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Conception and in vivo investigation of peroral sustained release floating dosage forms with enhanced gastrointestinal transit

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Summary

Previous published works have shown that hydrodynamically balanced systems (HBS) — i.e. sustained release oral dosage forms with a specific gravity lower than 1 and remaining buoyant on the gastric juice of the stomach — can have an enhanced gastrointestinal transit time. For this investigation, a double-layer sustained release compressed hydrophilic matrix was formulated in order to achieve a foreseeable and reproducible flotation of the tablet. A carbon dioxide generating blend was, for this purpose, added to one of the layers, this gas being entrapped in the gelified hydrocolloid as liberated by the action of the gastric medium. The in vivo behaviour of this floating tablet was then compared to a classical HBS capsule and to a similar but non-floating double-layer hydrophilic matrix on subjects alternatively in fasted or fed state. As these three dosage forms contain a riboflavin (RF) soluble derivative, it was possible to measure the RF urinary excretion rates and, consequently, to conclude that in vivo buoyancy is preponderant over bioadhesion for both floating capsules and tablets. These dosage forms also significantly increase the gastric residence time when compared to the non-floating dosage form. Compared to the classical HBS capsule, the floating tablet is showing in vivo equivalent floating properties when administered after a light meal and higher RF urinary excretion rates when administered to fasted subjects.

Introduction

During the last decade, considerable research effort has been directed towards the development of peroral sustained release dosage forms. Despite this, several physiological limitations remain to be controlled such as, for example, the gastrointestinal (GI) transit time. The low bioavailability of some of these forms is indeed generally attributed either to an incomplete drug release or to the too short residence time of the pharmaceutical dosage form in the absorbing section of the GI tract.

Several different approaches have recently been developed to achieve an extended GI transit time of these oral drug delivery systems, and more particularly, to sustain their residence time in the stomach.

(a) Incorporation of passage-delaying food excipients, principally fatty acids, to decrease the gastric emptying rate (Grönig and Heun, 1984; Palin et al., 1982).

(b) Bioadhesive research, based upon the ad-

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hesive capacity of some polymer with glycoproteins (mucins) closely applied to the surface epithelium of the stomach and intestine (Hung Seng Ch'ng et al., 1985; Park and Robinson, 1984). However, such adhesion may cause problems if the drug released is locally irritating to mucosa, as reported for various drugs on oesophagial tissue by Carlborg and Densert (1980).

(c) Floating dosage forms, having a bulk density lower than gastric fluids and remaining therefore buoyant on the stomach contents without affecting the gastric emptying rate. Review of literature has revealed the recent development of these so-called hydrodynamically balanced systems (HBS) (Sheth and Tossounian, 1978; Yie W. Chien, 1983; Erni et al., 1983; Sheth and Tossounian, 1984).

HBS is a formulation essentially composed of a drug intimately mixed with gel-forming hydrocolloids swelling after oral ingestion in contact with gastric fluid and maintaining in this soft gelatinous outside surface barrier a relative integrity of shape and a bulk density of less than one. The drug, slowly released in the stomach by diffusion through the gelatinous barrier, then goes down towards the proximal intestine area.

The present investigation includes formulation, dissolution, buoyancy and in vivo release tests realised on, on the one hand, classical HBS capsules and, on the other hand, new floating bilayer compressed matrices. One of the tablet layers mainly contains a carbon dioxide generating blend and a hydrophilic polymer. The carbon dioxide, being entrapped in the gelified hydrocolloid as liberated by the action of the gastric medium, produces the upward motion of the tablet and maintains its buoyancy. The other tablet layer, and also the entire capsule, are hydrophilic matrices and contain the drug which is released in a prolonged and controlled way.

Sodium riboflavin 5'-phosphate (RF5'PNa) is used as drug tracer. This vitamin B_2 derivative is more water-soluble than riboflavin (RF) itself but is subject to the same absorption and transport mechanisms and is excreted in the urine in the form of RF (Jusko and Levy, 1967). The RF5'PNa absorption sites are mainly limited to the upper region of the small intestine. This allows one to demonstrate indirectly the reality of the increase of the dosage form residence time above the absorption area. It has indeed been established by Levy and Hewit (1971) and Levy et al. (1972) that all gastric transit time variation of a dosage form containing vitamin B_2 affects both the compound absorption rate and the quantity absorbed.

