Pharmaceutical Research, Vol. 6, No. 4, 1989

Research Article

Correlation of Phenylpropanolamine Bioavailability with Gastrointestinal Transit by Scintigraphic Monitoring of ^{111}In-Labeled Hydroxypropylmethylcellulose Matrices

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Received June 8, 1988; accepted October 7, 1988

Two controlled-release hydroxypropylmethylcellulose (HPMC) matrix formulations, a single-unit and a multiple-unit system, have been evaluated in human volunteers. Both formulations contained the sympathomimetic drug phenylpropanolamine hydrochloride and each was radiolabeled with ^{111}In-bound Amberlite IR 120 ion-exchange resin. The formulations were administered to each of six healthy male volunteers and gastrointestinal (GI) transit was monitored using a gamma camera. Serum samples were taken at set time intervals and assayed for phenylpropanolamine content, thus allowing blood drug levels to be correlated with the position of the dosage form in the GI tract. The multiple-unit system emptied from the stomach gradually over a period of about 180 min, when administered after a light breakfast, whereas the single-unit dosage forms had extremely variable gastric emptying times (range, 60 to >570 min). However, both formulations provided prolonged phenylpropanolamine blood levels. The differences in the blood profiles obtained with the two formulations were attributed to variations in their *in vitro* release rates and not to any differences in their GI transit times.

KEY WORDS: bioavailability; scintigraphy; gastrointestinal transit; controlled release; phenylpropanolamine; hydroxypropylmethylcellulose.

INTRODUCTION

Gastrointestinal (GI) transit is one of the most important factors which may affect the bioavailability of a drug from a controlled release formulation. Multiple-unit controlled-release systems (e.g., pellets) have been shown to have a more predictable GI transit than conventional single-unit systems (1,2), and as a result the former often provide improved drug absorption (3–5), although this is not always the case (6).

Hydroxypropylmethylcellulose (HPMC) is a swellable hydrophilic polymer which is used in the formulation of controlled-release dosage forms (7). Previous studies have revealed that the *in vitro* release rate of drugs from HPMC matrices can be regulated by incorporating into the formulation either an ionic surfactant (8,9) or an ion-exchange resin (10). The surfactant/resin is believed to interact with the drug, inhibiting the latter's diffusivity and/or its solubility.

In the present study, both single- and multiple-unit HPMC matrix formulations were prepared containing the sympathomimetic drug phenylpropanolamine. Both formulations were radiolabeled by incorporating ^{111}In-bound ion-exchange resin. The GI transit of the matrices was monitored using the noninvasive technique of gamma scintigraphy. Blood samples were obtained at regular time intervals, permitting serum drug concentrations and related parameters to be correlated with the position of the dosage form within the GI tract.

MATERIALS AND METHODS

Preparation of ^{111}In-Labeled Matrices

Amberlite IR 120 cation-exchange resin was radiolabeled with ^{111}In, a gamma-emitting isotope, by soaking the resin in a 0.04 *N* hydrochloric acid (HCl) solution of $^{111}InCl_3$ (Amersham International, Amersham, U.K.) and stirring gently for 5 min. The resin was recovered by filtration, washed with 0.04 *N* HCl, and dried in a fan oven at 55°C for 20 min.

The strength of the ^{111}In binding to Amberlite IR 120 resin has been evaluated *in vitro* by Copping (11). He showed that the indium was strongly bound to the resin over a wide pH range (0 to 14).

Two batches of HPMC matrices were prepared, the formulas of which are given below.

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0724-8741/89/0400-0274$06.00/0

Diameter	12.5 mm	3.1 mm
Weight	500 mg	25 mg
Methocel K100M (Colorcon Ltd., Orpington, U.K.)	50% (w/w)	70% (w/w)
Phenylpropanolamine HCl BP (Blagden Campbell Chemicals Ltd., Croydon, U.K.)	15% (w/w)	15% (w/w)
Lactose	34% (w/w)	—
^{111}In-labeled resin	1% (w/w)	15% (w/w)

The ingredients were dry mixed and the blend was directly compressed on a Manesty F3 single punch tableting machine.

