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Evaluation of the effect of food and specific gravity of tablets on gastric retention time

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Summary

In the present study the effect of food and specific gravity on the gastric retention time of floating (spec. grav. 0.96) and non-floating (spec. grav. 1.59) tablet formulations was investigated using gamma scintigraphy in humans. The results obtained indicate that the presence of food in the stomach appears to significantly prolong gastric retention of both the floating and non-floating tablets while specific gravity does not seem to play an important role in the residency time of the tablets in the stomach.

Introduction

The in vivo behavior of various types of drug delivery systems such as beads (Theodorakis et al., 1975; Davis et al., 1984a), suppositories (Jay et al., 1983), aerosols (Smith et al., 1984) osmotic pump devices (Davis et al., 1984b) has been monitored using gamma scintigraphy. This technique has also been successfully used to determine the effects of drugs (Horowitz et al., 1985), age (Evans et al., 1981) and smoking (Grimes et al., 1978) on gastric emptying rate.

The present study was undertaken to evaluate the effect of specific gravity and food on the gastric emptying of tablets in man.

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Materials and Methods

The materials used were [^{111}In]oxine (Meta-Physics, Emeryville, CA) Avicel PH 101 and 102 (FMC Corp., Philadelphia, PA) Methocel K4M, premium (Dow Chemical, USA, Midland, MI), gelatin USP Type A (Camerican Int., Teaneck, NJ), magnesium stearate NF and ^{99m}Tc (Mallinckrodt-Osteoscan, St. Louis, MO), dicalcium phosphate, unmilled (Stauffer Chemical Company, Westport, CN), ethyl cellulose NF Type 7 (Hercules Corp., Wilmington, DE), petroleum ether and benzene A.R. (J.T. Baker Chemical Co., Phillipsburg, NJ), and alcohol (Ethyl Corp., Baton Rouge, LA).

Preparation of radiolabeled floating tablets

A 0.1 ml sample of petroleum ether was injected via a syringe into a vial containing 1 mCi of [^{111}In]oxine and agitated for 10 min. At the end of

10 min a 0.1 ml sample was removed from the [^{111}In]oxine vial and triturated with 1.25 g of Avicel PH 101 in a 50 ml beaker. This mixture was then transferred to a petri dish and placed in an oven at 37°C for 20 min, to allow the petroleum ether to evaporate. Upon drying the mixture was incorporated into 11.25 g of a floating tablet mixture. After 15 min of mixing the [^{111}In]oxine powder formulation was passed through a size 20 mesh sieve three times, to ensure particle uniformity. As a final mixing step, the powder formulation was placed in an amber glass bottle, and shaken and rolled for 15 min. The floating tablet mixture was prepared by granulating a mixture of 237.5 g of Methocel K4M and 187.5 g of Avicel PH 102 with a solution of 20 g of gelatin in 200 ml of purified water USP. The granulation was dried overnight between 45 and 50°C and then passed through a 20 mesh screen. Magnesium stearate was added as a premix to the above-screened granulation and mixed for 5 min.

Radiolabeled tablets were manufactured by placing 500 mg of the above formulation in a round 0.5 inch die, fitted with 0.5 inch flat-face bevel-edged punches and applying 2100 lb. for 15 s via a table top press (Carver Press, Summit, NJ).

Preparation of radiolabeled non-floating tablets

The non-floating non-disintegrating tablets (spec. grav. 1.59) were manufactured using the following method: 1 ml (600 μCi) of ^{99m}Tc in purified water was added to 150 mg of dicalcium phosphate, and mixed thoroughly. This mixture was placed in an oven at 70°C for 30 min. Ten aliquots of approximately 15 mg (60–70 μCi) each of the [^{99m}Tc]dicalcium phosphate formulation were weighed out and set aside until its incorporation into the tablet mixture.

A separate granulation consisting of dicalcium phosphate (25 g), ethylcellulose (10 ml of 20% alcohol solution) was manufactured, dried in an oven at 70°C for 30 min and passed through a 20 mesh sieve. This granulation was then mixed with (0.5 g) of magnesium stearate in an amber glass bottle for 15 min and constituted the bulk formulation for the non-floating tablets. The non-floating non-disintegrating tablets were manufactured by placing approximately 420 mg of the bulk formulation into the die, then placing 15 mg of the ^{99m}Tc-labelled dicalcium phosphate in the center of the die, and then adding another 420 mg of the bulk formulation. A 0.5 inch bevel-edged flat-face punch and die set and pressures of 5200 lb. were used to produce the final tablet.

