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How well do floating dosage forms float?

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Summary

Peroral floating dosage forms have up to now been used and prescribed without having achieved any determination of their real floating capabilities versus time. Using a novel in vitro resultant-weight measuring system, the authors present different examples of floating-force kinetics obtained from polymeric matrix floating forms, amongst which several are marketed products and others have undergone in vivo experiments conducted on human volunteers. The floating curves are showing that the bulk density of a dosage form is not the most appropriate parameter for describing its buoyancy capabilities. These capabilities are, however, perfectly represented and monitored by resultant-weight measurements. Results also indicate that the magnitude of floating strength may vary as a function of time and usually decreases after immersion of the dosage form into the fluid consequently to the evolution of its hydrodynamical equilibrium. To prevent drawbacks of unforeseeable floating capability variations during in vivo studies, the authors suggest optimization of dosage form formulations to be realised with respect to the significance level, the stability and durability of the floating forces produced.

Introduction

The first explicit description of a peroral floating dosage form was probably made by Sheth and Tossounian (1975). The proposed Hydrodynamically Balanced Systems (HBS) appeared to be non-disintegrating hydrophilic matrix capsules or tablets that have a bulk density lower than that of the gastric fluids. The inventors claimed these floating forms to remain in a buoyant state upon the stomach contents for a prolonged period of time and recommended their use when aiming to enhance the gastrointestinal (GI) transit time of an orally taken medication or to obtain a sustained local action of the latter inside of the stomach.

From that time onwards an increasing interest has been directed towards this research field and various other floating drug-delivery systems, and formulations were proposed for achieving the same intended intragastric function (Banker, 1975; Michaels et al., 1975; Watanabe et al., 1976; Harrigan, 1977; Sheth and Tossounian, 1978, 1979; Ushimaru et al., 1985; Bolton and Desai, 1986; Ichikawa et al., 1987). In parallel, several in vivo investigations were performed on human volunteers, using either noninvasive imaging techniques

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or drug tracer measurements, in order to verify the possible effects of the density of a dosage form upon gastric retention (Bechgaard and Ladefoged, 1978; Müller-Lissner and Blum, 1981; Müller-Lissner et al., 1981; Erni et al., 1983; Sheth and Tossounian, 1984; Davis et al., 1986; Kaus, 1986; Ingani et al., 1987; Erni and Held, 1987; Mazer et al., 1988; Timmermans et al., 1989a,d). These investigations have led to conflicting conclusions since floating dosage forms were not systematically observed to have a significantly prolonged gastric residence time. This suggests that the effectiveness of the intragastric buoyancy process might be dependent on particular physiological conditions and/or on dosage form characteristics.

In prospect of further in vivo experiments to be realised, a basic comment should hence be made about the floating capabilities of the experimental dosage forms. Up to now bulk density and floating duration have been the main parameters used to describe the adequacy of the dosage forms buoyancy. However, according to known properties of fluids (Cromer, 1981), one may note that if the density can express the fact that an object will float or not, this parameter does not reflect the magnitude of the floating forces produced by the object. Moreover, a single density determination made before immersion does not enable one to foresee the floating force evolution of a dosage form, while the dry material of which it is made progressively reacts or interacts within the fluid to release its drug contents.

Therefore an in vitro measuring apparatus was recently conceived for determining the real floating capabilities exhibited by buoyant dosage forms as a function of time (Timmermans and Moës, 1988). After having demonstrated the validity of measurements obtainable from this apparatus (Timmermans and Moës, 1989b, c), various conventional HBS floating dosage forms were essayed with a view to explore whether the aspect of their floating force kinetics may reveal interesting information.

In this report, the floating curves of typical formulations are first compared and analysed in detail to indicate the basic findings that one may expect to be derived from this new type of measurements. Also, several samples are provided of floating force kinetics obtained in vitro with commercially available HBS capsules and with other floating forms that have already been tested within in vivo studies on human volunteers. These dosage forms are commented upon their ability to represent adequate buoyant materials.

