The Bilayer Floating Capsule: A Stomach-Directed Drug Delivery System for Misoprostol

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A bilayer floating dosage unit is proposed to achieve local delivery of misoprostol, a prostaglandin E_1 analogue, at the gastric mucosa level. The system is a capsule consisting of a floating layer maintaining the dosage unit buoyant upon the gastric content and a drug layer formulated to act as a sustained-delivery system. The differential design of the two layers allows the optimization of both floating capability and drug release profile. The layers are both composed of a hydrophilic matrix based upon hydroxypropylmethyl cellulose (HPMC). Parameters influencing the release profiles are described. The use of a large capsule increases the gastric residence time (GRT), as it impedes passage through the pylorus opening. γ-Scintigraphic studies were performed to visualize cohesion of the two layers *in vivo* and to determine GRT as a function of meal regimen. The average GRTs were 199 ± 69 min after a single meal (breakfast) and 618 ± 208 min after a succession of meals.

KEY WORDS: bilayer floating unit; prostaglandin; misoprostol; gastric residence time; hydrophilic matrix.

INTRODUCTION

Misoprostol is an analogue of the naturally occurring prostaglandin E_1, indicated for the treatment of gastric and duodenal ulcers. It has proved beneficial in the prevention and treatment of gastric ulcer disease induced by nonsteroidal antiinflammatory agents (NSAIDs). Misoprostol is cytoprotective, acting directly on the gastric mucosa. Misoprostol is well tolerated with diarrhea, the most commonly reported side effect.

Our objective was to design a dosage form with a sustained release and an optimal gastric residence time to maximize local delivery of misoprostol while reducing side effects. Several concepts can be used to achieve this goal, such as bioadhesive or floating systems. The targeting of drugs into the stomach via bioadhesion does not look promising as the phenomenon appears irregular (1).

The design of floating units has been discussed in several publications and patents; an extensive review was written by Buri *et al.* (2). A floating dosage unit is useful for drugs acting locally in the proximal gastrointestinal tract, for drugs requering gastric absorption, and for compounds that are poorly soluble or unstable in intestinal fluids.

Sheth and Tossounian (3) first proposed the simple and effective hydrodynamically balanced system (HBS). These authors utilized large quantities of hydroxypropyl methylcellulose (HPMC) and fatty materials to regulate flotation and drug release. This dosage unit has been marketed by Hoffmann–La Roche for a sustained-release form of diazepam (Valrelease) and for a combination of L-dopa and benserazide (Madopar) (3,4). Recently Cook *et al.* (5) demonstrated an increase in efficacy and a reduction of side effects with an HBS capsule containing iron salts. The use of an HBS capsule for the delivery of propanolol hydrochloride was reported by Khattar *et al.* (6).

Timmermans and Moës (7) have shown that the initial bulk density of the dosage unit and changes of the floating strength with time should be characterized prior to *in vivo* comparison between floating and nonfloating units. The lack of a sustained floating capacity might explain some of the controversies in the literature. The gastric residence time (GRT) of a dosage unit in the fed state can also be influenced by its size. Small-size tablets are emptied from the stomach during the digestive phase, while larger-size units are expelled during the housekeeping waves. Timmermans *et al.* (8) studied the influence of dosage form sizes on the GRT of floating and nonfloating units in man using γ-scintigraphy. GRTs were superior for floating units with a diameter smaller than or equal to 7.5 mm, while GRTs were similar for floating and nonfloating units with a larger diameter (9.9 mm). This study also demonstrated that the floating capsules remain buoyant on the gastric contents and are protected against emptying during the digestive phases. The nonfloating units lie in the antrum and are propelled during the digestive process toward the gastroduodenal junction, the pylorus acting as a sieve for the nonfloating units (8).

Other factors influence the GRT of dosage forms, such as whether the subject has eaten, the nature of the meal, the caloric content, and the frequency of feeding (9,10). Several other parameters act on the GRT, such as gender, age, posture, or concomitant administration of drugs (11). Recent γ-scintigraphic studies have shown slightly shorter gastric residence times for floating dosage forms versus nonfloating dosage forms when the subjects remain in supine posture (12).

MATERIALS AND METHODS

Materials

Materials used included misoprostol/HPMC, 1:100 (Searle UK); Methocel K4M and Methocel K100 (Dow chemicals USA); Pharmacoat 603 and 606 (Shin Etsu J); lactose (Ph. Eur.); magnesium stearate (Ph. Eur.); colloidal anhydrous silica (Ph. Eur.); hard gelatin capsule size 1 (Elanco F); and hard gelatin capsule Coni Snap Supro B (Capsugel CH). All other materials and solvents are analytical grade.