For comparison purposes, a similar but non-gas-generating bilayer compressed matrix and an immediate release reference tablet containing the same dose of RF5'PNa were also formulated. The in vivo behaviour of these dosage forms was evaluated by means of RF urinary excretion measurements among subjects alternatively fasted or after ingestion of a standardized meal, in order to: (1) show that buoyancy of the dosage forms also occurs in vivo and is preponderant over bioadhesion; (2) prove that this buoyancy can significantly increase the GI transit time of the floating dosage forms; and (3) examine the influence of a meal on the retentive characteristics of the dosage forms.

Materials and Methods

Materials

The following products were used.

Sodium riboflavin 5'-phosphate (Hoffman LaRoche)

Sodium bicarbonate, calcium carbonate, citric acid, magnesium stearate, lactose 100 mesh (Ph. Eur.)

Microcrystalline cellulose (Avicel PH101; F.M.C.)

Hydroxypropylmethylcellulose (Methocel K15M, K4M; Dow Chemicals)

Encompress (Mendell), Aerosil 200 (Degussa)

Sodium carboxymethylcellulose cross-linked (Ac-Di-Sol; F.M.C.)

Methods

Preparation of pharmeutical dosage forms

Mixing of powders until blend homogeneity is reached. All tablets were directly compressed on an instrumented alternative Korsh machine using a 7 mm diameter concave-faced punch and die.

Immediate Release Tablet (IRT):

RF5'PNa	20.6 mg
Avicel PH101	30.0 mg
Aerosil 200	0.4 mg
Mg stearate	1.2 mg
Ac-Di-Sol	3.75 mg
Lactose 100 mesh to	150 mg

Mean tablet hardness: 40 N (Erweka hardness tester)

Sustained Release Tablets: (double-layer compressed matrix)

	Sustained release tablet (SRT)		Sustained release floating tablet (SRFT)	
Layer A (mg)	Ca carbonate	–	Ca carbonate	15.4
	Citric acid	–	Citric acid	2.2
	Na bicarbonate	–	Na bicarbonate	1.1
	Methocel K15M	19.3	Methocel K15M	19.3
	Avicel PH101	11.0	Avicel PH101	11.0
	Aerosil 200	0.14	Aerosil 200	0.14
	Encompress to	55.0	Encompress to	55.0
Layer B (mg)	RF5'PNa	20.6	RF5'PNa	20.6
	Methocel K4M	21.6	Methocel K4M	21.6
	Avicel PH101	24.0	Avicel PH101	24.0
	Mg stearate	0.90	Mg stearate	0.90
	Aerosil 200	0.30	Aerosil 200	0.30
	Lactose 100m	to 120	Lactose 100m	to 120

Sustained Release Floating Capsule (SRFC):

The hard gelatin capsules clear A/A size 4 (Posilok; Elanco) are filled volumetrically with non-compressed powder by means of a manual filling method.

RF5'PNa	20.6 mg
Methocel K4M	68.8 mg
Mg stearate	1.00 mg
Aerosil 200	0.34 mg
Lactose 100 mesh to	125 mg

Mean capsule specific gravity: 0.61 ± 0.02 (S.E.)

Dissolution test

The in vitro RF5'PNa dissolution rates are determined using the USP Method II apparatus with a rotation speed of 60 rpm and a thermostatically controlled bath at $37 \pm 0.1°C$. The floating dosage forms are maintained immersed in a stainless-steel basket (18 mesh cloth) lowered to the bottom of the vessel, the stirring paddle being positioned so that a distance of 2.5 cm between the lower edge of the blade and the upper part of the basket is maintained during the test. The dissolution medium is a 850 ml HCl (0.1 N) solution. A sample of 10 ml is withdrawn at suitable time intervals, during 5 h, and replaced by an equivalent volume of fresh solvent.

The absorbance values of RF5'PNa samples are measured at 445 nm (Perkin Elmer Spectrophotometer) and all manipulations are performed in a dark-room to avoid RF alteration.

Buoyancy lag time measurements

Except for the basket, the same USP Method II dissolution apparatus is used. The time intervals between the introduction of the dosage form in the test solvent and its buoyancy are measured. The study is achieved with three HCl solutions of different pH values (1.30, 2.00 and 3.00). The test is performed during maximally 1 h.