Materials and Methods

Measurement principle and apparatus description

We previously described in detail (Timmermans and Moës, 1988, 1989b, c) an apparatus and a method enabling to monitor in vitro the total force F acting vertically on an immersed object. Interestingly, this force F determines the resultant-weight of the object in immersed conditions and may be used to quantify its floating or non-floating capabilities. The magnitude and direction of force F, and hence of the resultant-weight, correspond to the vectorial sum of the buoyancy (F_{buoy}) and gravity (F_{grav}) forces acting on the object (Cromer, 1981);

$$F = F_{buoy} - F_{grav}$$

$$= d_f g\, V - d_s g\, V = (d_f - d_s) g\, V$$

$$= (d_f - M/V) g\, V \qquad (1)$$

where F is the total vertical force (resultant-weight of object); g the acceleration of gravity; d_f the fluid density; d_s the object density; M the object mass; and V the object volume.

The resultant-weight apparatus operates by measuring the force equivalent to F required to maintain the object totally submerged into the fluid. As shown in Fig. 1 from a partial schematic view of the apparatus, a linear force transmitter device (FTD) (**1**) performs the double function of maintaining the test object (**2**) in a chosen fluid medium (**3**) and of transmitting the reacting force F, of either upward or downward direction (**4**), to the electromagnetic measuring module of a weighing balance (**5**) whereon it is connected. The lower extremity of the FTD is interchangeable for differently designed devices (needle-like or mesh-like holders) that are chosen for each new application

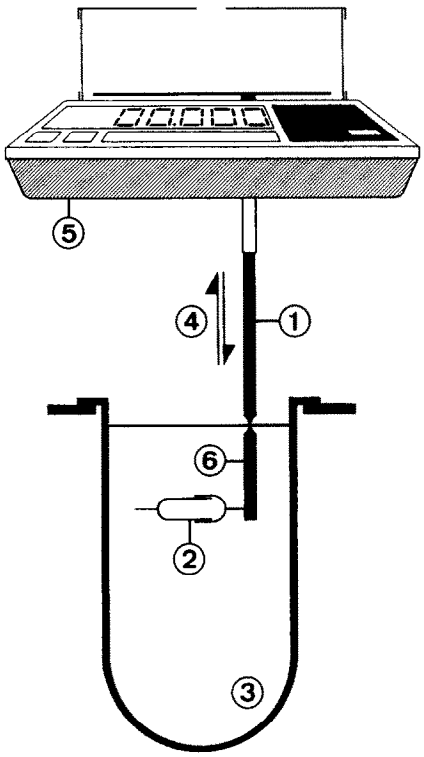

Fig. 1. Partial schematic view of the resultant-weight measuring system.

with respect to the morphology and characteristics of the test object to maintain submerged. In the case of hydrophilic matrix capsules which can be easily penetrated by a sharp needle, a spit-holder extremity (**6**) is used to impal the dosage forms lengthways. Around this measuring system, a complete technical equipment (here not shown) and a specific operating method have been developed to enable the achievement of resultant-weight measurements having the appropriate validity (mean accuracy ± SD; 0.9 ± 0.5 mg, minimal precision: 0.2% coefficient of variation, linearity deviation of zero base-line: ±2 mg within 12 h). Recording means connected to the measuring system permit sustained collection as a function of time of the continuously measured resultant-weight values.

Floating dosage forms

Types A, B and C. A hydrophilic matrix formulation was obtained by homogeneously mixing Methocel K4M (hydroxypropylmethylcellulose (HPMC) 4000 cps, Dow Chemicals), lactose 100 mesh (DMV) and riboflavin 5'PNa (Hoffmann-La Roche) at the respective percentages (w/w) of 50 : 49 : 1. This formulation was filled volumetrically by means of a manual method into size 4 (type A), size 1 (type B) and size 00 (type C) clear hard gelatin capsules (Posilok, Elanco). The formed capsules had a bulk density of 0.58 g/cm^3 (type A), 0.56 g/cm^3 (type B) and 0.57 g/cm^3 (type C).

Types D and E. The dosage forms set forth by Sheth and Tossounian (1984) were commercially available (Hoffman-La Roche) size 2 capsules of Valrelease (type D) and Valium CR (type E) which appeared to mainly contain Diazepam (respectively, 10 and 15 mg), HPMC polymers and undefined fatty materials. The forms had a bulk density of 0.71 g/cm^3 (D) and 0.72 g/cm^3 (E).