Dissolution

The *in vitro* dissolution behavior of the matrices was monitored using a method based upon the USP paddle apparatus (12). The drug was assayed spectrophotometrically. In order to measure the ^{111}In release, the matrices had to be removed at set time intervals so that their activity could be measured in a well counter. Corrections were then made for background activity and radioactive decay.

Two different dissolution media were used, a 0.1 *N* HCl solution and a phosphate buffer (pH 7).

Study Protocol

The study was conducted in six healthy male volunteers (age, 19 to 26 years; height, 1.70 to 1.82 m; weight, 67 to 85 kg), who participated with informed consent. Their dietary intake was controlled both immediately before and during the investigation. The study was approved by the Ethical Committee of Nottingham University and was conducted in accordance with Helsinki Guidelines for Ethics in Research.

On the morning of the study, after an overnight fast, each volunteer ate a light breakfast (1700 kJ). Thereafter, three of the subjects ingested one 12.5-mm matrix together with 200 ml of a 99mTc DTPA solution (Cis Biomedical Products, High Wycombe, U.K.). The radioactive solution helped to provide an outline of the stomach and it also acted as a control marker regarding the gastric motility of each volunteer. The other three volunteers ingested twenty 3.1-mm matrices contained in a size 00 capsule together with 200 ml of the radioactive drink. The subjects' food intake was controlled throughout the study. Lunch, which consisted of one ham and one cheese roll plus a glass of orange juice, was taken 3.5 hr after the dosage forms. An evening meal (steak, peas, and french fries followed by cheesecake and some orange juice) was taken after 9 hr. In the second part of the study (after a washout period of 1 week) the subjects were crossed over.

At set time intervals each subject stood in front of a gamma camera and anterior and posterior images were taken. A piece of 99mTc-labeled tape fixed externally above the liver of each subject acted as a marker. Radioactivity was measured in two areas of interest, the stomach and the colon. The ^{111}In and 99mTc activity could be recorded independently. Corrections were made for the scatter of some of the ^{111}In into the 99mTc channel, background activity, and radioactive decay. The geometric mean of anterior and posterior views was calculated to give a count independent of the depth of the source (13).

Assay of Serum Samples

Samples of serum were taken with an intravenous cannula. At least 10 ml of blood was collected at the following times after dosing: 0 (predose), 0.5, 1, 2, 4, 6, 8, 10, 12, 14, and 24 hr. Each sample was transferred to a nonheparinized glass tube and stored for 2 hr at room temperature to allow the blood to coagulate and the clot to retract. The samples were then centrifuged at 2300 rpm for 5 min; the serum was decanted into fresh glass tubes and stored at −20°C until assayed.

Serum samples were analyzed for phenylpropanolamine content using a high-performance liquid chromatographic (HPLC) technique based on the method described by Dowse *et al.* (14). The reproducibility of the assay was assessed by