In vivo study

Seven healthy informed volunteers (age range 23–47 years, weight 55–90 kg) entered the study which was conducted in a randomized and cross-over manner under medical supervision. Each subject swallowed successively the four different dosage forms following two distinct protocols: (1) fasting, together with 150 ml water, no meal being authorized within 3 h; and (2) immediately after ingestion of a light standardized breakfast composed of 150 ml orange juice, a cup of coffee and two french croissants.

At time of dosage form ingestion, the bladder is voided ($t = 0$) and urine is then collected at regular time intervals ($t = 1, 2, 3, 4, 6, 8, 14, 24$ h). After suitable dilution, the urine samples are assayed for RF content using a spectrofluorimetric method recommended by Burch et al. (1948) (Perkin Elmer Spectrofluorimeter). At least 72 h separate each of the RF absorption studies on one subject.

Results and Discussion

Buoyancy time measurements

The SRFC immediately floats on the various test media, swells and remains buoyant until completely eroded.

After an immersion lag time varying between 1–3 s at pH 1.30 and 6–7 min at pH 3.00, the SRFT comes up to the surface of the solvent and floats until complete erosion. The B layer containing RF5′PNa turns downwards and remains totally dipped in the test medium.

The SRT shows no floating capability within 5 h.

No disintegration of the sustained release dosage forms is observed after 7 h.

The IRT completely disintegrates within a few seconds after contact with the dissolution medium.

Dissolution test

The total RF5′PNa dose is released from the IRT within 5 min.

The mean in vitro release profiles (Fig. 1) shown by the three sustained release dosage forms maintained immersed in the dissolution medium, and their parallelism or slope-equality tests for the linear zero-order part of RF5′PNa release rate profiles prove that there is no significant difference ($F_{cal} < F_{0.05}$) between these three dosage forms (SRT, SRFT, SRFC). Obviously, the RF5′PNa release from the SRFT B layer is not significantly influenced by the carbon dioxide generated by the A layer. The SRT is therefore an excellent reference dosage form as far as our in vivo comparative study is concerned.

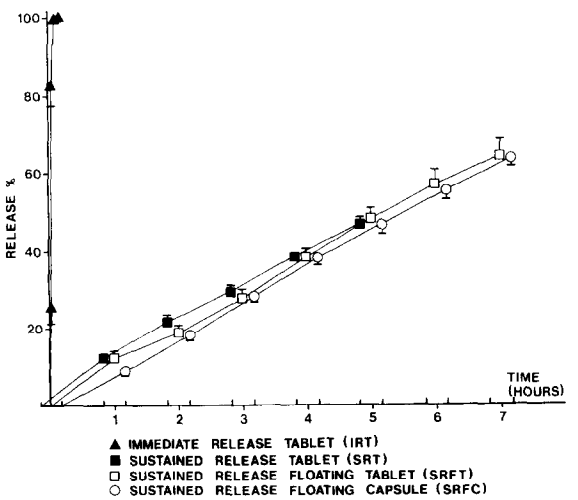

Fig. 1. Mean in vitro release ± S.D. (%) of RF5′-PNa oral dosage forms.

In vivo study

To express the results, we did not take into account the natural mean RF urinary excretion of the subjects which can be estimated to be around 0.56 mg/24 h (Delporte, 1974).

The IRT was utilised in this in vivo study only to bear witness to the study procedure reliability and the in vivo results obtained with this dosage form are similar to the relevant values published in the literature (Table 1).

Tables 1 and 2 as also Figs. 2 and 3 show, as expected, that the rapidly disintegrating IRT with a high RF5′PNa release rate gives the best in vivo RF excretion profiles of all when ingested with a meal, the total RF5′PNa dose dissolving in the food. The gastric contents then provide a reservoir percolating the site of maximum absorption. With fasted subjects, the RF urinary excretions observed are therefore much lower.

Compared to the IRT, the urinary excretion rate values obtained with the sustained release dosage forms are more evenly distributed and this confirms the in vivo RF prolonged and sustained release from these matrices.

When compared to SRT, the urinary excretion percentage of RF within 24 h is systematically higher after the administration of SRFT, whatever the ingestion protocol may be (fasted or fed).

From the 3rd hour after administration onwards, the RF cumulative urinary excretion percentages of the fasted subjects are significantly higher for the SRFT, whereas what is significantly more important is from the 6th hour onwards when the dosage form is swallowed after a light meal.