Type F. The dosage forms set forth by Erni and Held (1987) were commercially available (Hoffman-La Roche) size 1 capsules of Madopar HBS which appeared to mainly contain 100 mg levodopa, 25 mg benserazide, hydrocolloids and hydrogenated fatty substances. The capsule bulk density was 0.66 g/cm^3.

Type G. As set forth by Davis et al. (1986) and Stockwell et al. (1986), a blended formulation mainly composed of sodium alginate and sodium bicarbonate (Ph. Eur.) was filled into size 1 capsules. The reported bulk density was 0.63 g/cm^3.

Types H and I. Double-layer compressed matrices of 7 mm diameter (type H) and size 4 capsules (type I) were prepared as set forth by Ingani et al. (1987), using a formulation mainly composed of riboflavin 5'PNa, lactose and Methocel K4M for the capsule and one of the tablet layer's; Methocel K15M and a carbon dioxide generating blend for the second tablet layer. The forms had a bulk density of 1.14 g/cm^3 (type H) and 0.61 g/cm^3 (type I).

Types J and K. The dosage forms type J was a size 1 capsule filled with a hydrophilic matrix formulation mainly composed of Methocel K4M and lactose 100 mesh at the percentages (w/w) of 50 : 50. As we reported elsewhere (Timmermans et al., 1989a, d), an optimized formulation was obtained by mixing Methocel K4M, magnesium stearate (Ph. Eur.) and sodium bicarbonate at the

respective percentages (w/w) of 88 : 10 : 2. This formulation was filled into size 1 capsules (type K). The dosage forms had a bulk density of 0.58 g/cm^3 (type J) and 0.50 g/cm^3 (type K).

Operating method

Using the resultant-weight apparatus, each different type of dosage form was tested in triplicate. The test medium was 1200 ml air-free HCl at pH 1.2 with 0.05% Tween 80 and was thermostatically controlled at 37.0 °C. The FTD of the apparatus was assembled with a spit-holder extremity (Fig 1, 6) (0.8 mm diameter needle) whereon the dosage form remained fastened lengthways at an unvarying immersion depth (5.0 cm) throughout the measuring procedure. Resultant-weight measurements obtained as a function of time were continuously recorded for 8 h, this was done for each dosage form, as well as in the absence of a test sample placed under the FTD (zero baselines).

Simulated meal media

The floating force kinetics of the capsules type J and K were measured in five different test media (1200 ml at 37.0 °C).

- Medium 1: HCl at pH 1.2 with 0.05% Tween 80.
- Medium 2: Intralipid 10% (lipid/water emulsion for parenteral nutrition; Kabi Vitrum, Stockholm) adjusted at pH 1.2 and containing 0.05% Tween 80.
- Medium 3: Nutrison Standard,
- Medium 4: Nutrison Na-min,
- Medium 5: Nutrison energie-plus (Nutricia, Holland), media 3 to 5 being mixtures for total enteral nutrition that simulate normal meals.

Standard parameters derived form resultant-weight curves

The floating time of a dosage form was defined as the duration separating time $t = 0$ (immersion into fluid medium) from the time point corresponding to the intersection between the positive resultant-weight curve and the zero base-line. The floating performances of a dosage form were quantified by measuring the area under the floating curve (buoyancy AUC); i.e., the mean area ($n = 3$) delimited between the positive resultant-weight curve and the zero base-line from time $t = 0$ to 8 h.

Results and Discussion

Continuous curves of resultant-weight measurements obtained as a function of time for the different types of floating dosage form are shown in Figs 2 to 8. In each graph, the horizontal mean zero base-line (dotted lines) indicates the stability of measurements provided by the apparatus under identical conditions but with no sample maintained by the FTD. Floating times and buoyancy AUC values of dosage forms derived from their respective resultant-weight curves are given in Table 1.