Methods

Bilayer capsules were first prepared manually, then a Zanasi LZ64 capsule filling machine was modified to allow production of the bilayer capsules. The release layer was

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filled using the dosing unit, then the floating layer was added by volumetric filling. To minimize mixing of the two layers, an overfilling of the buoyant layer was needed.

Misoprostol dissolution tests were conducted following the USP dissolution test, the capsules being held in a stainless-steel ring. Medium was 500 ml water at 37°C; stirring rate, 50 rpm. After filtration the samples were tested by HPLC (column, 15 cm × 4.6 mm; Dupont Zorbax C8, 5 μm; mobile phase, water/acetonitrile (40:60, v/v); flow rate, 1.0 ml/min; detection, UV 200 nm).

Resultant-weight measurements were obtained as described previously (13,14). Floating characteristics were tested by monitoring the total force F acting vertically on the immersed dosage unit. This force F determines the resultant weight of an immersed object. Dosage forms were maintained immersed during the entire measuring procedure by a spit-holder extremity into a 1200 ml HCl (pH 1.2) + 0.05% Tween 80 test medium or in buffer at pH 6.0 + 0.05% Tween 80, thermostatically controlled at 37°C.

Diameter measurements of the floating layer were performed using an optical microscope system (Zeiss LAB16 with image projection and micrometer eyepiece). Dosage forms were maintained immersed in the same conditions as described above.

γ-Scintigraphic studies were conducted with 13 healthy young volunteers (age range, 23–32 years; weight range, 60–83 kg). The study protocol was approved by the Ethical Committee of the Erasme Hospital Belgium. The subjects had signed an informed consent statement prior to enrollment. The subjects were admitted to the study after an overnight fast and ingested meal regimen A or meal regimen B.

A placebo bilayer floating unit was prepared in a Supro B capsule and each layer was labeled with a different radiopharmaceutical. Release layer: Pharmacoat 606, 36.0 mg; Methocel K100, 10.0 mg; Methocel K4M, 4.0 mg; 100-mesh lactose, 82.2 mg; Mg stearate, 2.7 mg; Aerosil 200, 0.07 mg; and ^{111}In oxinate deposited on 10 mg sodium chloride (0.500 mCi). Floating layer: Methocel K4M, 200.0 mg; 100-mesh lactose, 37.4 mg; Mg stearate, 12.5 mg; Aerosil 200, 0.1 mg; and ^{201}Tl deposited on amberlite IR120 ion exchange (0.300 mCi).

Meal regimen A was as follows: 0830, standardized breakfast (100 g solid, 600 ml liquid, 650 kcal). No more drink or other food was allowed during the course of the study.

Meal regimen B was as follows: 0830, standardized breakfast (335 g solid, 685 ml liquid, 1300 kcal); 1100, appetizer snack (72 g solid, 200 ml liquid, 399 kcal); 1200, lunch (630 g solid, 815 ml liquid, 1036 kcal); 1600, snack (95 g solid, 185 ml liquid, 477 kcal); 1800, dinner (585 g solid, 515 ml liquid, 772 kcal). Afterward the subjects were not allowed to eat.

At 0900, each subject ingested the bilayer floating unit with 150 ml water; the subjects were then ambulatory and remained in an upright posture. The previously described scintigraphic monitoring technique was used (8).

RESULTS AND DISCUSSIONS

Monolithic Floating Unit

Misoprostol is a relatively unstable oily material; its stability can be improved by incorporation into HPMC at a 1:100 drug/HPMC ratio (15). The first formulations were of HBS type: high concentrations of HPMC were used to act as a gel forming agent that hydrates and forms a gelatinous barrier, keeping the powder within the dosage form dry and at a density lower than 1. The diffusion through the gelatinous barrier and the dissolution of the polymer control the release process.

Examples of monolithic capsules are given in Table I, and the dissolution profiles are shown in Fig. 1. The release rate of misoprostol was a function of the HPMC K4M content. An increase in Methocel K4M concentration induced a decrease in the release rate. An average GRT of 3 hr was expected for this type of dosage form (8); however, after 3 hr only 50% of the misoprostol was released (Fig. 1). These release profiles were considered unsuitable for our application.

Resultant-weight measurements were performed to determine the floating characteristics of the dosage units. A positive and high resultant weight indicates good buoyancy properties; if the resultant weight is negative, the dosage form is sinking. A decrease in the value of the resultant weight as a function of time implies reduction of buoyancy capabilities. The resultant-weight curves shown in Fig. 2 were initially positive; however, the dosage unit formulated with 25% Methocel K4M (formulation D, Table I) sank after 2.5 hr, while formulation A, containing 49% Methocel K4M, maintained buoyancy.