The SRFT superiority can only be ascribed to its longer stay in the GI tract above the RF resorption site and to the buoyancy of the dosage form in the stomach. This last mechanism (bulk density lower than 1) should indeed be considered as preponderant, because if bioadhesion phenom-

TABLE 1

Mean RF urinary excretion rates ± S.D. (μg/h)

Time (h)	IRT	SRT	SRFT	SRFC
Fasting				
1	390 ± 118	174 ± 73	146 ± 72	120 ± 53
2	326 ± 300	239 ± 137	348 ± 118	213 ± 100
3	163 ± 156	99 ± 48	304 ± 124	145 ± 54
4	112 ± 91	96 ± 38	182 ± 44	125 ± 46
6	96 ± 65	76 ± 34	119 ± 53	103 ± 47
8	65 ± 55	54 ± 29	108 ± 40	85 ± 47
14	43 ± 22	52 ± 19	63 ± 41	82 ± 50
24	42 ± 18	37 ± 15	54 ± 20	47 ± 18
Standardized breakfast				
1	1075 ± 573	149 ± 65	90 ± 58	46 ± 36
2	2135 ± 933	159 ± 73	170 ± 79	150 ± 142
3	1115 ± 937	130 ± 77	307 ± 199	395 ± 241
4	592 ± 288	198 ± 205	375 ± 293	668 ± 390
6	289 ± 175	136 ± 81	424 ± 323	377 ± 213
8	160 ± 86	70 ± 27	457 ± 556	455 ± 553
14	97 ± 55	46 ± 10	122 ± 59	149 ± 107
24	46 ± 23	37 ± 20	76 ± 28	70 ± 29

ena were prevailing (Park and Robinson, 1984), the results obtained with the two types of sustained release bilayer compressed matrices, made with the same polymer blend, should not be significantly different.

The in vivo behaviour of the two floating dosage forms (SRFT and SRFC) is similar when these are ingested immediately after the standardized breakfast. The mean RF cumulative urinary excretions of these two dosage forms are not significantly different from the 2nd hour until the end of the experiment. The SRFC thus shows, when compared to the SRT, the same buoyancy effect as the SRFT but only for fed subjects.

The results obtained with the fasted subjects indicate no significant difference between SRT and SRFC. In comparison with the SRFT, the RF urinary excretions obtained with the SRFC are also significantly lower from the 3rd to the 6th hour with the fasted subjects.

However, from these results one cannot assert that the SRFC gastric transit time is shorter than the SRFT one when the dosage forms are ingested on a empty stomach. In fact, this in vivo RF

TABLE 2

Comparison between dosage forms by means of paired t-test (mean RF cumulative urinary excretions data)

Time (h):	1	2	3	4	6	8	14	24
Fasting								
SRT/SRFT	−	−	++	++	++	++	++	++
SRT/SRFC	−	−	−	−	−	−	−	−
SRFT/SRFC	−	−	+	+	+	−	−	−
Standardized breakfast								
SRT/SRFT	−	−	−	−	++	+	++	++
SRT/SRFC	++	−	−	−	+	++	++	++
SRFT/SRFC	+	−	−	−	−	−	−	−

− = $P > 0.05$; + = $0.01 < P \leqslant 0.05$; ++ = $P \leqslant 0.01$.

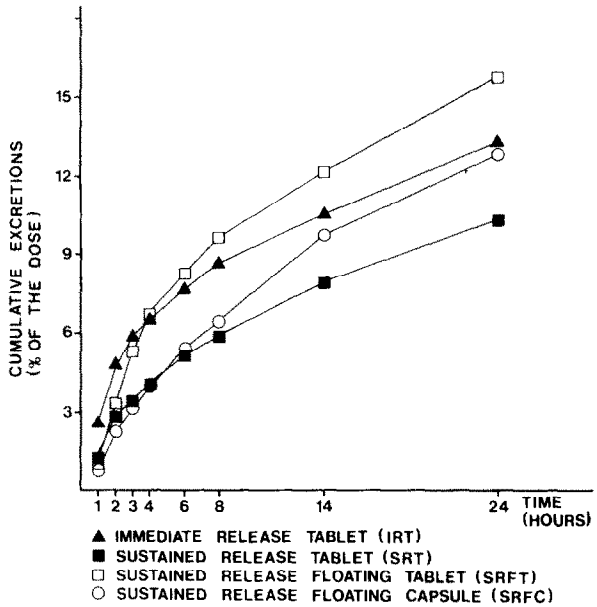

Fig. 2. Fasting: mean RF cumulative urinary excretions (%).

release difference seems to be explicable by the reduced outer contact surface of the SRFC with the gastric juice on account of its partially immersed buoyancy. Moreover, the RF urinary excretions observed after ingestion of the SRT after a light meal are only higher than those obtained with the SRFC during the 1st hour. Afterwards, this tendency is reversed which proves that the SRT leaves the stomach much sooner than the SRFC.