Comparative resultant-weight essays performed by means of differently designed holder extremities (needle-like or mesh-like devices) have shown that the best manner to achieve proper measurements was impaling the hydrophilic matrix capsules on the spit-holder extremity. It allowed normal interaction between the dosage forms and the fluid, facilitated formation of a fully hydrated gel barrier at the outer surface, and did not alter the hydrodynamical evolution of the formulation in function of time.

The total force F acting on an immersed object determines the magnitude and direction of the apparent weight of this object in the fluid, herein called the resultant-weight. By convention, a positive resultant-weight signifies that force F is exerted vertically upwards and that the object is able to float, whereas a negative resultant-weight means that force F acts vertically downwards and that the object sinks. The crossing of the zero base-line by a resultant-weight curve from positive towards negative values indicates the transition of a dosage form from floating to nonfloating conditions. Intersect of lines consequently corresponds, on time axis, to the floating time of the dosage form.

As may be understood from Eqn 1, the direction of force F, and hence the resultant-weight sign, is given by the difference between the density of the fluid and that of the object. If the density of the object expresses the fact that it will float ($d_s < d_f$) or not ($d_s > d_f$), this parameter does

TABLE 1

Experimental floating times and area under the curves (AUC) derived from the resultant-weight kinetics of dosage forms

	Types of dosage forms										
	A	B	C	D	E	F	G	H	I	J	K
Floating time (min)	253	> 480	> 480	> 480	> 480	> 480	190	427	> 480	> 480	> 480
Buoyancy AUC (mg h)	338	1296	2746	890	1072	1046	749	266	827	3672	3841

nevertheless not quantify the floating or non-floating capabilities of this object. To obtain the magnitude of these capabilities, as provided by a resultant-weight measurement, the term $(d_f - d_s)$ needs to be multiplied by the volume of the object.

Such considerations are illustrated in Fig. 2. Three differently sized capsules of similar density at the start (0.57 g/cm^3) are shown to have a different initial resultant-weight value (A, 111 mg; B, 272 mg; C, 472 mg; at time, $t = 0$). These values are directly proportional to the respective sizes of the capsules. In this example it may be said that, although having the same density, capsule type C floats just after immersion approximately four times better than capsule type A. Moreover, when resultant-weight measurements are performed as a function of time, they show that the floating capabilities of the dosage forms may undergo various modifications upon contact with the fluid. The curves translate the evolution of the hydrodynamical equilibrium and can be used to outline the effects upon buoyancy of some of the phenomena occurring to the forms.

For example, the curves of Fig. 2 can be interpreted as follows. After dissolution of the gelatin capsule, water intake produces a weight increase without significantly affecting the volume; and a resultant-weight decrease is usually observed. The outermost hydrophilic polymer then hydrates and swells and a gel barrier is formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration-swelling-release process is repeated towards new exposed surfaces, thus maintaining the integrity of the dosage form. During this process, the evolution of the floating forces will be dependent on the balance between the weight and the volume variations of the dosage forms (Eqn 1). If water intake appears to be compensated by an adequate swelling, the floating forces may then remain quasi-constant for a while; as observed with capsules A, B and C during at least 1 h. Water penetration has also the effect of withdrawing the air from the non-compressed formulation powder. Each bubble escape, corresponding to an abrupt loss of floating strength, induces a step-wise resultant-weight decrease as a function of time.

The rate of resultant-weight decrease here appears to be very similar for capsules A, B and C filled with an identical formulation. Only capsule A is, however, seen to sink during the experiment, since it has the lowest initial resultant-weight value. It may be noted that for the two types of capsules that have a floating time of greater than 8 h (B and C), the differences in floating behaviour might

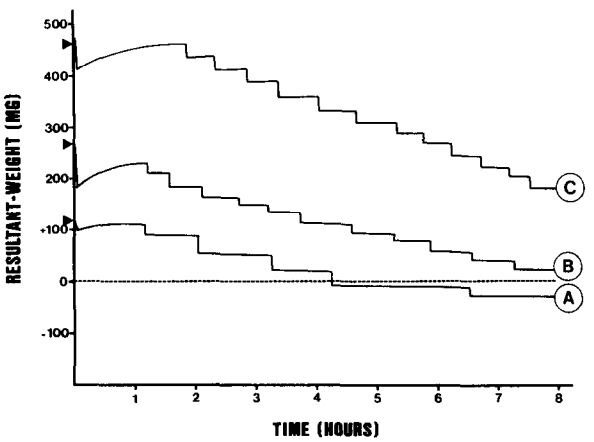

Fig. 2. Floating-force kinetics of hydrophilic matrix capsule type A (size 4), B (size 1) and C (size 00) having an identical bulk density at the start.

