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International Journal of Pharmaceutics 174 (1998) 55–62

international journal of pharmaceutics

Air compartment multiple-unit system for prolonged gastric residence. Part II. In vivo evaluation

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Received 15 April 1997; received in revised form 1 July 1998; accepted 3 July 1998

Abstract

The intragastric behaviour of a floating multiple-unit system was assayed in humans. The floating units used in this study, composed of a calcium alginate core separated by an air compartment from a calcium alginate/polyvinylalcohol membrane, had shown an excellent buoyancy ability in the previous in vitro investigation. The present in vivo study was conducted in three different sessions (fasted state, fed state after a meal and fed state after a succession of meals) by administering to each subject at the same time both floating and control systems, loaded with barium sulfate, and monitoring them in the gastric region at determined time intervals using X-ray apparatus. Unlike the control, the floating system remained buoyant on the gastric content under both fasted and fed states. In the fasted state, the intragastric buoyancy of the system did not influence its gastric residence time (GRT). In the fed state after a meal, all the floating units showed a floating time (FT) of about 5 h and a GRT prolonged by about 2 h over the control. In the fed state after a succession of meals, most of the floating units showed a FT of about 6 h and a GRT prolonged by about 9 h over the control, though a certain variability of the data owing to mixing with heavy solid food ingested after the dosing was observed. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Calcium alginate; Floating dosage form; Gastric retention; Multiple-unit dosage form

1. Introduction

Oral floating devices are made to be retained in the stomach for a long time assuring a slow delivery of the drug above its absorption site providing increased and more reproducible bioavailability (Fischer et al., 1987; Ichikawa et al., 1991; Desai and Bolton, 1993). Though this conception led floating systems to be put on the market, no definite opinion has been formed about their actual efficacy (Timmermans and Moës, 1994). In fact, some authors noted floating systems as having only insignificantly prolonged

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PII S0378-5173(98)00230-0

gastric residence time (GRT) compared with non-floating systems (Desai and Bolton, 1993). Others reported that the presence of food, rather than buoyancy, is the most important determinant of GRT (Mazer et al., 1988).

In this regard, the present investigation aims to assess in humans the intragastric behaviour of an air compartment multiple-unit system able to float immediately on being placed into artificial gastric fluid and obtainable by a new simple technological approach. The units, each constituted by a calcium alginate core separated by an air compartment from a calcium alginate/polyvinylalcohol membrane, had shown excellent buoyancy in the previous preformulative investigation (Iannuccelli et al., 1998). In order to assay the actual floating ability on the gastric content and its usefulness in achieving an extended gastric transit, the in vivo floating time (FT) and the GRT of the floating system were determined and compared with those of a non-floating (control) system in both fasted and fed states.

2. Materials and methods

2.1. Materials

The following chemicals were obtained from commercial suppliers and used without further purification. Sodium alginate [MW about 115000, extracted from *Laminaria hyperborea*, containing 30% mannuronic acid and 70% guluronic acid], polyvinylalcohol (PVA) 100000 and calcium chloride dihydrate were purchased from Fluka Chemie (Buchs, Switzerland). Tween 20 (polyoxyethylen sorbitan monolaurate) was purchased from Atlas Europol (Ternate, Italy) and barium sulfate (Mixobar 60% Ventricolo) from Byk Gulden Italia (Milan, Italy). All the solvents (analytical grade) were purchased from Carlo Erba (Milan, Italy).

Table 1
Percentage of floating and control units staying buoyant on the gastric content or remaining inside the stomach (buoyant and non-buoyant) under fasted and fed conditions

Feeding condition	Time after dosing (min)	Floating units		Control units	
		Units buoyant on the gastric content (%)	Units inside the stomach (%)	Units buoyant on the gastric content (%)	Units inside the stomach (%)
Fasted	15	100	100	0	100
	60	0	0	0	0
Fed state after a meal	15	100	100	0	100
	60	100	100	0	100
	120	100	100	0	100
	180	95	100	0	100
	240	90	100	0	55
	300	90	100	0	0
	360	0	25	0	0
Fed state after a succession of meals	30	100	100	0	50
	120	88	100	0	0
	240	85	100	0	0
	360	70	100	0	0
	540	67	83	0	0
	660	46	76	0	0

Fig. 1. X-ray photograph of the gastric region 15 min after dosing of the floating and control units in the fasted state.