To improve the release rate while keeping adequate buoyancy and an acceptable dosage form diameter, formulation parameters were modified, e.g., HPMC viscosity, nature of the diluent, lubricant content, disintegration agents, Tween 80, and a carbon dioxide generating blend. We were unable to reach appropriate release (90 ± 10%) within 3–4 hr. The antagonism between good release rate characteristics and floating properties appeared to be insolvable in a monolithic dosage form and led us to propose a more sophisticated design.

Bilayer Floating Unit

The concept of a bilayer capsule was introduced to optimize separately the buoyancy layer and the drug release formulation layer. To impede further early release through the pylorus, the bilayer units were formulated in Supro B hard gelatin capsules, characterized by a larger diameter than traditional capsules.

Table I. Examples of Misoprostol 400-μg Monolithic Capsules Formulated with Various Concentrations of Methocel (HPMC) K4M

Ingredient(s)	Formulation[a]			
	A	B	C	D
Misoprostol/HPMC, 1:100	40.0	40.0	40.0	40.0
Methocel K4M	117.0	102.5	86.0	70.3
Lactose	78.1	102.4	128.7	164.0
Magnesium stearate	4.8	5.0	5.2	5.6
Aerosil 200	0.1	0.1	0.1	0.1

[a] All quantities are milligrams. All formulations prepared in hard gelatin capsules, size 1.

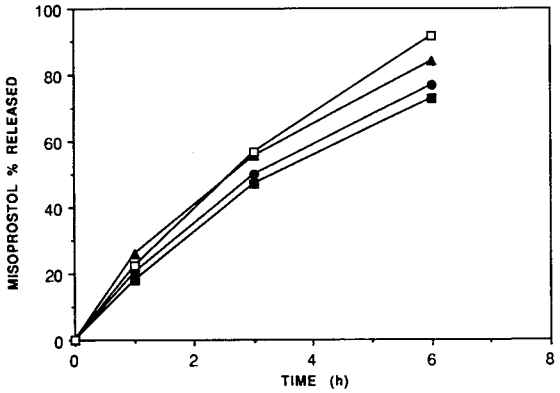

Fig. 1. Influence of Methocel K4M concentration on misoprostol release profiles from the monolithic dosage unit: formulations A (■), B (●), C (△), and D (□).

The cohesion of the two layers was tested in a modified USP disintegrating test (mesh at both sides of the basket), the test starting with immersion of capsules without agitation for 15 min before normal disintegration test procedure. The two layers did not separate during the test. The release layer progressively eroded during the disintegration test, while the buoyancy layer kept its integrity.

The Floating Layer

Large concentrations of high-viscosity polymer (Methocel K4M) were incorporated into the buoyant layer (Table II), inducing the formation of a strong viscous gel layer that slowed down the rate of water diffusion into the floating layer, allowing the maintenance of an overall density close to the density of the dry powder. The floating force kinetics of a bilayer capsule was determined at pH 1.2 and pH 6.0. The magnitude of floating force was adequate (resultant weight, between 170 and 209 mg) and stable during 8 hr at the two pH's tested. In comparison to the monolithic unit (Fig. 2), more stable floating profiles were obtained with the bilayer dosage forms. The integrity of the floating layer was maintained longer due to the very high methocel K4M concentration.

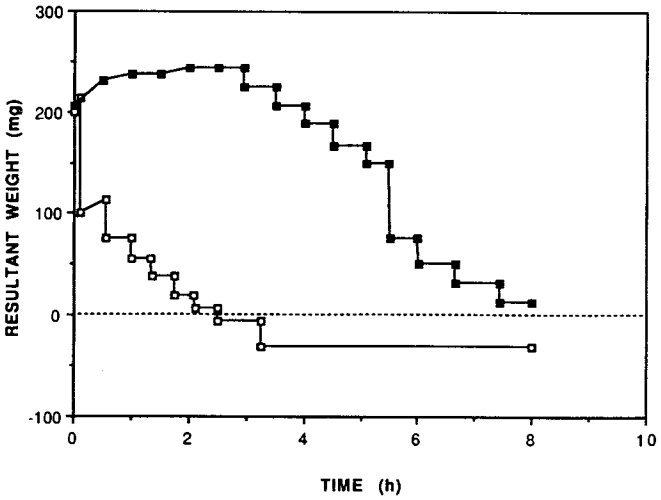

Fig. 2. Influence of the Methocel K4M concentration on the floating behavior of the misoprostol monolithic dosage unit: formulations A (■) and D (□).