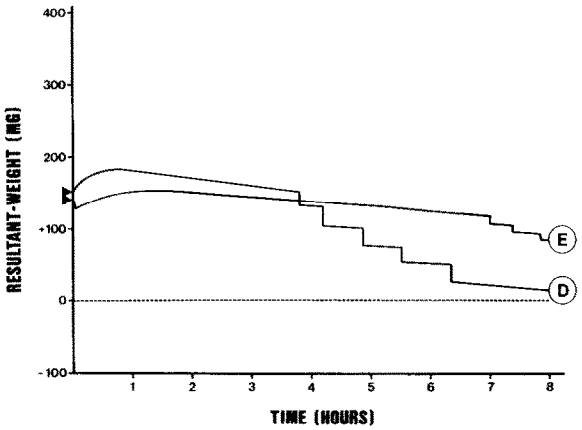

Fig. 3. Floating-force kinetics of Valrelease (D) and Valium CR (E) HBS capsules.

not have been disclosed without resultant-weight measurements. The superiority of capsule C shown by its higher floating-force profile can be accurately quantified by comparing the buoyancy, AUC, values of each dosage forms (Table 1).

Valrelease and Valium CR belong to the concept of HBS controlled release floating dosage forms developed by Hoffmann-La Roche seachers (Sheth and Tossounian, 1979, 1984). An improved bioavailability of benzodiazepine medications can be expected through a sustained delivery of these acid-soluble drugs into the stomach.

The floating force profiles recorded with these forms (Fig. 3) are not basically different from the previous ones. However, in this case the air bubble release (step-wise floating-force decrease) is seen to start later; i.e., after about 4 h for capsule D and 7 h for capsule E. This beneficial delay with regard to buoyancy is more than likely assignable to the presence of fatty materials which slow the water penetration and the escape of air through the gelified barrier. The slight compaction of powder here realised for capsule filling purposes also reduces the air contents of these formulations. As a result, the capsules have nevertheless a relatively high bulk density (0.71 g/cm^3) which in addition to their small size hinders their obtaining high floating-force profiles.

Another HBS dosage form that has been marketed more recently by the same company is Madopar. As reported by Erni and Held (1987), the purpose of this floating form is here to reduce the in vivo variations in release rate of levodopa and benserazide by achieving a controlled release in an environment of reasonably constant pH; i.e., into the stomach.

The in vitro floating force kinetics of Madopar shown in Fig. 4 is very similar to the Valium ones inasmuch as this capsule appears to have been formulated in the same manner with hydrocolloids and hydrogenated fatty materials for main ingredients. The initial resultant-weight value is somewhat higher due to the larger capsule size. The floating capabilities are appropriate for at least 4 h whereafter air bubbles are seen to be withdrawn by water intake.

Gas-generating blends have sometimes been formulated to improve the floating capabilities of a dosage form. The alginate and bicarbonate containing capsule described by Davis et al. (1986) is an example of this which has been assayed in man.

Carbon dioxide generated upon contact with an acidic medium is intended to remain entrapped in the outermost hydrated polymer, to make the dosage form swell and to consequently enhance its buoyancy. As shown in Fig. 5, this process is seen to be effectively achieved for the capsules type G but only during the first 20 min that follows immersion. The multiple peaks appearing on the ascending portion of the resultant-weight curve indicated that the gel barrier is repeatedly torn by carbon dioxide bubbles which are released outside