2.2. Methods

2.2.1. Preparation of the floating units

The floating units, each composed of a calcium alginate core separated from a porous calcium alginate membrane by an air compartment, were prepared by using the technique and the composition which provided the optimum buoyancy in the previous in vitro investigation (Iannuccelli et al., 1998). To make the units radiopaque, about 10 mg of barium sulfate was incorporated in each unit by using polymer solutions containing 3% w/v barium sulfate to form both the core and the membrane. The units so loaded with barium sulfate had a weight of 22.7 ± 2.5 mg, a diameter of 4.5 ± 0.1 mm, an apparent density of 0.5 ± 0.1 mg/mm^3 and they showed the same in vitro buoyancy as the unloaded units.

2.2.2. Preparation of the control units

The control units were obtained by removing the membrane, and so also the air compartment, from the floating units loaded with barium sulfate as described above.

2.2.3. In vivo X-ray study

The in vivo study was carried out by administering to humans floating and control units and monitoring them through a radiological method. Six healthy subjects (one male, five females; mean age 37 ± 13 years; mean weight 55 ± 10 kg) participated after giving informed consent. The study, approved by the local Ethical Committee, involved an open randomized crossover design in which the comparison with the control was carried out on the same subject. Ten floating units (floating system) and 10 control units, i.e. without air compartment (control system), were administered through hard gelatine capsules (size 1). The study was conducted by administering to each subject both floating and control systems concurrently on three separate sessions. (a) Fasted state, the subjects fasted overnight then swallowed the floating system together with the control with 150 ml water. Afterwards the subjects were not allowed to eat or drink; (b) Fed state after a meal, the subjects swallowed the floating system together with the control immediately after ingestion of a standardized lunch composed of a beefsteak and potatoes (500 g solid, 300 ml liquid) with a total caloric value of 1400 kcal. Afterwards the subjects were not allowed to eat or drink; (c) Fed state after a succession of meals, the subjects swallowed the floating system together with the control immediately after ingestion of a light standardized breakfast composed of 150 ml fruit juice, 1 ham roll, cereals and 100 ml milk (110 g solid, 250 ml liquid) with a total caloric value of 600 kcal. Two hours after dosing they received an appetizer snack composed of one slice of cake and 125 ml fruit juice (100 g solid, 125 ml liquid) with a total caloric value of 400 kcal and 5 h after dosing a standardized lunch as described above for the session b). Afterwards no food or drink was taken.

During the experiments the subjects remained in a sitting or upright posture. In each subject the position of the floating and control units was monitored by X-ray photographs (Siregraph-B, Siemens, Karlsruhe, Germany) of the gastric region at determined time intervals. The radiopaque membrane and the dark area of the air compartment enabled to distinguish the floating from the control units. Consequently, a crossover study could be performed on a single occasion (floating units versus control units).

The relative intragastric heights of the units were calculated by considering: top of the stomach = 1 and bottom of the stomach = 0. The data are averaged on the units observed in all the subjects. Moreover, the percentage of the units staying buoyant on the gastric content and that of all the units staying inside the stomach (buoyant and non-buoyant) were calculated at each time interval for all the subjects. Thus, the FT and GRT of both floating and control units were defined as the maximum floating time and the maximum gastric retention time of most of the units (> 70%), respectively.

3. Results and discussion

The study aimed to examine whether the air compartment multiple-unit system could float and be retained in the stomach. A radiological method was adopted to monitor the units in the gastric region of humans in different feeding conditions.

Unlike the control, the floating units remained buoyant on gastric content under both fasted and fed states. However, differences in buoyancy performance and gastric retention were observed according to the feeding condition (Table 1).

In the fasted state, all the floating units were observed to be buoyant on the liquid at 15 min, whereas the control had sunk by the same time (Figs. 1 and 2). One hour after dosing all the floating and control units were found in the intestine. The small FT value (15 min) of the floating units observed in all the subjects was related to

