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THE INFLUENCE OF TABLET DENSITY ON THE HUMAN ORAL ABSORPTION OF SUSTAINED RELEASE ACETAMINOPHEN MATRIX TABLETS

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ABSTRACT

Low density bilayer compressed matrix tablets of acetaminophen were tested for in vitro dissolution and in vivo oral absorption. The upper layer contained a carbon dioxide-generating blend and the lower layer contained hydroxypropyl methylcellulose (HPMC) and acetaminophen. Carbon dioxide liberated by the action of the acidic dissolution medium on the upper layer is entrapped in the gelled hydrocolloid, providing buoyancy of the tablet and sustained release of the drug. For comparative purposes, similar but non-gas generating bilayer compressed matrix tablets were formulated and tested in vitro under the same conditions. These high density tablets were found to yield similar dissolution profiles as the low density tablets. The absorption characteristics of the bilayer compressed matrix tablets were compared with those of rapidly disintegrating acetaminophen tablets (TYLENOL® tablets, 500 mg) under fasted and fed conditions in six healthy subjects. Under fasted conditions, saliva profiles showed a rapid absorption for TYLENOL® tablets but slower absorption for both compressed matrix tablets. Saliva profiles of TYLENOL® tablets under fed conditions were similar to those for the fasted case. In contrast, the peak saliva levels of acetaminophen for both compressed matrix tablets were significantly increased under fed conditions. The time to maximum saliva concentrations (Tmax) of all three dosage forms was not significantly affected by food intake. The relative bioavailability of the low density tablets under fasted and fed conditions was

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not significantly different from those of TYLENOL® tablets, but was significantly greater than that of high density tablets under fasted and fed conditions. A possibility exists that the buoyancy mechanism enabled the tablet to maintain more prolonged residence time in the gastrointestinal tract.

INTRODUCTION

A significant limitation to the bioavailability of oral controlled release drug delivery systems is gastrointestinal (GI) transit. The normal movement of conventional oral dosage forms through various segments of the GI tract limits the residency of drug delivery systems. The time for absorption in the GI transit in humans, estimated to be 8 - 10 hr from mouth to colon, is relatively brief with considerable fluctuation.

A number of investigators have attempted to increase the gastric residence time (GRT) of dosage forms using concepts such as swelling (1), flotation (2-4) and adhesion (5,6). Sheth and Tossounian (2,3) claimed that a floating system containing HPMC and drug acquires, upon contact with gastric fluid, a bulk density of less than one due to the swelling of hydrocolloids. It then remains buoyant in the gastric fluid with a resultant prolonged GRT. However, using gamma scintigraphy Davis et al. (7) demonstrated that both floating and non-floating single-unit dosage forms generally have short GRTs under fasted conditions (< 2 hr) but prolonged GRT (≥ 4 hr) under fed conditions. They concluded that the presence of food, rather than buoyancy, is the most important determinant of GRT.

Hydrophilic matrix tablets are becoming popular in drug therapy as a means of extending the release characteristics of certain drugs. The major disadvantage of these hydrophilic swellable polymeric systems is that drug release rate will continuously decrease with time (8,9). The mean small intestinal transit time for approximately 3 hr (10,11). Obviously the shorter the residence time, the less time there is for the dissolution and absorption processes. Variability in bioavailabilty could be observed if the drug is poorly or erratically absorbed from the large intestine.

In the present study, the influence of the density of the matrix on drug absorption kinetics and bioavailability were investigated. HPMC was the hydrophilic polymer used to form the matrix and a carbon dioxide generating blend (i.e., sodium bicarbonate and calcium carbonate) was

incorporated to provide in vitro buoyancy of tablets in 0.1 N HCl. Acetaminophen was chosen as the drug for an in vivo study for the following reasons: (i) it has low toxicity and a relatively short biological half-life (<3 hr); (ii) it can be analytically determined easily in saliva; (iii) it is neither bound to saliva protein nor it is adsorbed onto the buccal mucosa (12); and (iv) its concentrations in blood show a good correlation with those in saliva (13,14).

