15.0	14.0	11.8	7.9	26.4	42.9	22.4	55
T_{max} (h)[h]	3.0	2.0	4.0	3.0	2.5	1.5	0.5	0.5	2.13	58.5
F^{i}_{rel}	0.88	0.85	0.79	1.15	0.98	0.61	1.38	1.51	1.02	30

[a] Coefficient of variation.
[b] Slope of the terminal log-linear region of saliva acetaminophen concentration-time curve calculated by least squares regression.
[c] Half-life = 0.693/K.
[d] AUC for the third dose (24–36 h).
[e] AUMC for the third dose (24–36 h).
[f] MRT = AUMC/AUC.
[g] Maximum observed concentration.
[h] Time to maximum observed concentration.
[i] Relative bioavailability = AUC (24–36 h) molded tablet/AUC (12–18 h) for Extra-Strength Tylenol® caplets adjusted to a 2400-mg dose.

Minimum saliva acetaminophen concentration (C_{min}) beginning at time 0 h and at the end of each dosing interval for each of the administered product were also averaged at each time point and is shown in Fig. 7. This plot shows negligible drug accumulation in the body relative to the first dose and the probable achievement of a steady state. Average minimum saliva acetaminophen concentrations of 5 μg/ml or greater were maintained throughout each dosing interval by the sustained-action molded tablet. Computer simulation using a dual input function following multiple oral administration of the molded tablet did

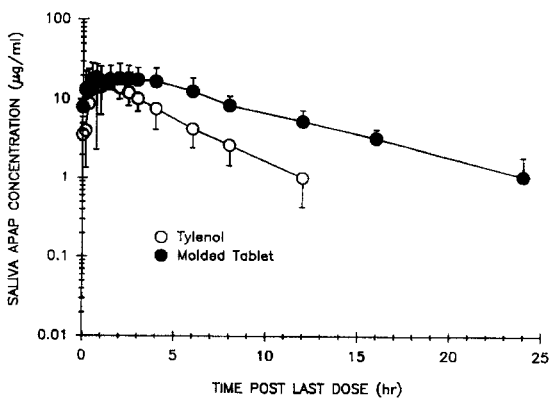

Fig. 6. Average saliva acetaminophen concentration-time profiles for all subjects. Extra-Strength Tylenol® caplet (1000 mg dose, 12–24 h data) and molded tablet (2400 mg dose, 24–48 h data). Standard deviation error bars are shown except in those cases when they are smaller than the symbol.

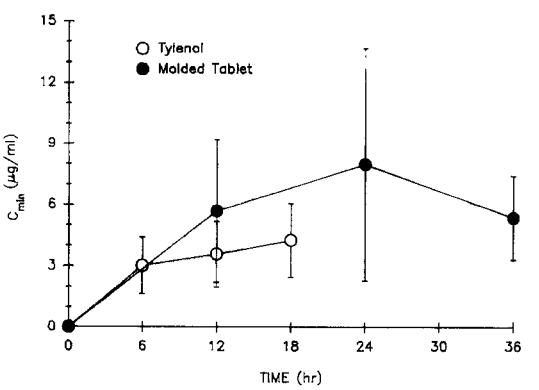

Fig. 7. Average minimum saliva acetaminophen concentration (C_{min}) for Extra- Strength Tylenol® caplet (1000 mg dose; 0, 6, 12 and 18 h data) and molded tablet (2400 mg dose; 0, 12, 24 and 36 h data). Standard deviation error bars are shown.

Table 5
Summary statistics for average pharmacokinetic parameters[a] following oral administration of acetaminophen products calculated by non-compartmental methods at steady state

Parameters	Extra-Strength Tylenol® Caplets	Molded Tablets	ANOVA[b]
K (h^{-1})[c]	0.295 ± 0.068	0.154 ± 0.06	< 0.01
$T_{1/2}$ (h)[d]	2.47 ± 0.62	4.93 ± 1.25	< 0.01
AUC (μg.h/ml)	141.3 ± 55.5[e]	142.8 ± 69	N.S.
MRT (h)[f]	2.54 ± 0.4	4.85 ± 0.47	< 0.01
C_{max} (μg/ml)	50 ± 24.7[g]	22.4 ± 12.3	0.01
T_{max} (h)[h]	1.22 ± 0.56	2.13 ± 1.25	N.S.
F^{i}_{rel}	—	1.02 ± 0.3	N.S.