Consequently, and in spite of experimental conditions usually considered as unfavourable for a gastric transit time increase – i.e. on the one hand, small dosage forms with dimensions near the critical inlet diameter (1–2 mm) towards the duodenum (MacGregor et al., 1977) and, on the other hand, the ingestion of an oral dosage form by fasted subjects or after a light meal with a light fats content (Meeroff et al., 1973; Palin et al., 1982) — the floating dosage forms, and principally the SRFT, show clear enhancement of the gastric retention time compared to the non-floating reference dosage form (SRT).

The GI transit time of a dosage form evidently varies from one subject to another but also within one subject, under the influence of a large number of factors such as eating a meal. According to Inglefunger and Abbot (1940), the transit duration in the duodenum of the alimentary bolus should not be longer than 5–10 min. Moreover and according to Davis et al. (1984a and b), the intestinal transit time up to the colon would not exceed 3–4 h.

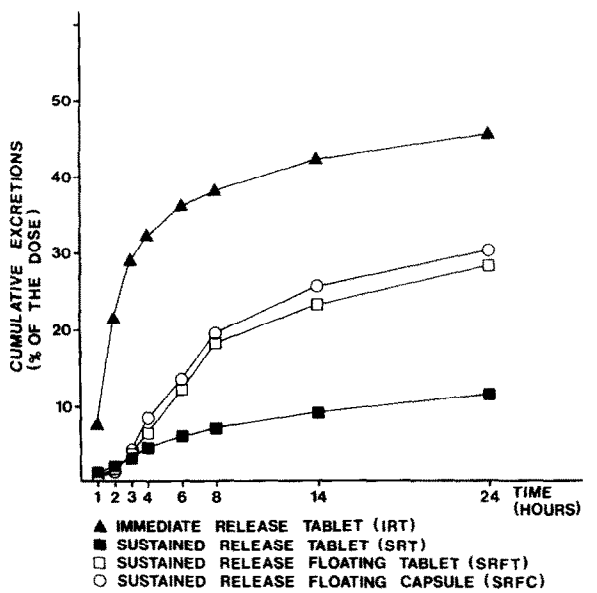

Fig. 3. Fed state: mean RF cumulative urinary excretions (%).

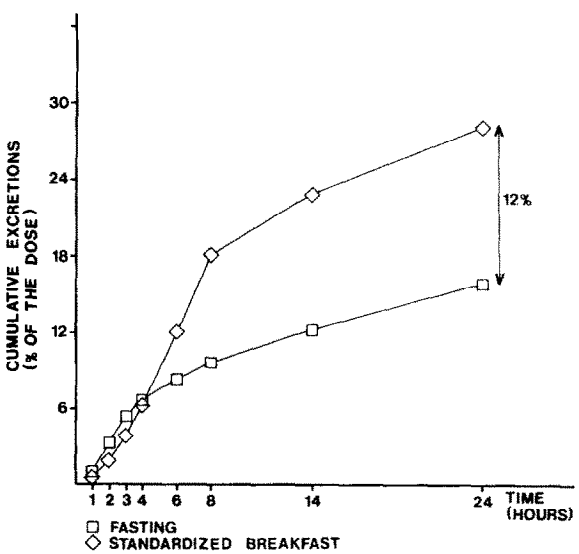

Fig. 4. SRFT: mean RF cumulative urinary excretions (%).