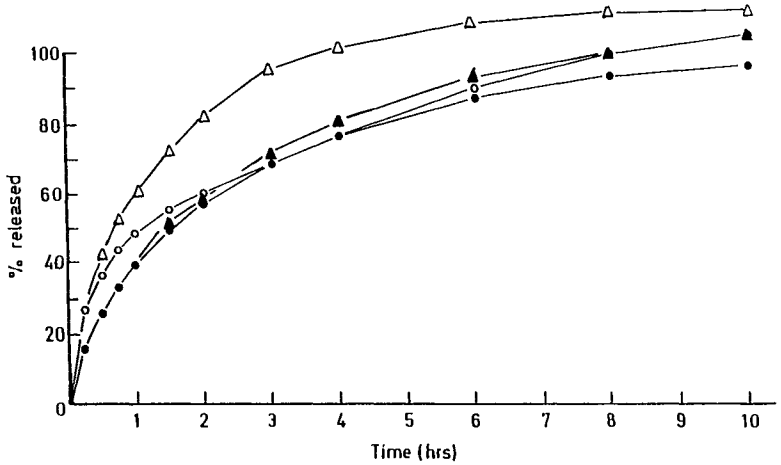

Fig. 1. Release of phenylpropanolamine from 3.1- and 12.5-mm-diameter HPMC matrices. (○) 3.1 mm, pH 7; (●) 12.5 mm, pH 7; (△) 3.1 mm, pH 1; (▲) 12.5 mm, pH 1.

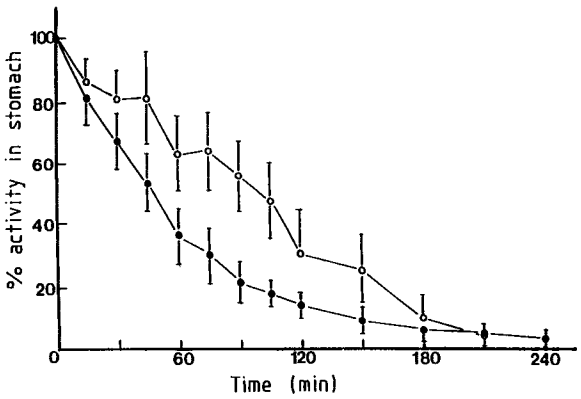

Fig. 2. Gastric emptying of radiolabeled liquid and 3.1-mm matrices. (○) Matrices; (●) liquid. Mean ± SE; $N = 6$.

extracting three spiked serum samples at the upper and lower limits of the concentration range studied. The coefficient of variation was found to be 8.3% at 50 ng ml^{-1} and 3.3% at 200 ng ml^{-1}. Under the conditions of this assay the absolute detection limit for phenylpropanolamine was approximately 25 ng per sample.

RESULTS

Dissolution

The two sizes of HPMC matrix (3.1 and 12.5 mm) were formulated such that their *in vitro* drug release profiles would be as similar as possible. Almost identical dissolution profiles were obtained in pH 7 buffer, but this similarity was not reflected so closely in acid media (Fig. 1), the smaller tablets releasing phenylpropanolamine more rapidly.

The *in vitro* liberation of ^{111}In from these matrices into pH 7 buffer was relatively slow. Greater than 50% of the activity was still present within the matrices after 7 hr. Under acid conditions the ^{111}In release was more rapid. Despite this loss of activity, there was no difficulty in identifying the position of the matrices within the GI tract.

Table I. Gastric Emptying of 3.1-mm-Diameter HPMC Matrices[a]

	Subject No.							
Time	1	2	3	4	5	6	Mean	±SE
0	100	100	100	100	100	100	100	0
15	50	89	97	95	100	90	87	7.6
30	33	95	90	84	94	91	81	9.8
45	8	87	93	101	97	101	81	14.9
60	0	71	86	61	80	81	63	13.2
75	0	76	86	64	82	78	64	13.2
90	0	66	76	48	78	69	56	12.0
105	0	56	68	13	76	73	48	13.4
120	0	26	68	1	82	7	31	14.6
150	0	26	55	0	62	11	26	11.1
180	0	4	49	0	3	5	10	7.8
210	0	2	25	0	0	0	5	4.0
300							0	0

[a] All times are minutes.

Table II. Gastric Emptying of 12.5-mm-Diameter HPMC Matrices

	Subject No.					
	1	2	3	4	5	6
Time (min)	180	>570	>570	150	60	105

Gamma Scintigraphy

The radiolabeled liquid emptied exponentially with a mean T50% (time for half the activity to leave the stomach) of approximately 50 min (Fig. 2). The minimatrices (3.1 mm) emptied linearly with a T50% of 100 min (Table I). Both of these values compare closely with the results obtained in a previous study which utilized similar conditions (15).

