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Evaluation of the gastric retention properties of a cross-linked polymer coated tablet versus those of a non-disintegrating tablet

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Summary

The gastric emptying time of tablets coated with a cross-linked polymer that enabled them to balloon and float in gastric media has been compared with that of uncoated, non-disintegrating tablets in both fasted and fed states, with healthy human volunteers using gamma camera scintigraphy. In the fed state, the balloon tablets prolonged the gastric emptying time by an average of 6 h over that of the uncoated tablets. The emptying times for both coated and uncoated tablets were much shorter in the fasting state. The balloon tablet did not significantly prolong the gastric emptying time in the fasted state.

Introduction

A variety of approaches have been used to control the release and bioavailability of orally administered drugs (Park and Robinson, 1984; Sjögren, 1985; Heller, 1987; Hui et al., 1987; Ingani et al., 1987; Lippold, 1990; Gross and Robinson, 1990). Enteric coated products have polymer coatings that are insoluble in gastric media and so prevent or retard drug release in the stomach. Drugs that may be enteric coated include those that are unstable in the gastric environment or those that irritate the gastric mucosa. Some dosage forms are coated with barrier coatings which allow drug release to occur slowly over the entire length or at least appreciable length of the gastrointestinal tract. There are other situations where it is beneficial to hold dosage forms in the stomach for a prolonged period of time. Examples of such instances are where a drug's main site of action is in the stomach, such as antacids or certain enzymes, or where the drug is best absorbed in the stomach or upper intestine as is the case with albuterol (solbutamol). Delayed gastric emptying also prolongs the overall gastrointestinal transit time for drugs that are absorbed in the intestine and may result in improved bioavailability for some drugs. Until recently, dosage forms did not exist to accomplish this end. Bioadhesive dosage forms that

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stick to the gastric mucosa to prolong gastric emptying time (Gupta et al., 1990), and dosage forms that are based on density differences between themselves and gastric contents (Davis et al., 1986), are two methods that have been tried to delay gastric emptying. Other methods which have been studied include floating capsules (Muller-Lissner and Blum, 1981), and dosage forms that swell to retard gastric emptying. There is evidence that the absence or presence of food in the stomach greatly influences the emptying of dosage forms from the stomach (Hofmann et al., 1983; Davis et al., 1984).

The objective of this study was to observe the effect of the fasted state and fed state on the stomach emptying of a gastric retention balloon dosage form, and to compare the emptying times of the balloon dosage form with those of uncoated, non-disintegrating tablets. The two different dosage forms were labeled with different radionuclides to allow concurrent monitoring.

Experimental

Preparation of ^{111}In-labeled balloon dosage forms

The balloon dosage form was comprised of a core uncoated tablet made of sucrose, lactose, sodium bicarbonate and magnesium stearate. The core tablet was coated with a coating composition consisting of polymethyl vinyl ether/maleic anhydride, polyoxyethylene sorbitan monolaurate (Tween 20), and glyceryl triacetate. The coating materials were dissolved in ethyl acetate and used to coat the tablets. Each uncoated tablet mixture was labeled with 0.2 mCi ^{111}In, which was previously encapsulated in 20–25 mg of ethyl cellulose, prior to compression. The ethyl cellulose-^{111}In complex was prepared first by extracting the ^{111}In oxyquinoline solution (Amersham, FDA approved radiopharmaceutical) containing approx. 1.1 mCi ^{111}In and 0.05 mg, 8-quinolinol oxine in 1 ml of saline, with four 0.75-ml portions of chloroform. The combined chloroform extract containing about 75% of the ^{111}In as $In(oxine)_3$ was then added to 120 mg of ethyl cellulose dissolved in 2 ml chloroform, and the resulting solution was evaporated to dryness in a small glass mortar at 100 °C. The solid ^{111}In-ethyl cellulose residue was powdered, its specific activity determined, and appropriately divided into the amounts required for each tablet. This calculated amount for each tablet was diluted with a portion of the core tablet mixture and then placed by hand centrally, within the tablet mixture in the cavity of the punch and die prior to compression. This minimized any possibility of extraction of radioactivity during the coating process. The labeled core tablets each weighed 850 mg and were compressed at 3000 lb load using 7/16 inch standard concave punches. The tablets were coated using a dip coating method. In this method, the tablet was held at one end of a tygon tubing which was connected to a vacuum source. One-half of the tablet was dipped in the coating liquid and allowed to dry in air. When the coated side dried completely, the tablet was turned over and the other half coated as described. Each half of the tablet was dipped three to four times in the coating liquid, allowing the coating to dry completely between dips. Each tablet had a coating weight of about 80 mg prior to curing. The coating was cured by placing the coated tablets in an environmental chamber at 50% R.H. and 40 °C for 48 h to bring about the cross-linking of the polymer components. When cured tablets were dropped in 0.1 M HCl, in a beaker at 37 °C, the coating separated from the tablet core and formed a balloon around the core tablet. When that happened, the entire tablet (core and balloon coating) floated to the surface of the medium. Generally, this flotation occurred within 15 min of dropping the tablet in the medium. The size of the balloon tablet increased to three to six times the size of the original tablet.