In vitro control tests

In vitro tests were performed on a representative sample of the tablets produced. Hardness, floating time, dissolution, specific gravity, and content uniformity of the tablets were determined. The content uniformity (activity per tablet) was determined using a dose calibrator (Victoreen 888, Cleveland, OH). Hardness of the tablets was determined using a hand-held hardness tester (Pfizer, Mineola, NY).

Floating time was determined by using the USP disintegration apparatus with 900 ml of 0.1 N HCl solution at 37°C used as a testing medium. Time required to float was noted.

Dissolution tests were performed by placing a radioactive tablet in a dissolution basket which was then placed in a beaker containing 900 ml of 0.1 N HCl solution, kept at 37°C, and rotated at 50 rpm. Every hour a 10 ml sample was removed from the dissolution vessel via a 10 ml syringe that had a cotton plug at its tip. Ten ml of fresh medium was used as a replacement. The samples were counted in a gamma scintillation counter (Packard, Downers Grove, IL) for 100 s to determine the amount of activity in each sample.

Specific gravity was determined by the displacement method using benzene A.R. as a displacing medium.

Labelling uniformity was determined by fragmenting representative tablets, with subsequent determination of radioactivity per mg of each fragment.

In vivo studies

A cross-over study (performed in two phases, consisting of 4 subjects in each phase) was designed to study the effects of food on a floating tablet dosage form. Phase 1 of the study was a single isotope study with each subject receiving a ^{111}In-labelled floating tablet under either fasted or fed conditions. Phase 2 was a dual-labeled study

TABLE 1

Demographic factors of 8 healthy subjects participating in the floating tablet study

Subject	Sex	Weight (lbs.)	Height (ft.in.)	Age (years)
1	male	150	5'6"	36
2	male	160	5'10"	23
3	male	245	6'3"	26
4	male	210	6'4"	23
5	male	155	6'0.5"	26
6	male	145	5'7"	27
7	male	185	6'1"	23
8	male	190	6'4"	26

TABLE 2

Composition of labelled floating and non-floating tablets

Ingredient	Floating tablet (mg/tab)	Non-floating tablet (mg/tab)
[^{111}In]oxine-Avicel PH 101	50	–
[^{99m}Tc]Dicalcium phosphate	–	15
Methocel K4M	237.5	–
Avicel PH 102	187.5	–
Gelatin USP Type A	20	–
Dicalcium phosphate, Milled	–	764
Ethyl Cellulose NF Type 7	–	61
Magnesium Stearate	5	15
Approximate tablet weight	500	855

with each subject receiving simultaneously both a ^{111}In-labelled floating tablet and a ^{99m}Tc-labeled non-flating tablet, on either a full or fasted stomach. ^{111}In and ^{99m}Tc emit different energy gamma rays which can be simultaneously followed by external scintigraphy. The study involved a total of 8 healthy male volunteers whose age ranged from 23 to 36 years (Table 1).

Subjects were fed a standard meal that consisted of 204 g beef patty sandwich, regular potato fries (68 g), apple pie (85 g) and 240 ml of 2% skim milk, one half-hour prior to dosing. The total caloric value of the meal was estimated to be 1156 calories. The fasted subjects were fed the standard meal approximately 5 h prior to dosing.

Each subject was administered the dosage form with 240 ml of tap water and then immediately placed in a supine position under the head of a gamma camera (G.C. Searle Co., Skokie, IL). The subjects were scanned for 30 min in a supine position and then allowed to ambulate for 30 min. The subjects were also given 240 ml of water at 2 and 4 h intervals. The scanning procedure was repeated throughout the duration of the study which was 7 h.

Results and Discussion

Table 2 lists the composition of the floating and non-floating tablets. Table 3 describes the physical parameters of the two tablet formulations which were administered. As can be seen from Table 2, the floating tablets (spec. grav. 0.96) had an average weight of 500 mg and a hardness of 9.5 lb. The non-floating tablets (spec. grav. 1.59) weighed 855 ± 2.5 mg and a hardness of 13 lb. The floating tablets were labeled with ^{111}In ($t_{1/2}$ 2.83 days) and the non-floating tablets with ^{99m}Tc ($t_{1/2}$ 6 h). Content uniformity (radioactivity per tablet) was found to be acceptable.