[a] Average values ± standard deviation.
[b] Analysis of variance, significance level of difference among treatments; N.S. (not significant at $P \leq 0.05$).
[c] Slope of the terminal log-linear region of saliva acetaminophen concentration-time curve calculated by least squares regression.
[d] Half-life = 0.693/K. Note that a flip flop model exists for the sustained release molded APAP tablet, so this becomes an apparent $T_{1/2}$ based on the terminal slope and is not the true half-life of APAP.
[e] Area under the curve adjusted to a 2400-mg dose.
[f] Mean residence time.
[g] Maximum observed concentration adjusted to a 2400-mg dose.
[h] Time to maximum observed concentration.
[i] Relative bioavailability = AUC (24–36 h) molded tablet/AUC (12–18 h) for Extra-Strength Tylenol® caplets.

predict maintenance of an average minimum concentration of 5 μg/ml (Hossain and Ayres, 1992). The average dose-corrected saliva acetaminophen concentration following administration of Extra-Strength Tylenol® caplets decreased to subtherapeutic levels (< 5 μg/ml) at the end of 12 h.

Selected average bioavailability parameters following administration of each acetaminophen product are given in Table 5. Three-way analysis of variance (ANOVA) for statistical significance among treatments, periods/days, and subjects were performed using STATGRAPHICS. Period effects were not found to be significant at $P \leq 0.05$. Statistically significant differences ($P < 0.01$) between treatments were observed for terminal slopes (K), half-life ($T_{1/2}$), and mean residence time (MRT) at steady state (Table 5). Thus, the apparent, but not true, half-life of acetaminophen in saliva is prolonged as would be expected for a sustained release product (slow drug input). Because input is slower for the molded tablet, transit of drug molecules will be slower. This is reflected in the magnitude of MRT for the molded tablet and is consistent with sustained release of acetaminophen. The difference between maximum observed saliva acetaminophen concentrations (C_{max}) corrected for dose was significant ($P = 0.01$). Dose adjustment of the C_{max} for the 1000-mg dose of conventional Extra-Strength Tylenol® upward to the 2400-mg dose of APAP SR molded tablet confirm that the SR tablet does not dose-dump. The difference between mean time to maximum observed saliva acetaminophen concentration (T_{max}), dose normalized area under the curve (AUC), and relative bioavailability (F_{rel}) were not significant ($P \leq 0.05$). Both products appear to possess equal extent of absorption.

Although statistically not significant, mean T_{max} was longer for the molded tablet. This may be due to the combination of three different acetaminophen release rates (Table 1) resulting from the immediate release portion, 2.5% Aquacoat sustained-action portion, and the 4% Aquacoat portion in the molded tablet dosage form. Significant differences in apparent K ($P = 0.04$) and dose corrected AUC ($P = 0.02$) were observed among subjects, which would be expected due to intersubject biological variation.

4. Conclusions

Bioavailability of the sustained-release molded tablet is comparable to that of the immediate-re-

lease product. Hence, the extent of bioavailability from the molded tablet has not been affected by presystemic biotransformation due to either first-pass hepatic extraction or metabolism in the epithelium, and/or lumen of the gastrointestinal tract, or by a combination of these processes as reported to occur at single doses below 625 mg (Rawlins et al., 1977; Ameer et al., 1983; Borin and Ayres, 1989). Dosage from two molded tablets contained 400 mg immediate-release and 2 g sustained-release drug. Amount of drug absorbed at steady state from lower doses (325 mg) was reported to be not different from that absorbed from higher doses (650–1000 mg) following multiple oral administration of immediate-release Tylenol® tablets (Sahajwalla and Ayres, 1987).

Polymer-coated acetaminophen beads were effective in maintaining an average minimum saliva acetaminophen concentrations of 5 μg/ml over a 12-h dosing interval. The dose administered as a sustained-release APAP molded tablet could apparently be reduced, possibly to below 4 g/day, while maintaining the desired 5 μg/ml trough level of APAP. This would allow conservation of dose. In vitro dissolution data were consistent with successful performance of the molded tablet following in vivo administration. Prolonged release of therapeutic acetaminophen concentrations would likely extend antipyresis and analgesia, thereby reducing the required frequency of administration. This type of dosage form should be of benefit to any age patient who can swallow the disintegrated tablet without chewing the released beads.

References

Adithan, C. and Thangam, J., A comparative study of saliva and serum paracetamol levels using a simple spectrophotometric method. *Br. J. Clin. Pharmacol.*, 14 (1982) 107–109.

Ahmed, M. and Enever, R.P., Formulation and evaluation of sustained release paracetamol tablets. *J. Clin. Hosp. Pharm.*, 6 (1981) 27–38.

Ameer, B., Divoll, M., Abernathy, D.R., Greenblat, D.G. and Shargel, L., Absolute and relative bioavailability of oral acetaminophen preparations. *J. Pharm. Sci.*, 72 (1983) 955–958.

Baker, R.W., *Controlled release of biologically active agents*, John Wiley and Sons, New York, 1987, pp. 4–12.

Borin, M.T. and Ayres, J.W., Single dose bioavailability of acetaminophen following oral administration. *Int. J. Pharm.*, 54 (1989) 199–209.

Borzelleca, J.F. and Cherrick, H.M., Excretion of drugs in saliva. *J. Oral Ther. Pharmacol.*, 2 (1965) 180–187.

Chiou, W.L., Estimation of hepatic first-pass effect of acetaminophen in humans after oral administration. *J. Pharm. Sci.*, 64 (1975) 1734–1735.