An in vitro dissolution study with balloon tablets containing quinidine gluconate in the core showed a sustained release profile with 88% of the drug being released over an 8 h period. This would indicate that the coating remained intact after swelling and drug release was by diffusion through the coating.

Preparation of ^{99m}Tc-labeled non-disintegrating tablets

The non-disintegrating tablet consisted of calcium phosphate dihydrate and stearic acid with

magnesium stearate as the lubricant. The radiolabeling material was prepared by adding sodium pertechnetate (^{99m}Tc), in saline solution as obtained from a generator, to a 3M company radiopharmacy kit of albumin microspheres. The resulting dispersion was sonicated in a sonication bath for 5 min, and then filtered to recover labeled microspheres, which were then partially dried by passing a dry air stream through the filter. The labeled solid was then analyzed for specific activity, and the appropriate amount taken to provide the described activity in the individual tablets. This amount of labeling material for each tablet was diluted with 50 mg of the non-disintegrating tablet mixture and compressed into a 3/16 inch tablet. This small tablet was then placed in the center of the remaining tablet mixture and compressed at 3000 lb load using a 7/16 inch standard concave punch and die set. Each non-disintegrating tablet weighed 600 mg.

Gamma camera scintigraphy with ^{111}In- and ^{99m}Tc-labeled tablets

Seven healthy male volunteers aged 18–56 years, height 5 ft 9 inch–6 ft 5 inch, weight 160–235 lb, participated in the study. Gamma images were obtained with a 15 inch field of view Anger Camera (General Electric Maxi Camera 400 Autotime Zs) interfaced with a GE Formatter Camera and Star computer and equipped with a medium-energy parallel-hole collimator. ^{99m}Tc decays were detected in a 26 keV window centered at 140 keV, while ^{111}In decays were simultaneously detected in a 58 keV window centered at 250 keV. The volunteers were repeatedly imaged in a standing position (anterior view) at 15–25-min intervals following dosing. The ^{99m}Tc and ^{111}In-labeled tablets were administered together with 6–12 oz of water while the subject was positioned in front of the camera, allowing visualization of each tablet as it passed down the esophagus and into the stomach. Flotation times for the ^{111}In-labeled balloon dosage form were readily obtained by observation of the persistence scope as the subject stood in front of the camera. Between scans, the subjects were free to walk, stand or sit. The dose of ^{111}In and ^{99m}Tc was measured in a calibrated Capintec dose calibrator shortly before administration. ^{99m}Tc tablets typically contained 0.30–0.60 mCi, while the ^{111}In tablets contained 0.07–0.10 mCi. In some cases, subjects were administered additional (one to three) low-dose ^{99m}Tc non-disintegrating tablets (0.01–0.05 mCi each) to relocate the bottom of the stomach and verify gastric emptying/retention of the balloon dosage form. In the fasted state, subjects did not eat food or drink other than water from 9 p.m. on the night before the test. In the fed state, volunteers ate a typical breakfast (two scrambled eggs, one small sausage patty, one English muffin and a small 'pat' of margarine, controlled serving of low fat prepared hashbrown potatoes, orange juice and 1/2 pint of low fat milk) for a caloric value of slightly less than 1000 cal, on the morning of the test. Approx. 15 min elapsed between finishing breakfast and initiating the test. The volunteers ate lunch in the fed state, for a caloric value again slightly less than 1000 cal, 4 h into the test. The composition of the typical lunch was beef and Swiss cheese sandwich, 1/2 medium size banana, one package corn chips, and 1/2 pint skim milk.