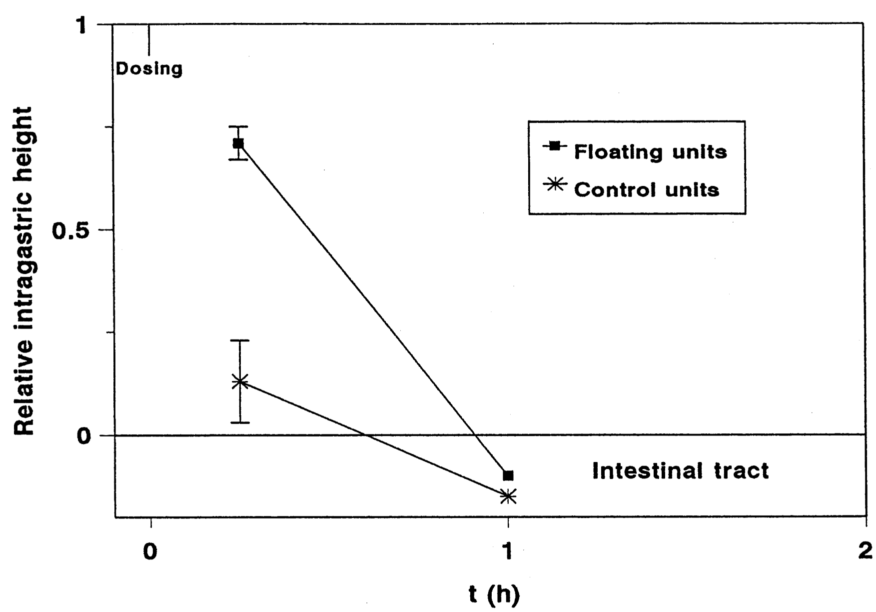
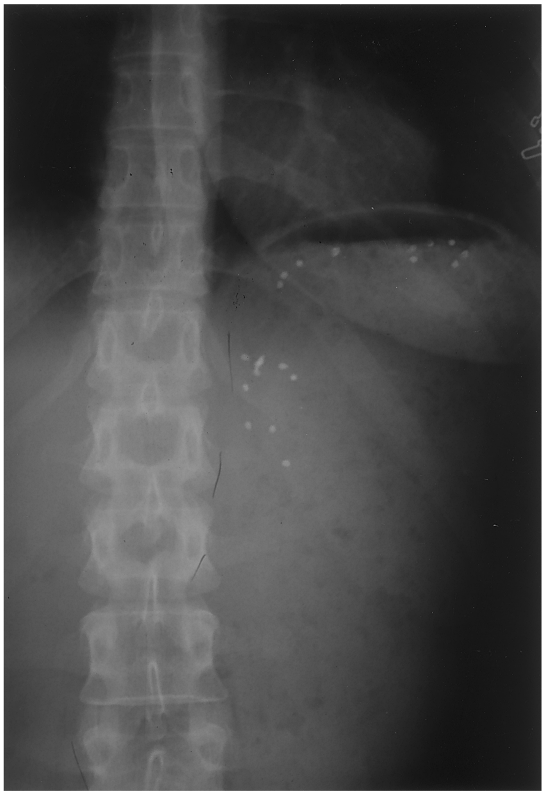


Fig. 2. Relative intragastric height of the floating and control units as a function of time in the fasted state.



a

b

Fig. 3. X-ray photographs of the gastric region 15 min (a) and 5 h (b) after dosing of the floating and control units in the fed state after a meal.

their quick gastric emptying along with the ingested liquid. This resulted in a FT value corresponding to GRT (15 min) and in no difference in GRT between floating and control units (Table 1). Therefore, in such conditions, the buoyancy property did not enhance the GRT.

In the fed state after a meal, almost all of the floating units were observed to be buoyant on the gastric content up to 5 h (FT) after administration (Fig. 3a, b). Six hours after dosing almost all the units were detected in the intestine (Fig. 4). The correspondence between FT and GRT values (5 h) (Table 1) and the mean relative intragastric heights (decreasing from about 0.9 to 0.8 with the gastric content level, Fig. 4) indicate a continuous floating condition inside the stomach. In contrast, all the control units were found mixed with the food in the body of the stomach, at a mean relative intragastric height of about 0.6 (Fig. 4), at 15 min after administration (Fig. 3a). Similarly to the ingested food, they remained at this level of the stomach up to 3 h (GRT) and, then, they emptied (Fig. 3b). Therefore, in the fed condition after a meal, the floating units showed a GRT prolonged by about 2 h over the control. The enhanced GRT of the floating units over the food gastric residence is attributed to their intragastric position in the upper part of the stomach protecting them from the strong antral peristaltism. This favourable position is, however, closely related to the presence of a gastric content (food or gastric secretions).

The session conducted in a fed state after a succession of meals aims to reproduce the drug administration in a real-life condition. Besides, a dosing after breakfast represents the most suitable way for the assumption of an once-a-day floating delivery system where, in addition, the supine position of the patients should preferably be avoided (Timmermans and Moës, 1994).

All the floating units dosed after the breakfast were observed to be buoyant on gastric content at 0.5 h (Fig. 5a). Most of the floating units (about 85%) remained in a buoyant condition at 4 h after dosing showing mean relative intragastric heights decreasing with the gastric level (Fig. 6). At 9 h (FT) after dosing about 70% was found buoyant on gastric content whereas the remaining was observed in a lower part of the stomach (Fig. 5b). Therefore, unlike a light meal (snack), the ingestion of a heavy solid food (lunch) after dosing led to a failure in buoyancy for some units. Notwithstanding this, almost all the floating units remained inside the stomach for 6 h after dosing, about 75% for 11 h (GRT) (Table 1).