Gastric emptying times for the large matrices were variable, ranging from 50 to over 570 min (Table II). Such variable gastric emptying times are common for large nondisintegrating dosage forms (1).

The mean small intestinal transit times were calculated as 218 ± 24 (SE) and 206 ± 30 min for the small and large matrices, respectively. These values correlate well with the mean values of 204 to 225 min reported by Davis *et al.* (16–18). Such data imply that small intestinal transit times are not affected by either the size or the shape of the dosage form.

Absorption Profile

Individual serum phenylpropanolamine levels for each volunteer are listed in Tables III and IV. The mean serum concentration versus time profiles are presented in Fig. 3.

Phenylpropanolamine is readily absorbed from the GI tract and it has a biological half-life, in humans, of approximately 5 hr (19). The blood-level/time profiles obtained in this study are similar to those recorded for other sustained-release phenylpropanolamine preparations (20,21), indicating that both of the HPMC formulations tested were capable of providing sustained drug release, *in vivo*.

The relative bioavailability of phenylpropanolamine from HPMC minimatrices was determined by comparing the mean area under the serum concentration/time curves (AUC) for the 3.1-mm matrices with the corresponding area

Table III. Serum Phenylpropanolamine Concentrations After Ingestion of Twenty 3.1-mm-Diameter Matrices[a]

	Subject No.							
Time	1	2	3	4	5	6	Mean	±SE
0	0	0	0	0	0	0	0	0
35	52.7	0	0	0	0	—	10.5	10.5
65	128.7	27.9	48.1	14.1	0	33.4	42.0	18.6
130	107.0	107.7	103.3	87.0	76.1	133.6	102.5	8.1
245	131.9	177.1	220.4	149.6	150.5	189.2	169.8	13.2
365	108.0	194.9	178.3	125.6	—	209.7	163.3	19.8
455	81.9	157.1	141.9	150.8	95.6	163.7	131.8	14.0
590	71.2	110.0	84.5	74.4	78.1	127.2	90.9	9.2
690	73.2	118.7	49.6	81.6	66.9	69.8	76.6	9.4
810	53.5	72.0	35.7	49.9	—	61.0	54.4	6.0
1380	0	6.4	0	0	0	17.5	4.0	2.9

[a] All times are minutes. All PPA concentrations are ng ml^{-1}.

Table IV. Serum Phenylpropanolamine Concentrations After Ingestion of a 12.5-mm-Diameter Matrix[a]

Time	Subject No. 1	2	3	4	5	6	Mean	±SE
0	0	0	0	0	0	0	0	0
35	29.3	47.3	—	13.0	7.6	60.7	31.6	10.1
65	55.2	95.4	63.6	63.6	60.7	110.4	74.8	9.2
130	94.6	135.2	69.5	78.6	93.6	101.1	95.4	9.3
245	115.8	164.0	126.2	112.7	91.8	39.5	108.3	16.8
365	87.4	159.5	126.0	131.9	91.3	54.2	108.4	15.4
455	83.6	115.5	106.7	93.9	88.7	124.7	102.2	6.6
590	79.2	118.3	83.9	87.9	76.0	—	89.1	7.6
690	54.8	93.9	83.5	93.9	67.3	84.8	79.7	6.4
810	41.0	79.0	59.9	82.0	47.4	55.7	60.8	6.8
1380	12.6	12.7	16.5	16.3	13.6	10.7	13.7	0.9

[a] All times are minutes. All PPA concentrations are ng ml^{-1}.

calculated for the large matrices. Values of 1686 (SE, 118) and 1553 hr ng ml^{-1} (SE, 121 hr ng ml^{-1}) were recorded for the 3.1- and 12.5-mm matrices, respectively. These data suggest that the two dosage forms exhibited similar bioavailabilities and that the differences in their GI transit rates did not dramatically influence the extent of phenylpropanolamine absorption.