Results and Discussion

Tables 1 and 2 summarize the results of the study. Table 1 also gives descriptions of the subjects involved in the study. When the gastric retention balloon tablet and the non-disintegrating tablet were administered to fasted subjects, there was no real difference in gastric emptying

TABLE 1

Test subject description and balloon tablet flotation times

Subject no.	Height	Weight (lb)	Age (year)	Flotation time (min)	
				Fasting	Fed
1	6 ft 8 in	180	35	7	5–15
2	6 ft 5 in	230	56	9	< 15
3	6 ft 5 in	235	27	8	18
4	6 ft 0 in	220	27	7	13
5	5 ft 10 in	160	18	8	< 10
6	5 ft 10 in	160	28	5	5–15
7	5 ft 9 in	162	39	6	19

time between the two dosage forms. In all of the subjects except one, each of the two types of tablets was emptied within a median time of 100 min or less. In five of the seven subjects, in the fasted state, both tablets had emptied or failed within about 60 min. The one subject who retained both dosage forms for a longer period of time (a median of 196 min) was the subject who was considerably older than the rest of the subjects in the test group. However, in that subject as well, there was no difference in emptying time in the fasted state. In general, the gastric motility of older subjects is known to be reduced compared to that of younger subjects (Mojaverian et al., 1988). In the two fasted subjects where one tablet was emptied slower than the other tablet, the tablet that was retained longer in each case was the balloon tablet. The difference in emptying times, however, was 21 min or less, and it is clear that the balloon tablet was not retained for a longer period in the fasted state, in comparison to the control tablet. Fig. 1 shows typical images taken from one subject immediately after administering the two dosage forms in the fasted state, 22 min later, and 49 min after administration.

The short emptying times recorded in this investigation, in the fasted state, are in agreement with results reported by other investigators (Muller-Lissner and Blum, 1981; Hofmann et al., 1983; Davis et al., 1986). This rapid emptying has been attributed to periods of strong contractile

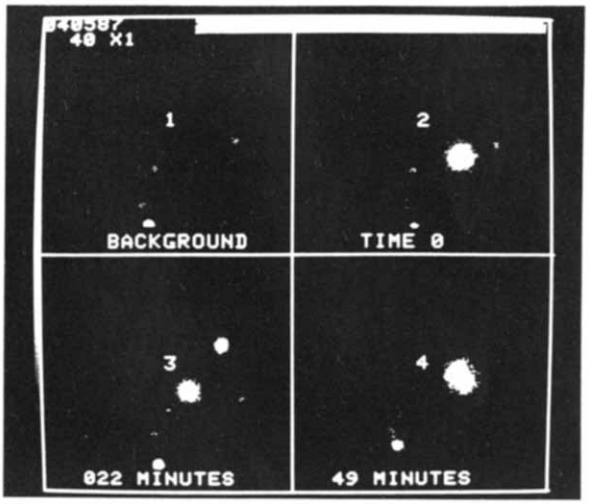

Fig. 1. Typical scintigraphic images taken immediately after administering balloon tablets and non-disintegrating tablets, 22 min after and 49 min after, under fasted state.

activity, which occur under fasting conditions every 1.5–2 h, and effectively sweep undigested material from the stomach. These gastrointestinal motility patterns have been extensively discussed in the literature (Code and Schlegel, 1974; Code and Marlett, 1975; Minami and McCallum, 1984; Fara, 1985; Rubinstein et al., 1988; Walter-Sack, 1990). As a result of this activity, dosage forms administered to fasted subjects could be emptied as rapidly as within 30 min or less, depending on the presence of this strong motor induced con-

TABLE 2

Gastric emptying times of balloon tablets and non-disintegrating tablets under fasted and fed states