The tablets also were found to be uniformly labeled after fragmentation of representative samples with subsequent determination of radioactivity per unit weight of each fragment.

In vitro dissolution studies, conducted in 0.1 N HCl indicated that both types of tablets lost approximately 76% of their radioactivity in 8 h.

In Phase 1 of the study a floating tablet was administered to four human subjects under fasted and non-fasted conditions in a cross-over study design. Mean gastric retention time for the floating tablet was found to be 80 min (range 30–127 min) in contrast to 364 min (range 301 to >426 min) under non-fasted conditions (Table 4). To determine whether the almost 4-fold difference in gastric retention time of the tablets was due to the presence of food in the stomach and/or the specific gravity of the tablets, Phase 2 of the study was undertaken. In Phase 2 each subject ingested the non-floating and floating tablets simultaneously with 240 ml of water; at 2 and 4 h intervals an additional 240 ml of water was given. Interestingly, the results showed that the specific

TABLE 3

Physical parameters of orally administered radiolabeled tablets to human subjects

Study number	Average wt. (mg)	Thickness (in.)	Hardness (lbs.)	Floating time (min)	Specific gravity	Activity (μCi)	Isotope
1	500 ± 5	0.155–0.165	9.5	< 2	–	32.9 ± 3.2	In-111
2	506 ± 5	0.155–0.165	9.5	< 2	0.96	31.4 ± 6.0	In-111
2	855 ± 2.5	0.150–0.160	13	*NF > 480	1.59	65.9 ± 7.1	Tc-99m

NF = non-floating.

TABLE 4

Effect of food on gastric retention time (GRT) of floating tablet [a]

Subject number	Study number	GRT (min) in fasted subjects	GRT (min) in non-fasted subjects
1	1	30	301
2	1	122	> 426
3	1	20 < x < 60	322
4	1	127	> 406

[a] Floating tablets (sp. gr. 0.96) had an average weight of 500 mg and a hardness of 9.5 lb.

gravity of the tablets did not significantly affect their gastric retention time (Table 5). In contrast, the presence of food in the stomach as shown in Phase 1 of the study, exerted a significant effect on the gastric retention times of the tablets.

Thus, the floating tablet exhibited a mean gastric retention time of 132 min under fasted conditions and 406 min under fed conditions. Surprisingly similar results were obtained with the non-floating tablets which exhibited a mean gastric retention time of 152 min under fasted conditions and 376 min under fed conditions.

The results obtained in the present study are in agreement with those obtained by other workers (Muller-Lissner et al., 1981) who studied the effect of specific gravity and food on gastric emptying of slow-releasing capsules in humans. These workers showed that gastric-emptying times of capsules with specific gravities of 0.51 and 1.31 exhibited no significant differences in either fasted or non-fasted groups of volunteers. A significant increase in the gastric retention times of both capsules was observed with fed subjects. Similar results were obtained in our laboratories with 12 fasted human subjects who were administered orally two batches of beads (0.7 mm in diameter) that possessed specific gravities of 1.0 and 1.3. Specific gravity did not seem to play an important role in the

TABLE 5

Effect of food on gastric retention time (GRT) of simultaneously administered floating [a] *and a non-floating* [b] *tablet*

Subject number	Study number	Floating tablet		Non-floating tablet	
		GRT (min) in fasted subjects	GRT (min) in non-fasted subjects	GRT (min) in fasted subjects	GRT (min) in non-fasted subjects
5	2	128	> 436	140	334
6	2	177	> 412	199 < x < 229	> 412
7	2	145	351	148	355
8	2	76	> 426	90 < x < 121	402
Ave. =		132 ± 42	406 ± 38	152 ± 46	376 ± 37

[a] Floating tablets (spec. grav. 0.96) had an average weight of 500 mg and a hardness of 9.5 lb.

[b] Non-floating tablets (spec. grav. 1.59) had an average weight of 855 mg and a hardness of 13 lb.

mean residence time of the beads in the various compartments of the gastrointestinal tract (Digenis et al., 1986).

These findings differ from those of other workers (Sheth et al., 1984) who postulated an increase in gastric retention of tablets and capsules by a buoyancy effect. These workers demonstrated significantly increased gastric retention times for diazepam and chlordiazepoxide when formulated in the hydrodynamically balanced system (HBS) capsule dosage form compared to conventional tablet dosage form. The increase in retention time of HBS dosage forms may be due to other effects such as adhesion to the gastric mucosa or food rather than the effect of floating per se.

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