Table II. Examples of Misoprostol Bilayer Capsules Formulated with Different Concentrations and Viscosities of HPMC

Ingredient(s)	Formulation[a] E	F	G	H	I	J
Drug layer						
Misoprostol/HPMC, 1:100	40.0	40.0	40.0	40.0	20.2	20.2
Methocel K4M	19.0	33.0				
Methocel K100			21.0	33.0		
Pharmacoat 606					60.0	
Pharmacoat 603						60.0
Lactose	63.4	34.7	76.1	54.3	59.1	59.1
Stearate Mg	2.5	2.2	2.8	2.6	1.4	1.4
Aerosil 200	0.1	0.1	0.1	0.1		
Floating layer						
Methocel K4M			80.0%[b]			
Lactose			14.96%			
Stearate Mg			5.0%			
Aerosil 200			0.04%			

[a] All quantities are milligrams. All formulations prepared in hard gelatin Supro B capsules.
[b] The floating layer weight depends on the density of the drug layer.

The Coni Snap Supro B capsules (Capsugel CH) were selected because their large diameter improves GRT, without affecting patient compliance. The immersed dosage form, after dissolution of the capsule shell, increased the diameter of the floating layer form 8.2 to 10 mm within 10 min, and this diameter was maintained for at least 8 hr. This large size increase of the floating layer was due mostly to the fast hydratation rate of Methocel K grade.

The Release Layer

The drug release layer included a gelling agent forming a gelatinous barrier. The release layer had to be nondisintegrating to avoid delivery of large particles containing drug in the intestine, where they might induce side effects. The influence of the concentration and the viscosity of HPMC on the misoprostol release profiles were tested. The bilayer compositions are shown in Table II and the release profiles in Fig. 3, the floating layer being constant for all the dosage forms. As expected, an increase in HPMC viscosity and in concentration induced a decrease in release rate. By using various viscosities and concentrations, profiles from very rapid with Pharmacoat 603 to very slow with Methocel K4M were obtainable. All the bilayer capsules tested were nondisintegrating; the release process was controlled both by diffusion through the gelatinous barrier formed by the polymer and by the dissolution/erosion of the gelatinous layer.

During dissolution tests, a complete erosion of the release layer was observed for formulations including Pharmacoat 603 or 606. Release rates were a function of the stirring rate (Fig. 4). Even under unstirred conditions, 100% release was reached with the Pharmacoat 603 formulation. *In vivo*, mild agitation is expected as the floating capsule remains on the gastric content.

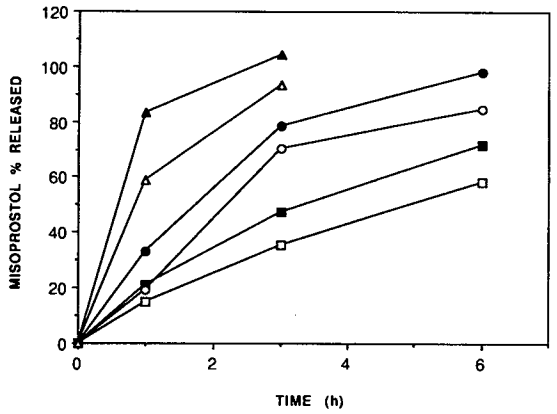

Fig. 3. Influence of hydroxypropyl methylcellulose viscosity and concentration on misoprostol release profiles from bilayer units: formulations E (■), F (□), G (●), H (○), I (△), and J (▲).

In Vivo γ-Scintigraphic Studies

One bilayer formulation showing an adequate release profile was selected and tested *in vivo* on young healthy volunteers. The two layers were labeled separately with ^{111}In and ^{201}Tl to enable visualization of the behavior of the dosage form *in vivo*. Misoprostol was not introduced in the labeled dosage unit. The γ-scintigraphic studies allowed us to study the influence of meal regimen on gastric residence time, intragastric buoyancy, and cohesion between the two layers. The relative intragastric height measurements show that the bilayer unit was effectively in a buoyant state on gastric content (Fig. 5). By remaining in the upper part of the stomach, the bilayer unit was protected against emptying during the digestive phase. After a new administration of liquid or solid meals, the increase in stomach content was visualized and the bilayer dosage form remained buoyant on gastric content. Those data demonstrated *in vivo* the adequate floating capacity of the bilayer unit.