Subject no.	Gastric emptying time (min)					
	Fasted state			Fed state		
	Balloon tablet	Matrix tablet	Time difference (min)	Balloon tablet	Matrix tablet	Time difference (min)
1	45	45	0	384	40– 63 (51.5) [a]	332.5
2	179–214 (196.5)	179–214 (196.5)	0	160–220 (190)	15– 30 (22.5)	167.5
3	69	41– 61 (51)	18	420–458 (439)	187–206 (196.5)	242.5
4	12– 44 (28)	12– 44 (28)	0	529	41– 79 (60)	469
5	22– 49 (35.5)	22– 49 (35.5)	0	500 +	< 30	470 +
6	87–114 (110.5)	70– 86 (78)	22.5	445–470 (457.5)	52– 70 (61)	396.5
7	28– 31 (29.5)	28– 31 (29.5)	0	498 +	122–139 (130.5)	367.5 +

[a] Numbers in parentheses are median values.

tractile activity. It is possible to have emptying of the balloon dosage form during Phase III activity where the contractions are the strongest. The strong contractile activity was clearly capable of ejecting even the large balloon dosage form from the stomach.

Table 2 shows that in the fed state, in all subjects, the balloon dosage form emptied at a much later time than did the non-disintegrating tablet. With the exception of one subject, who again was the oldest subject of the group, the prolonged retention of the balloon dosage form exceeded 4 h. In five of the seven subjects, the prolonged retention of the balloon dosage form exceeded 5.5 h. In four of the seven subjects, the prolonged retention of the balloon dosage form exceeded 6 h, and in two of the subjects, it approached or exceeded 8 h.

Gastric emptying of the test or control dosage forms in each subject, fasted and fed, was determined by carefully studying the photographic plates on which the images at each time point were recorded. Use of small low-dose technetium-labeled tablets proved to be an effective