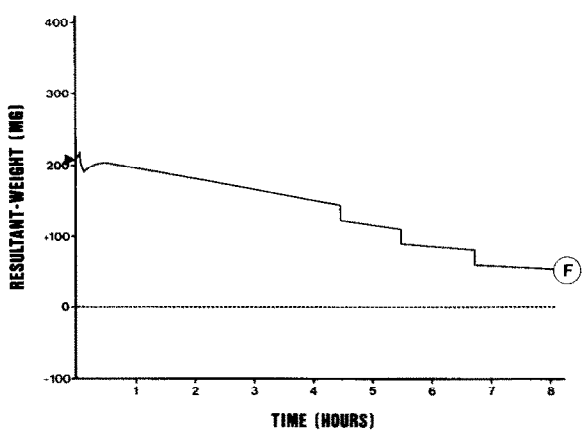

Fig. 4. Floating-force kinetics of Madopar HBS (F) capsule.

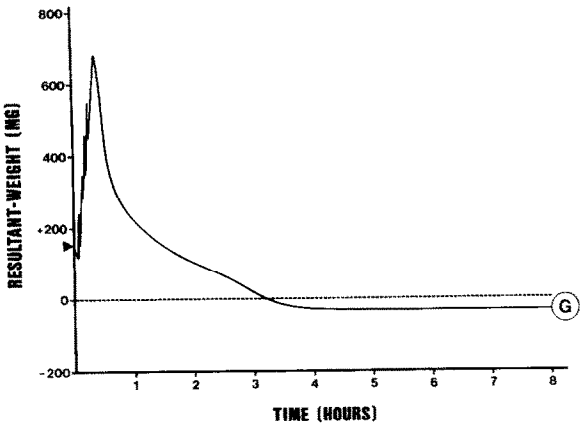

Fig. 5. Floating-force kinetics of matrix capsule (G) composed of an alginate/carbon dioxide-generating system.

the form and hence do not contribute to the floating force increase. This extensive release is assumed to be the consequence of a too important bicarbonate contents. The integrity of the gel layer being altered by this phenomenon in the way of an increased porosity, this promotes in turn water penetration into the formulation. After fast emptying of all carbon dioxide, the floating forces are rapidly decreasing. Although, according to the authors, these capsules could be observed remaining continously buoyant in the stomach of the volunteers, in this in vitro experiment they are measured to sink after about 190 min.

Gas-generating blends can be conveniently placed within the dosage form in a distinct layer of the drug formulation in order to avoid interaction with the controlled drug release. In an earlier study (Ingani et al., 1987), we investigated the in vitro and in vivo performances of such a double-layer compressed matrix wherein one layer was a carbon dioxide swelling system and the second layer was riboflavin-sustained delivery formulation. This matrix had been selected for presenting the longest in vitro floating duration out of several formulation essays and different weight ratios between the layers.

However, the retrospectively determined floating-force curve shown in Fig. 6 indicates that, if this double-layer matrix remains indeed buoyant for 7 h, then its floating capabilities never reach a significant state. For comparison, the buoyancy AUC of this matrix (Table 1) is seen to be three times inferior to that of a capsule (type I), having been formulated to release riboflavin at an identical rate. The compression of a formulation powder is thus observed to lower the floating capabilities of a dosage form. Moreover, the initial bulk density of the matrix is in this case superior to that of the fluid. The matrix having a negative resultant-weight consequently sinks when immersed and needs then to await sufficient swelling of the gas-generating layer before buoyancy occurs. The pH dependence of the carbon dioxide generation process is assumed to be an in vivo drawback regarding the important differences in gastric pH which are usually encountered in man and that might in turn be responsible for unforseeable variations of the buoyancy lag time of the matrix. This bilayer matrix nevertheless offers, as reported by Ingani et al., the advantage to allow separate regulation of the floating capabilities and of the drug-release kinetics, and to have a more homogeneous eroding behaviour due to compression when compared to a classical HBS capsule.