The individual gastric residence times (GRT) are reported in Table III. The mean gastric residence time of the bilayer dosage form was 199 ± 69 min for the session with the light breakfast only. After a succession of meals, the data show a remarkable enhancement of the average gastric residence time, to 618 ± 208 min. As a meal was administered before the completion of the previous digestive phase, the floating capsule was further retained in a buoyant state for an additional digestive phase. The frequent feeding study was performed to mimic real-life conditions. Even a light snack can prolong the gastric residence time of a dosage form. The gastric residence time of the bilayer dosage form depends on the meal emptying rate and on the time interval between meal administrations. The floating dosage unit should be ingested after meals. As reported previously, to prevent early emptying from the stomach, the supine posture should be avoided in the hours following dosing.

The superimposition of the ^{111}In and ^{201}Tl images demonstrated the cohesion of the two layers. During the gastric

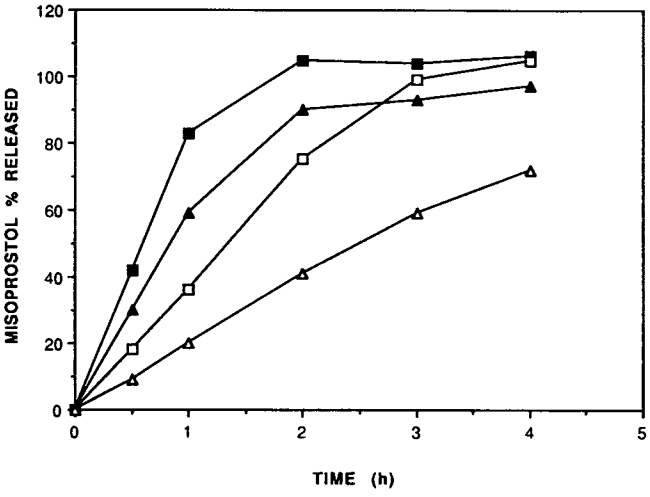

Fig. 4. Influence of paddle stirring rate on misprostol release profiles from bilayer units: formulations I (△) and J (□). Filled symbols, 50 rpm; open symbols, 0 rpm (1-min homogenization before sampling).

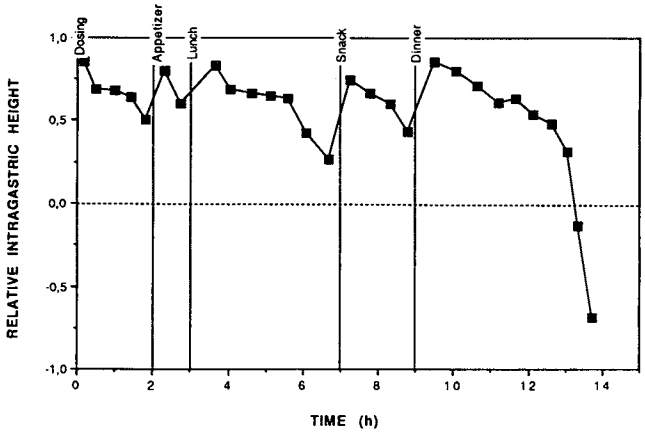

Fig. 5. Intragastric relative height of the bilayer as a function of time determined by γ-scintigraphy study. Session with succession of meals, subject 14. Relative intragastric height: 1, top of the stomach; 0, bottom of stomach; −1, intestinal tract.

Table III. Individual Gastric Residence Times Obtained with the Bilayer Floating Dosage Form After Two Types of Regimen

Breakfast only (A)		Succession of meals (B)	
Subject No.	GRT (min)	Subject No.	GRT (min)
1	100	11	>900
2	155	12[a]	
3	205	13	398
4	304	14	779
5	122	15	>900
6	291	16	507
7	225	17	473
8	195	18	404
9	197	19	729
10[b]	118/229	20	476
Mean	199		618
±SD	69		208
CV (%)	35		34

[a] Subject had undergone surgical resection of hiatal hernia and was excluded from the study.

[b] Not taken into account for calculation due to layer separation.

residence time period, the separation of the two layers was observed only in one subject receiving food regimen A (subject 10), whereas in all other subjects, no layer separation was observed. The study demonstrated the adequate cohesion of the two layers *in vivo* as expected from the *in vitro* data.

The bilayer floating capsule of a sufficient size is a promising system to deliver prostaglandins in general and misoprostol, in particular at the proximal gastrointestinal tract level, for which a U.S. patent application has been filed (16). The rate of delivery can be easily managed and will be further adapted as a function of the results of ongoing clinical studies.

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