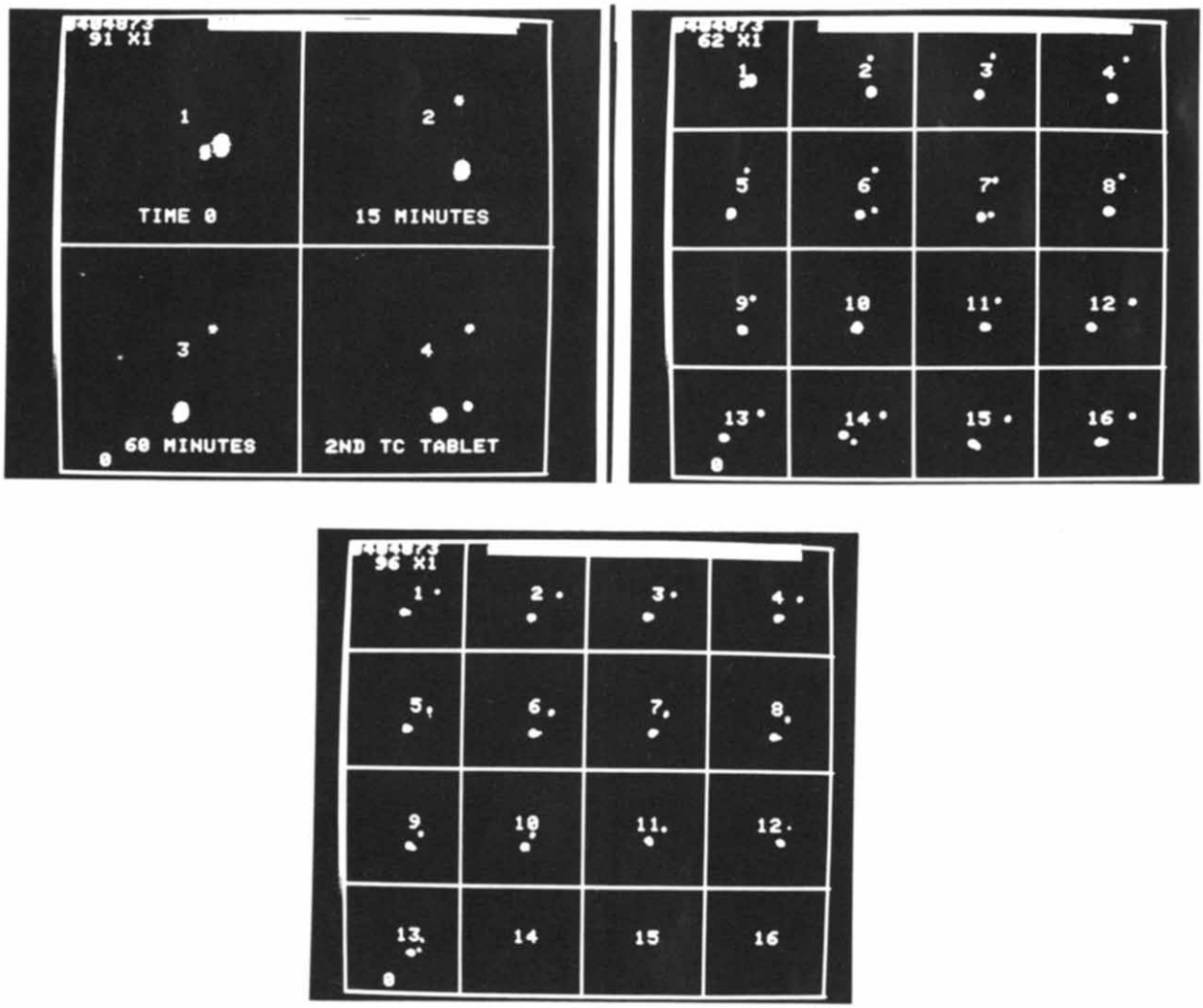

Fig. 2. (a–c) Scintigraphic images taken from one test subject following administration of balloon and non-disintegrating tablets under fed conditions. (a) Time 0–60 min; (b) time 0–303 min; (c) time 303–500 min.

means of defining the bottom of the stomach when there was any question as to the position of either tablet during the test procedures. Fig. 2 (a–c) shows typical images taken from one subject. Fig. 2a shows the two tablets side-by-side immediately after administration. By the 15th minute, the balloon tablet had floated and widely separated from the control tablet. By the 60th minute, the technetium labeled control tablet had emptied. This was confirmed by the administration of a low dose technetium tablet, which rested above the initial control tablet but below the balloon dosage form. Fig. 2b shows images taken from the same subject from immediately after administering both tablets to 303 min. Fig. 2c shows images taken from 303 to 500 min after administration. Where a question existed as to whether one tablet or the other had emptied, the last time when it was clear that the tablet was still in the stomach was noted and the first time point at which the tablet was clearly out of the stomach was recorded. Intermediate time points were ignored. The median time between when the tablet was last seen in the stomach and the first time it was seen out of the stomach was taken as the emptying time. It is recognized that this approach may record an emptying time that is longer than the true emptying time. However, this time window of uncertainty was seldom longer than 30 min, in which case the 'bias' could not be greater than 10–15 min on average. Further, the bias should be the same for both the test (balloon) and control (non-disintegrating) tablets.

It appeared that the balloon tablet floated somewhat more quickly in the fasted state compared to the fed state. The composition of the cross-linked polymer coating of the balloon tablet hydrates more rapidly at a higher pH. This would lead one to believe that the hydration, swelling and flotation of the coated tablet would be more rapid in the fed state. However, this effect was not seen. The higher viscosity of the gastric contents in the fed state may play an inhibiting role in flotation and may account for longer flotation times in the fed state.

The average prolongation of gastric retention of the balloon dosage form in comparison to the non-disintegrating dosage form in the fed state, was 350 min or nearly 6 h. Clearly the balloon dosage form produced very prolonged and significant gastric retention times in comparison to control non-disintegrating tablet.

There was surprisingly little difference in the average emptying time, or pattern of emptying times, for the matrix tablet in the fasted and in the fed subjects. The average time was 66 min with a range of 28–196 min in the fasted subjects vs an average of 79 min and a range of 30–196 min in the same subjects fed.

This study has demonstrated that in the fasted state, under the influence of the strong motor activity (the migrating myoelectric complex), no difference existed in gastric emptying of the 'balloon' test tablet and non-disintegrating control tablet. The study also demonstrated a very prolonged average retention of approx. 6 h of the balloon tablet over the control non-disintegrating tablet in a fed state. A double labeling technique is reported which permits simultaneous comparison of the gastric emptying of two different products, in human subjects, using gamma camera scintigraphy. The technique also describes how the radionuclide materials may be immobilized and incorporated to permit tracking of two types of tablet dosage forms.

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