One of the basic options taken after the development of the resultant-weight apparatus was to attempt the optimization of dosage forms with respect to their buoyancy strength significance and stability. Several in vivo investigations had come to the conclusion that food intake was a main determinant for prolonging the gastric resi-

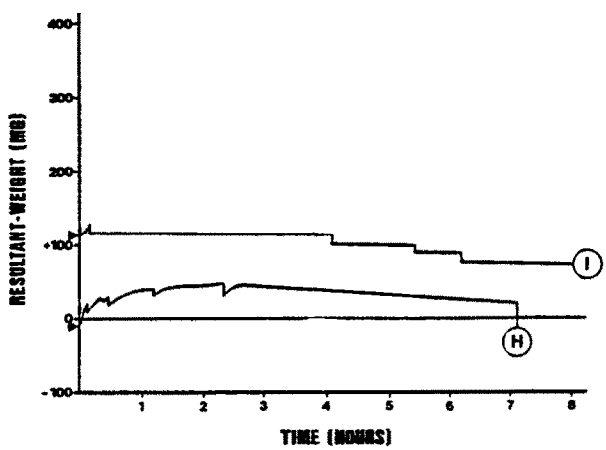

Fig. 6. Floating-force kinetics of a double-layer compressed matrix equipped with a gas generating layer (H), and of a size 4 matrix capsule (I).

dence time of undigestible dosage forms (Müller-Lissner and Blum, 1981; Davis et al., 1986). This must also be the first condition for a floating form to be protected against emptying, because it can only be buoyant if there is sufficient gastric contents for the dosage form to float. We, in addition, considered that dosage forms of poor and/or unstable floating capabilities should be discarded from experimentation, since they might not be able to remain reliably buoyant above the gastric contents. A number of arguments support this claim.

The least one may expect from a floating form is that it never reaches negative resultant-weight values, since this means the sinking of the form. A lasting buoyancy has not been recorded with all the dosage forms we examined. Optimization should therefore first be conducted with regard to the floating duration which has to cover at least the entire gastric residence period of the form. Moreover, the floating strength of hydrophilic matrix systems has been observed to have a natural tendency to decrease with time consequently to the evolution of the hydrodynamical equilibrium. One has to bear in mind that when the resultant-weight of a form gradually lessens and comes near to the zero base-line, it also gets closer to a state of indifferent equilibrium with respect to its environment. In such conditions, the behaviour of the dosage form is no longer dissociable from that of other materials of the gastric contents due to the similarity of their bulk densities. The dosage form might then more than likely be liable to the propelling emptying waves and other peristaltic movements occurring to the gastric contents during the digestive phase.

Therefore a minimal level of floating strength seems to be necessary to keep a floating form reliably buoyant on the surface of the meal. Above this level, relative buoyancies probably play only an insignificant role in gastric retention. However, the problem remains to fix a threshold value of required floating force. Mainly two reasons incline us to believe that the floating capabilities should be kept as high as possible in anticipation of the various in vivo conditions that can be encountered.

First, the buoyancy of the form depends on the

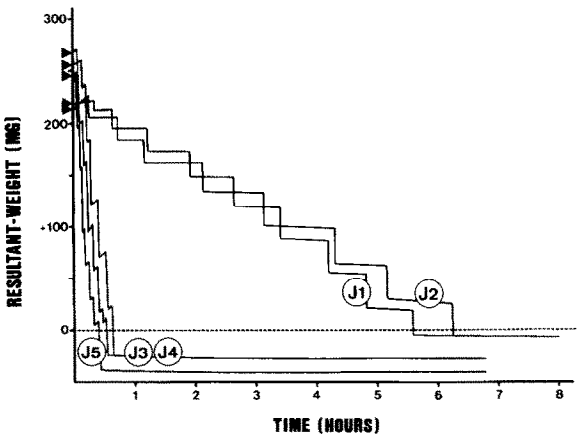

Fig. 7. Floating-force kinetics of size 1 matrix capsule (J) filled with a *non-optimized* hydrophilic formulation. Measurements obtained in the five following test media: (J1) simulated gastric fluids. (J2) simulated lipid phase (Intralipid emulsion). (J3), (J4) and (J5) simulated meal contents (Nutrison mixtures).

density of the gastric contents (Eqn 1) which in turn may vary from one meal to another. Meals of low density proportionally reduce the floating forces of the dosage form.