In contrast, the control units was found partly (50%) in the antrum, partly in the intestine at 0.5 h, all of them in the intestine at 2 h after dosing (Fig. 5a and Fig. 6) exhibiting, then, a gastric emptying much faster than when they were given after a substantial food intake (lunch).

Therefore, in such feeding conditions, the floating units showed a GRT prolonged by about 9 h over the control. Furthermore, this study revealed that even the dosing after a light meal, such as a breakfast, can prolong the GRT of the units.

4. Conclusions

The evaluation in humans of the air-compartment multiple-unit system intragastric behaviour demonstrated the actual floatability of the units on the gastric content. Dosing the subjects after a meal (breakfast or lunch) enhanced the GRT of the system over the food gastric emptying. Feedings following the drug administration led to a further GRT prolongation, though heavy meals should be avoided.

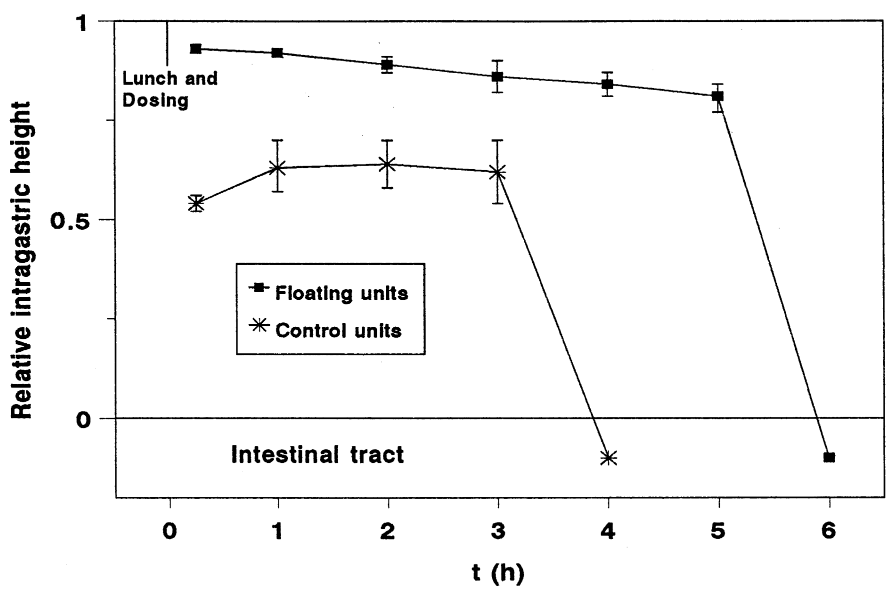
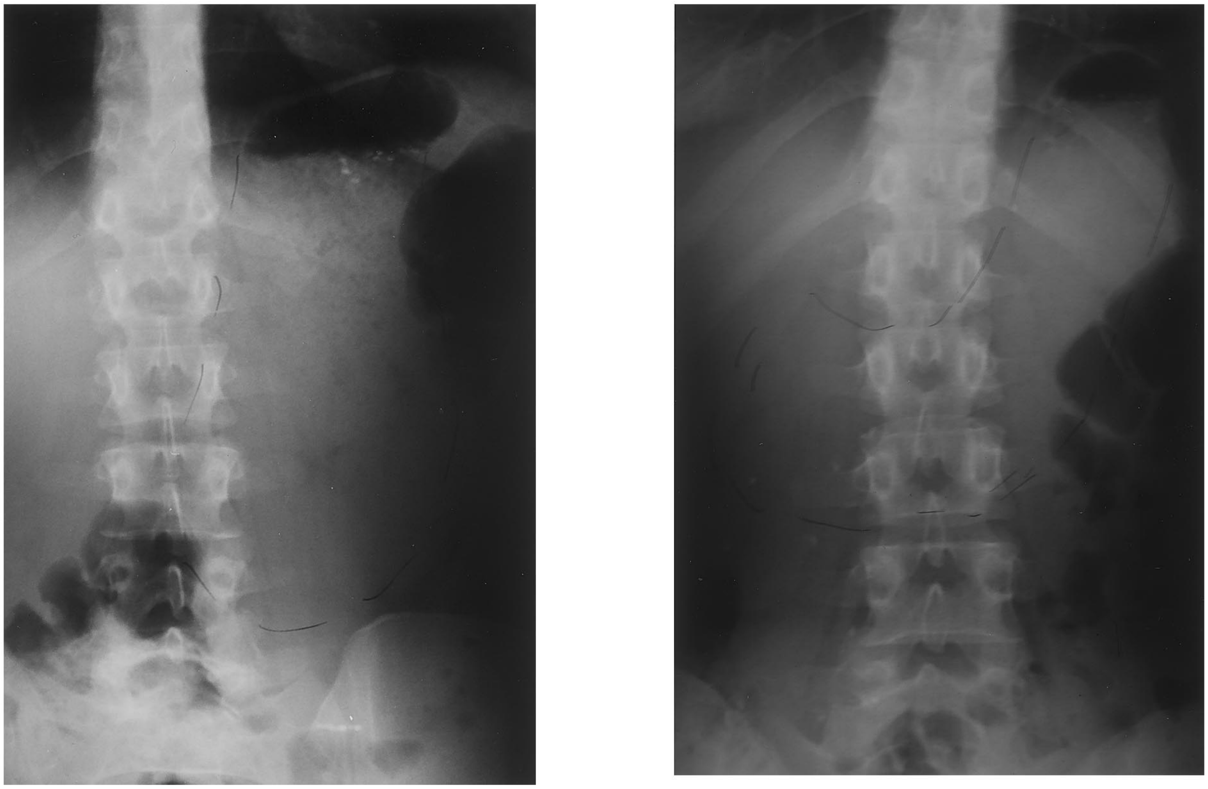