Cummings, A.J., King, M.L. and Martin, B.K., A kinetic study of drug elimination: the excretion of paracetamol and its metabolites in man. *Br. J. Pharmac. Chemother.*, 29 (1967) 150–157.

Danhof, M. and Breimer, D.D., Therapeutic drug monitoring in saliva. *Clin. Pharmacokinet.*, 3 (1978) 39–57.

Forrest, J.A.H., Clements, J.A. and Prescott, L.F., Clinical pharmacokinetics of paracetamol. *Clin. Pharmacokinet.*, 7 (1982) 93–107.

Glynn, J.P. and Bastain, W., Salivary excretion of paracetamol in man. *J. Pharm. Pharmac.*, 25 (1973) 420–421.

Heading, R.C., Nimmo, J., Prescott, L.F. and Tothill, P., The dependence of paracetamol absorption on the rate of gastric emptying. *Br. J. Pharmacol.*, 47 (1973) 415–421.

Hossain, M. and Ayres, J.W., Pharmacokinetics and pharmacodynamics in acetaminophen controlled release beads design. *J. Pharm. Sci.*, 81 (1992) 444–448.

Jaffe, J.M., Colaizzi, J.L. and Barry, H., Effects of dietary components on GI absorption of acetaminophen tablets in man. *J. Pharm. Sci.*, 60 (1971) 1646–1650.

Kamali, F., Fry, J.R. and Bell, G.D., Salivary secretion of paracetamol in man. *J. Pharm. Pharmacol.*, 39 (1987) 150–152.

Keinanen, S., Heitula, M., Simila, S. and Kouvalainen, K., Antipyretic therapy. Comparison of rectal and oral paracetamol. *Eur. J. Clin. Pharmacol.*, 12 (1977) 77–80.

Lovejoy, F.H. Jr., Aspirin and acetaminophen: A comparative view of their antipyretic and analgesic activity. *Pediatrics*, 62 (1978) 904–909.

Maron, J.J. and Ickes, A.C., The antipyretic effectiveness of acetaminophen suppositories versus tablets: A double-blind study. *Curr. Ther. Res.*, 20 (1976) 45–52.

McGilveray, I.J. and Mattock, G.L., Some factors affecting the absorption of paracetamol. *J. Pharm. Pharmacol.*, 24 (1972) 615–619.

Nimmo, W.S., Drugs, diseases and altered gastric emptying. *Clin. Pharmacokinet.*, 1 (1976) 189–203.

Perucca, E. and Richens, A., Paracetamol disposition in normal subjects and patients treated with antiepileptic drugs. *Br. J. Clin. Pharmacol.*, 7 (1979) 201–206.

Phuapradit, W. and Bolton S., The influence of tablet density on the human oral absorption of sustained release acetaminophen matrix tablets. *Drug Dev. Ind. Pharm.*, 17 (1991) 1097–1107.

Quiding, H., Oikarinen, V., Sane, J. and Sjoblad, A.M., Analgesic efficacy after single and repeated doses of codeine and acetaminophen. *J. Clin. Pharmacol.*, 24 (1984) 27–34.

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

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

Sahajwalla, C.G. and Ayres, J.W., *New product formulation and multiple dose pharmacokinetics of acetaminophen.* Ph.D. thesis, Oregon State University, Corvallis, Oregon, 1987.

Seymour, R.A. and Rawlins, M.D., Pharmacokinetics of parenteral paracetamol and its analgesic effects in post-operative dental pain. *Eur. J. Clin. Pharmacol.*, 20 (1981) 215–218.

STATGRAPHICS User's Guide, STSC Inc., Rockville, MD, 1987.

Tarlin, L., Landrigan, P., Babineau, R. and Alpert, J.J., A comparison of the antipyretic effect of acetaminophen and aspirin. *Am. J. Dis. Child.*, 124 (1972) 880–882.

Temple, A.R. Review of comparative antipyretic activity in children. *Am. J. Med.*, 75 (1983) 38–46.

Walson, P.D., Galletta, G., Braden, N.J. and Alexander, L., Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin. Pharmacol. Ther.*, 46 (1989) 9–17.

Welling, P.G., Oral controlled drug administration. *Drug Dev. Ind. Pharm.*, 9 (1983) 1185–1225.

Wilson, J.T., Brown, R.D., Bocchini, J.A. Jr., Kearns, J.L., Efficacy, disposition and pharmacodynamics of aspirin, acetaminophen and choline salicylate in young febrile children. *Ther. Drug Monit.*, 4 (1982) 147–180.

Wilson, J.T., Clinical pharmacology of pediatric antipyretic drugs. *Ther. Drug Monit.*, 7 (1985) 2–11.

Yaffe, S.J., Comparative efficacy of aspirin and acetaminophen in the reduction of fever in children. *Arch. Intern. Med.*, 141 (1981) 286–292.