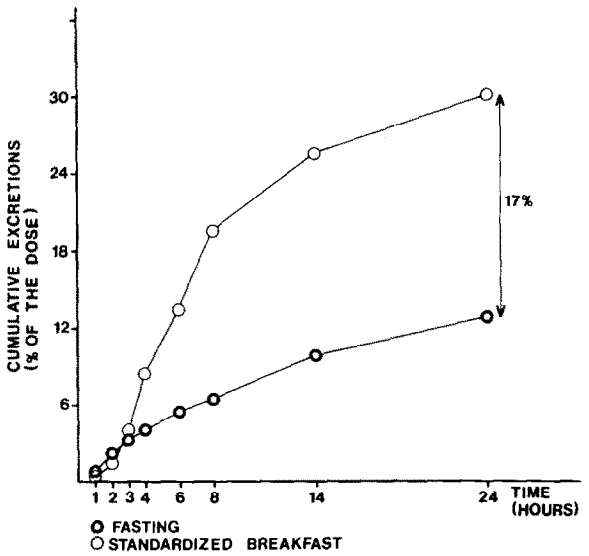

Fig. 5. SRFC: mean RF cumulative urinary excretions (%).

Concerning the influence of concomitant food ingestion on the in vivo behaviour of the sustained release dosage forms, Figs. 4 and 5 indicate that the RF excreted percentage within 24 h is significantly higher (paired t-test, $P \leqslant 0.05$) for the two floating dosage forms (SRFT, SRFC) when these are taken following ingestion of a light meal.

On the contrary, the RF excreted percentage within 24 h of the non-floating SRT does not significantly increase after ingestion of the same standardized meal (Fig. 6).

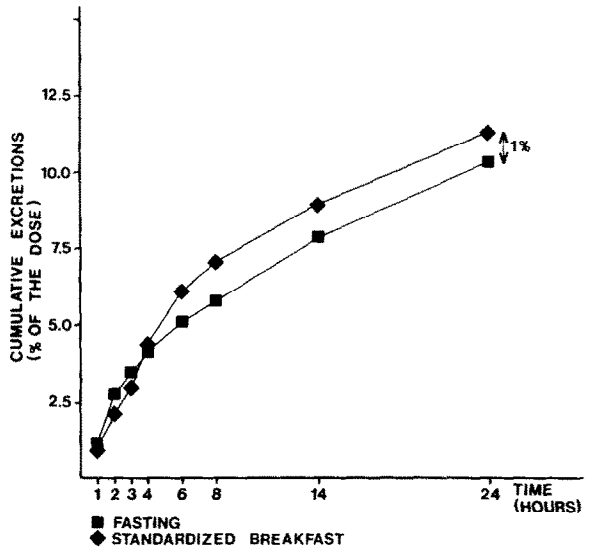

Fig. 6. SRT: mean RF cumulative urinary excretions (%).

If we only take into account that RF will dissolve in food and that the gastric contents of fed subjects then provide a reservoir percolating the site of maximum absorption, the ingestion of a meal should affect all sustained release dosage forms in the same way. As this is not the case, the in vivo RF excretion difference (fasted/fed) between the floating (SRFT, SRFC) and the non-floating (SRT) forms can only be explained by a longer gastric transit time of the floating forms, the meal inducing the closing of the pylorus and promoting the buoyancy process in the stomach.

Conclusion

The study realised on the new type of floating bilayer compressed matrix has shown the preparation feasibility of this dosage form and the possibility of its industrial scale production with high output rates.

This study has also shown that the bilayer SRFT can be opportunely utilized to increase the gastric residence time of a drug to improve its biological availability.

Compared to a classical HBS floating capsule already described by several authors, the double-layer matrix offers many advantages: this compressed dosage form shows a more homogeneous behaviour with regard to erosion and is less sensitive to the GI peristaltism. On the other hand, the formulation of a matrix dosage form with two distinct layers allows the separate regulation of the floating capabilities and the drug release kinetics. In addition, this dosage form denotes, at least in vivo, equivalent floating properties, if not superior ones when subjects are fasted; the advantageous influence of a light meal on the dosage forms' gastric residence time being the same for all the tested floating forms.

Consequently, this type of sustained release matrix could be advantageously used for conveying drugs which are sufficiently stable and soluble in acid media, better resorbed in the proximal or middle portion of the GI tract, requiring a sus-

tained release period to improve the bioavailability of poorly soluble products in non-acid media, or aiming to produce a local and specific effect in the stomach. The incorporation of practically insoluble or unstable drugs in acid medium must be of course avoided.

If all the actually recommended floating dosage forms present undeniable advantages, a more comprehensive and systematic study of the formulation and preparation parameters which can influence the buoyancy would now be required. For this purpose, an apparatus able to measure with accuracy and reproducibility the in vitro floating strength of an immersed dosage form is now being conceived and constructed in our laboratory.

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