Secondly, the nature of the meal may unforseeably alter the hydrodynamical evolution of the form and accelerate its propensity to sink. This phenomenon is illustrated in Fig. 7 where the floating-force kinetics of a classical matrix capsule (type J) have been measured within different test media. Whereas the capsule floats for about 6 h on either gastric fluid or a lipid phase (J1, J2), it is observed to rapidly sink in the presence of the three simulated meal media (J3, J4, J5). Due to the action of food, the capsules have become non-floating objects in less than 40 min. It is not in the scope of this paper to discuss the causes of interaction between hydrophilic polymers and food characteristics, however, one may note that this capsule formulation is far from representing an adequate buoyant material for in vivo use. On the other hand, when a capsule of the same size filled with an optimized formulation is measured (Fig. 8), it is seen to maintain appropriate floating properties in contact with the usual gastric fluids (K1) as well as on immersion into the different simulated meal media (K2, K3, K4, K5). Here optimization of buoyancy strength is clearly

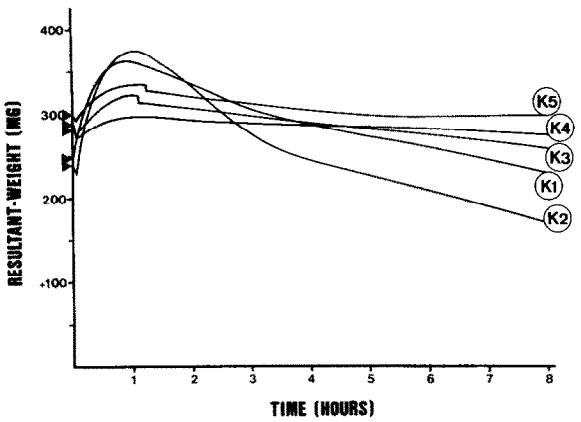

Fig. 8. Floating-force kinetics of size 1 matrix capsule (K) filled with an *optimized* hydrophilic formulation. Measurements obtained in the five following test media: (K1) simulated gastric fluids. (K2) simulated lipid phase (Intralipid emulsion). (K3), (K4) and (K5) simulated meal contents (Nutrison mixtures).

achieved, as indicated by the aspect of curves. Whereas the matrix is composed of a gas-generating blend, no bubble release through the gel barrier can be disclosed. After 8 hours the floating forces show none or only a slight decrease in comparison with the values recorded immediately after immersion.

Our assumption that optimized dosage forms with high and stable floating forces in vitro might stay adequately buoyant in vivo was recently confirmed by monitoring, in fed volunteers, the intragastric position of non-floating versus floating dosage forms; the latter being prepared with the optimized formulation here presented (Timmermans et al., 1989a,d). The first published results also indicated that the proper buoyancy of a floating form offers advantages over non-floating forms, certainly for small and medium-size capsules, in terms of a prolonged gastric retention and of a reduction of inter-subject variability of transit time.

Improving the buoyancy capabilities of a floating dosage form may, as it is here, only require minor adjustements of the formulation to slow water intake and to enhance swelling. The extreme feasibility of floating-force determinations as well as the various improvements of floating behaviour brought by optimization incline us to highly recommend the application of these in vitro procedures to any dosage form intended to float in a lasting way inside the stomach.

Conclusions

It has become apparent that no prognostic assessment of floating capabilities evolution may be provided by a density measurement made on a dosage form in a dry state. In vitro resultant-weight determinations performed as a function of time have enabled to disclose important and sometimes critical variations within the floating force kinetics of dosage forms which had been estimated to be well-floating on the basis of their density characteristics or for having been observed to remain buoyant in a beaker for a certain period of time.

It is more than likely that dosage forms with non-optimized and unstable floating forces may be expected to behave in vivo in an unpredictable way and may not necessarily remain buoyant inside the stomach above any type of meal contents.

Optimization of the floating forces can, however, be realised, for example, by either slowing water penetration inside the formulation or by improving the swelling properties of the dosage form. In addition, our current experimentation on optimization has already permitted us to select different procedures that preserve the controlled and sustained release characteristics of the matrix system.

It is considered that only floating dosage forms that have had their floating capabilities quantified as a function of time and show that their characteristics are high and stable may conduct the investigators to more reliable conclusions about the effects of buoyancy upon gastric residence time.

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