EXPERIMENTAL

Materials - Acetaminophen (Amend Drug & Chemical Co., Irvington, NJ.), HPMC 4000, 60 HG (Ruger Chemical Co., Irvington, NJ.), METHOCEL K4M CR grade (Dow Chemical Co., Midland, MI.), AVICEL PH 101 (FMC Corp., Newark, NJ.), magnesium stearate (Mallinckrodt Inc., Paris, KY.), calcium carbonate and sodium bicarbonate (J.T. Baker Chemical Co., Phillipburg, NJ.), isopropyl alcohol (Fisher Scientific Co., Fair Lawn, NJ.), and methylene chloride (Aldrich Chemical Co., Milwaukee, WI.) were all used as received.

Preparation of Matrices - Two batches of HPMC matrices were prepared, the following formulas of which are given below.

Ingredient	Low Density Matrix (LDM)	High Density Matrix (HDM)
Layer A		
Calcium carbonate, mg	50.00	-
Sodium bicarbonate, mg	10.00	-
HPMC 4000 (60 HG), mg	50.00	50.00
AVICEL PH 101, mg	-	60.00
Magnesium stearate, mg	0.55	0.55
Layer B		
Acetaminophen, mg	250.00	250.00
METHOCEL K4M, mg	20.00	20.00
AVICEL PH 101, mg	60.00	60.00
Magnesium stearate, mg	1.65	1.65

Each matrix was composed of two layers, layer A was prepared by dry mixing and layer B was prepared by wet granulation. The two layers were compressed on a Carver Press tabletting machine at 5000 lbs to produce a two-layered tablet.

Dissolution - The in vitro dissolution behavior of the tablets was monitored using a method based upon USP rotating basket apparatus (15). The drug was assayed spectrophotometrically at 242 nm. 0.1 N HCl was used as a dissolution medium.

Study Protocol - The study was conducted in six healthy volunteers (age, 27 to 34 years; height, 5 to 6.2 ft; weight, 115 to 170 lb), who participated with informed consent. In phase 1 (fasted condition), the subjects received 500 mg of acetaminophen as LDM, HDM, or TYLENOL® tablets in a 3-way crossover design. The tablets were ingested in the sitting position with 250 ml of water. The subjects were not allowed to drink any coffee, tea, or take any medication during the study. Two hours later, an additional 100 ml of water was taken. No food was permitted until 4 hr after dosing, at which time a standard lunch was provided. In phase 2 (fed condition), the subjects received the LDM, HDM, or TYLENOL® tablets in a 3-way crossover design after ingesting a standard breakfast. Two hours later, 100 ml of water was taken. No food was permitted until 4 hr later.

Saliva samples (3 ml) were collected in glass vials before dosing and at the specified time intervals up to 30 hr. Samples were kept frozen until assayed.

Assay of Saliva Samples - After thawing, saliva samples were centrifuged to remove insolubles. An appropriate volume of sample was extracted with ethyl acetate (3 x 6 ml). The clear supernatants were combined and then evaporated to dryness at 45 °C in a vacuum oven. The residue of acetaminophen was reconstituted with 2 ml of a stock solution containing 0.6 ug/ml of sulfanilamide in phosphate buffer, pH 6.8. An aliquot was injected directly on a 25-cm x 4.6-mm I.D. stainless steel column packed with Ultrasphere ODS (dp 5 um). The mobile phase consisting of a 7 : 93 (v/v) mixture of acetonitrile : 0.2 M phosphate buffer, pH 6.8 at a flow rate of 1.5 ml/min. Detection was carried out with a UV-detector adjusted at 242 nm. The acetaminophen concentration in the sample was determined using a calibration curve prepared by plotting the ratio of the peak height of acetaminophen to peak height of the internal standard (sulfanilamide) versus concentration of acetaminophen.