DISCUSSION

The gradual and predictable gastric emptying rate of multiple-unit controlled-release systems is presumed to be because the subunit is small enough to pass through the contracted pylorus (22). Previously, it was suggested that only subunits of less than about 2-mm diameter would empty gradually, but recent investigations in both dogs (23) and humans (24,25) have indicated that larger units may empty gradually from the fed stomach. These findings are further confirmed by the data presented here for 3.1-mm matrices. It appears that the critical size of an ingested subunit is not as small as was once thought.

Large indigestible particles (e.g., 12.5-mm diameter) usually leave the stomach during Phase III of the interdigestive myoelectric complex (IMC), a motility pattern composed of powerful peristaltic contractions (26). The observation that two of the large matrices remained in the stomach for longer than 9.5 hr implies that Phase III of the IMC did not arrive before the taking of either lunch or dinner. Although some tablets were unable to empty from the stomach, drug absorption would still be possible because both released drug in solution and some pieces of eroded polymer would be able to leave the stomach and reach the absorption sites.

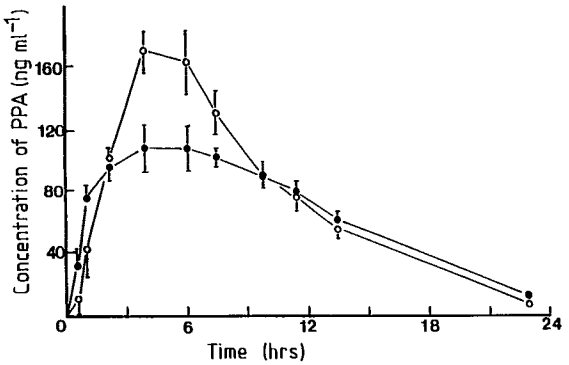

Fig. 3. Mean serum phenylpropanolamine concentrations plotted against time for two HPMC matrix formulations: (○) 3.1-mm matrices; (●) 12.5-mm matrix. Mean ± SE; $N = 6$.

The observed differences in the blood profiles for the two formulations are probably due to different release profiles rather than to variations in their GI transit times. In acid media the minimatrices released phenylpropanolamine more rapidly than did the large HPMC matrices (Fig. 1). Hence, during the first 2 hr after ingestion, when many of the matrices remained in the acidic environment of the stomach, the small matrices would release drug faster, leading to initially higher blood concentrations of phenylpropanolamine. Drug would also become depleted from the small matrices sooner, causing a corresponding earlier drop in blood levels.

An analysis of individual subject data shows that when the dosage form remained in the stomach for a relatively long period of time (e.g., single unit, subjects 2 and 3; multiple units, subject 3) (Tables I and II), drug release tended to be more rapid and higher peak levels were recorded which fell quickly (Tables III and IV). If the dosage form had a rapid GI transit (e.g., single unit, subjects 1 and 5; multiple units, subjects 1 and 4), then drug absorption tended to be more sustained and peak serum concentrations were not so high.

The slower onset of drug absorption with the minimatrices (Fig. 3) was probably due to the presence of the gelatin capsule in which these matrices were administered. The capsule would take time to dissolve, thus delaying the start of drug release from the 3.1-mm matrices. Since the large matrices were not administered in a capsule, there was no lag effect.

The minimatrices ingested by subject 1 transitted the upper GI tract rapidly, reaching the colon by 4 hr. However, since the serum drug levels did not decline rapidly after this time, it appears that drug absorption was taking place within the large intestine, if somewhat slowly.

To conclude, the HPMC/resin formulations tested in this study provided more prolonged blood levels of drug than those reported previously for conventional, fast-releasing, phenylpropanolamine dosage forms (20,21). The variable GI transit times of large single-unit controlled-release systems compared to multiple-unit formulations was confirmed, but this variability did not appear to significantly affect the blood-level/time profiles or relative bioavailability.

ACKNOWLEDGMENT

The authors wish to thank the Science and Engineering Research Council for financial assistance to L.C.F.

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