Fig. 4. Relative intragastric height of the floating and control units as a function of time in the fed state after a meal.



a b

Fig. 5. X-ray photographs of the gastric region 0.5 (a) and 9 h (b) after dosing of the floating and control units in the fed state after a succession of meals.

The prolongation of the GRT is known to offer advantages in terms of increased bioavailability of drugs having the absorption site in the stomach or in the upper intestinal tract (Ingani et al., 1987; Ichikawa et al., 1991; Menon et al., 1994). Therefore, the floating system designed could be suitable for the administration of such drugs. For this purpose, the drug loading can be easily performed by dissolving or dispersing the drug in the polymer solutions forming the core and the membrane of the units. The actual floatability of the units loaded with the barium sulfate (about 50%, w/w) suggests reasonably the possibility to incorporate effective doses of drugs without compromising the unit functionality. Moreover, a multiple-unit dosage form could allow modification of the drug dose by changing the number of the administered units. In this regard, further investigations will be directed to establish the drug release characteristics and the pharmacokinetics in order to evaluate the effectiveness of this air compartment multiple-unit system.

Acknowledgements

This work was supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST), Rome, Italy.

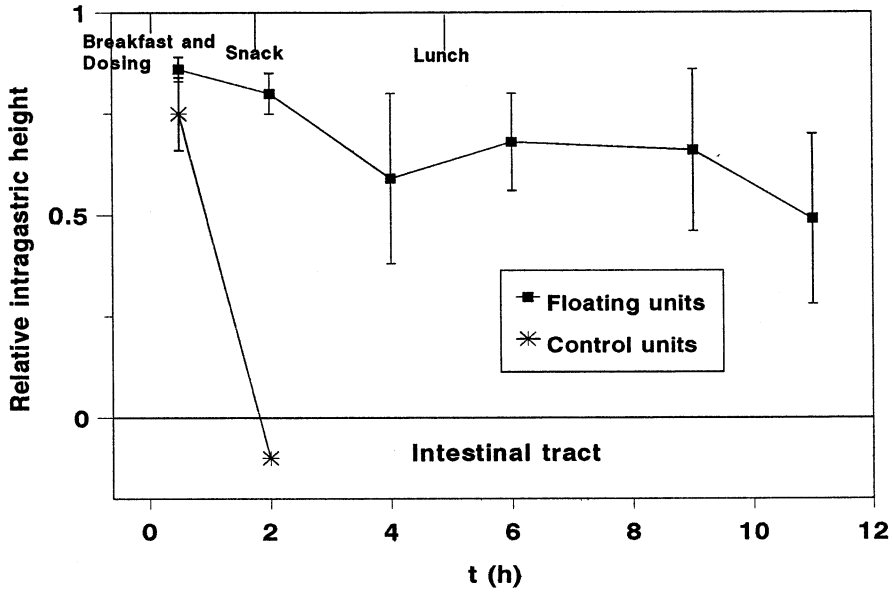


Fig. 6. Relative intragastric height of the floating and control units as a function of time in the fed state after a succession of meals.

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