RESULTS AND DISSCUSSION

One of the tablet layers of LDM tablet contained a carbon dioxide-generating blend and HPMC and the other layer contained a mixture of acetaminophen and HPMC. Exposure of the tablet to an acidic dissolution medium, generated carbon dioxide which, upon becoming entrapped in the hydrated layer of HPMC, provided the tablet with buoyancy. The tablet was able to float permanently at the top of the rotating basket within 15 minutes. No separation between the two layers of both LDM and HDM tablets was observed.

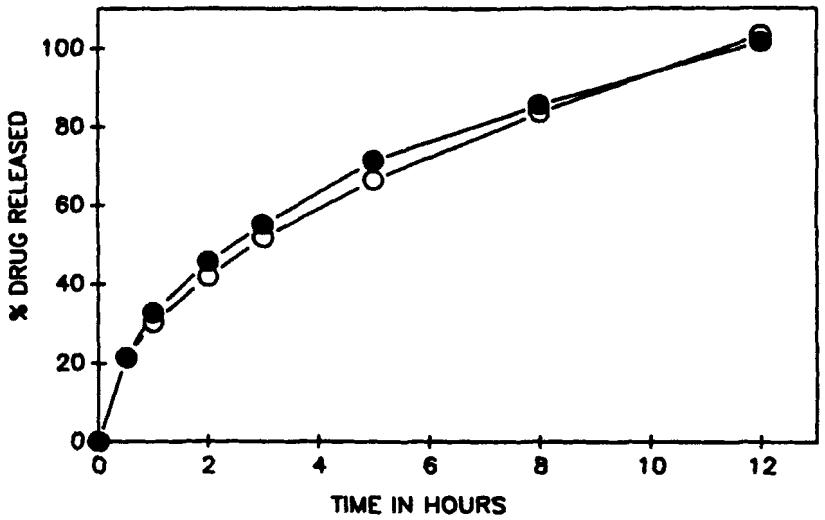

Figure 1. Release Profiles of Acetaminophen from Bilayer Sustained Release Acetaminophen Matrix Tablets in 0.1 N HCl. Conditions: USP Rotating Basket, 100 rpm; 900 ml of Dissolution Medium, 37°C. Key: (○) = LDM; (●) = HDM.

The LDM tablet remained intact and buoyant during the entire time that acetaminophen was released. There was no significant difference in the dissolution profiles of the LDM and HDM tablets in 0.1 N HCl, as shown in Figure 1. More than 95 % of acetaminophen was dissolved within 15 minutes for the TYLENOL® tablets.

Mean saliva concentration profiles of acetaminophen following oral administration of the three dosage forms under fasted and fed conditions are shown in Figures 2A and 2B, respectively. Individual pharmacokinetic parameters under fasted and fed conditions are given in Tables 1 and 2, respectively.

Saliva levels of acetaminophen under fasted conditions indicated a rapid absorption for TYLENOL® tablets as measured by Tmax (mean ± SD, 0.7 ± 0.2 hr) but remarkably slower absorption for the LDM and HDM tablets (Tmax, 3.0 ± 2.0 hr and 3.5 ± 1.0 hr, respectively). Under fed conditions, saliva profiles for TYLENOL® tablets were similar to those for the fasted case. In contrast, the LDM and HDM tablets had significant increases in Cmax under fed conditions (mean ± SD, 2027 ± 751 versus 4778 ± 2022 ng/ml and 1467 ± 579 versus 3378 ± 1566 ng/ml, respectively).

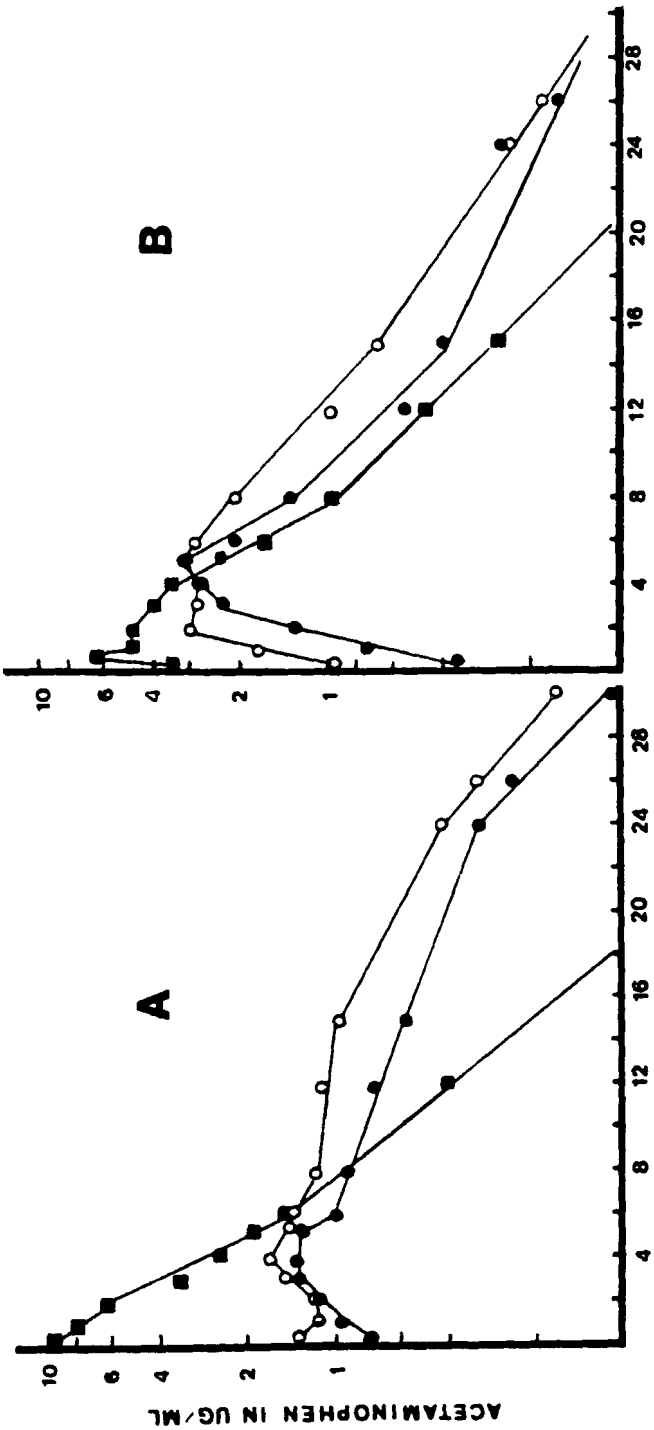

Figure 2. Semilogarithmic Plots of Mean Saliva Acetaminophen Concentration Versus Time after Oral Administration of LDM, HDM, and TYLENOL® Tablets (500 mg) to Six Subjects under (A) Fasted and (B) Fed Conditions. Key: (○) = LDM; (●) = HDM; (■) = TYLENOL® Tablets.

TABLE 1

Data for Bioequivalency Study in Six Subjects Comparing LDM and HDM Tablets of Acetaminophen with TYLENOL® Tablets (500 mg) under Fasted Conditions.

Subject	$[AUC]_{0\to\infty}$, ng/ml.hr			Cmax, ng/ml			Tmax, hr		
	A	B	C	A	B	C	A	B	C
DM	44267	30478	39618	2351	1562	9063	5.0	4.0	0.75
MR	26997	18923	38336	2787	1889	12743	4.0	4.0	0.75
WP	37473	41103	45872	2570	1944	14086	0.5	2.0	0.50
HL	22271	19199	40579	1794	1889	9912	4.0	5.0	1.00
SM	8725	3762	11259	690	560	7736	4.0	3.0	0.50
KV	22417	8232	18424	1970	958	8853	0.5	3.0	0.50
Mean	27025	20283	32348	2027	1467	10399	3.0	3.5	0.67
SD	12531	13846	13986	751	579	2474	2.0	1.0	0.20
CV, %	46.4	68.3	43.2	37.1	39.5	23.8	65.8	30.0	30.60

A = LDM tablets of acetaminophen (2x250 mg).
B = HDM tablets of acetaminophen (2x250 mg).
C = TYLENOL® tablets (500 mg).

TABLE 2

Data for Bioequivalency Study in Six Subjects Comparing LDM and HDM Tablets of Acetaminophen with TYLENOL® Tablets (500 mg) under Fed Conditions.

Subject	$[AUC]_{0\to\infty}$, ng/ml.hr			Cmax, ng/ml			Tmax, hr		
	A	B	C	A	B	C	A	B	C
DM	52058	40646	41825	6159	3506	5729	5.0	5.0	4.00
MR	38420	20027	33113	4761	4003	14621	5.0	4.0	0.75
WP	37560	37223	41525	7518	4187	8657	2.0	4.0	0.50
HL	35815	32332	25598	3439	5465	6357	5.0	5.0	2.00
SM	28717	11661	18509	5041	1860	6028	3.0	5.0	0.75
KV	10150	6171	15619	1749	1248	6539	1.0	2.0	0.50
Mean	33787	24677	29365	4778	3378	7989	3.5	4.2	1.42
Sd	13842	14174	11297	2022	1566	3410	1.8	1.2	1.38
CV, %	41.0	57.4	38.5	42.3	46.3	42.7	50.3	28.1	97.72

A = LDM tablets of acetaminophen (2x250 mg).
B = HDM tablets of acetaminophen (2x250 mg).
C = TYLENOL® tablets (500 mg).

TABLE 3

Pharmacokinetic Parameters of Acetaminophen from Human Saliva Profiles[a] after Oral Administration of LDM, HDM Tablets of Acetaminophen and TYLENOL® Tablets (500 mg) under Fasted and Fed Conditions.

Parameter	Fasted			Fed		
	LDM	HDM	TYLENOL®	LDM	HDM	TYLENOL®
Tmax (hr)	3.00[e] (0.5–5.0)	3.50[e] (2.0–5.0)	0.67 (0.5–1.0)	3.50[f] (1.0–5.0)	4.17[f] (2.0–5.0)	1.42 (0.5–4.0)
Cmax (ng/ml)[b]	2027[e] (690–2787)	1467[e] (560–1944)	10399 (7736–14086)	4778[g] (1749–7518)	3378[f,g] (1248–5465)	7989 (5729–14621)
AUC (ng/ml.hr)[c]	27025 (8725–44267)	20283[e] (3762–41103)	32348 (11259–45872)	33787 (10150–52058)	24677[h] (6171–40646)	29365 (15619–41825)
Relative AUC (%)	83.5	62.7	100.0	115.1	84.0	100.0

[a] Values are listed as the means (n=6), with range of values given in parentheses.

[b] Maximum of saliva level profile.

[c] AUC calculated from 0 to ∞ hr for all formulations.

[d] The AUC of the sustained release dosage form divided by the AUC of TYLENOL® tablet under the same conditons.

[e] Significantly different from TYLENOL® tablet (fasted) at the 0.05 level.

[f] Significantly different from TYLENOL® tablet (fed) at the 0.05 level.

[g] Significantly different from fasted condition (same dosage form) at the 0.05 level.

[h] Significantly different from LDM tablet (fed) at the 0.05 level.

The declining phase of the saliva concentration curves in the fasted conditions suggests a flip-flop model, since the absorption rate constant for the sustained release formulation may be less than the elimination rate constant. Administration of drug with food appears to have increased the absorption rate constant. The saliva concentration-time curve reverts to the expected pattern, with the declining phase representing the elimination of the drug.

The pharmacokinetic parameters and results of the statistical analysis are summarized in Table 3. The results indicate that the density of the matrix significantly influences the bioavailability of acetaminophen. It is possible that incomplete absorption occurred in the high density tablet because there was insufficient time for all of the drug to be released from the matrix. The lower tablet density apparently enables the tablet to maintain a more prolonged residence time in the GI tract, thus keeping the drug in contact with the absorption area and maximizing drug absorption.

CONCLUSION

A low density matrix tablet has been shown to increase absorption relative to a high density matrix formulation. For some drugs, tablet density may be an important factor in matrix formulations.

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