Expert Opinion

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Advances in gastro retentive drug-delivery systems

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Introduction: In recent years, various technological improvements have been achieved and new concepts have been developed, in the area of controlled release solid oral dosage forms, especially for products where an extended time of release is associated with an extended gastric retention time. These Gastro Retentive Systems have been quite investigated because they can improve the *in-vivo* performance of many drugs.
Areas covered: This paper summarizes current approaches in the research and development of gastro retentive dosage forms from recent literature. Apart from the numerous mechanisms of action involved, a short review of different key parameters is proposed, taking into account the stomach physiology. Most of the current technologies published, patented or marketed are presented. Promising drugs to develop in the near future are mentioned, and the importance of such systems in fixed Dose Combinations is also discussed. The importance of food effect is mentioned, and the impact of the multiple unit systems versus monolithic approach is discussed, especially regarding the dose intake.
Expert opinion: In conclusion, numerous mechanisms like floating, sinking, effervescence, swelling, bioadhesion, magnetic, etc. have been proposed over the years. While most of the proposed systems show promising dissolution profiles and *in-vitro* retention, only few of them have also shown success *in-vivo*. Currently, the polymeric swelling monolithic systems are the most prominent marketed forms. The possibility to combine different mechanisms in order to ensure true gastric retention even in the fasted state should be further investigated.

Keywords: drug delivery systems, fixed dose combinations, floating, gastroretentive, multiple units

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1. Introduction

Oral delivery of drugs is the most preferred administration route due to ease of administration, but drug bioavailability of such pharmaceutical oral dosage forms is influenced by various parameters. One important factor of physiological variability is the gastric residence time (GRT) of these dosage forms [1,2]. Indeed, gastric retention has received significant interest in the past few decades as most of the conventional oral delivery systems have shown some limitations related to fast gastric emptying time leading to a lower bioavailability. A gastro retentive dosage form (GRDF) can overcome this problem and is particularly useful [3,4]:

- For producing a lasting local action in order to reach the deeply buried *H. pylori* for its eradication with amoxicillin.
- For drugs which are primarily absorbed in the stomach or have a narrow absorption window.

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- For the weakly basic drugs e.g., a weaker solubility regarding the route in the Gastro Intestinal Tract (GIT).
- For the drugs which are degraded in the colonic area.

GRDF technology is characterized by prolonged retention of the dosage form in the stomach and sustained release of the drug. This behaviour can be achieved by the use of different technologies, where each technology has its specific advantages and limitations. The classification of these different modes of gastric retention has been listed [5,6]:

- High-density (sinking) systems,
- Magnetic systems,
- Expandable systems,
- Superporous hydrogel systems,
- Mucoadhesive systems,
- Floating systems,
- Combination of systems.

A good understanding of the stomach anatomy and physiology is essential independent from the technology developed: [7-9].

2. Stomach physiology

The stomach is divided into 3 anatomic regions: fundus, body, and antrum (pylorus). The stomach volume is about 1.5 L after a meal and in range of 250 – 500 ml in interdigestive phasis [10], it produces 2 L among the 8 L of all liquid present in gastro intestinal Tract [7]. The part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. The separation between stomach and duodenum is the pylorus. The pylorus, due to its size, plays a major role in gastric residence time of GRDF. Gastric emptying is the way out for the bolus and occurs during fasting as well as fed states. The pattern of motility is however distinct for the two states, the motility is stronger in fasting mode than in fed mode. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 h. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC) [11], which is further divided into following 4 phases as described by Streubel, *et al.* [12], Moes [13] and Hwang *et al.* [6]:

- Phase I (basal phase) lasts from 40 to 60 min with rare contractions.
- Phase II (preburst phase) lasts from 40 to 60 min with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
- Phase III (burst phase) lasts for 4 to 6 min. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
- Phase IV lasts for 0 to 5 min is a transition period of decreasing activity until the next cycle begins.

3. Key factors impacting GRDF efficacy

There are many factors impacting the gastric residence time of GRDF, these factors are function of human aspect, mechanism aspect of GRDF technology. For the human aspect the following parameters are of importance:

3.1 Food

Food effects and the complex motility of the stomach play a major role in gastric retention behaviour [14-16]. The fasting state is associated with a shortening of the gastric residence time (GRT) because of higher activity than in the fed state. In the fed state, the retention time is extended and the shear stress on the formulation is reduced due to less movement. which improves the dosage form integrity and then its delivery according to extended retention [17,18].

The nature of the food, i.e., volume, viscosity and caloric amount remains of importance; therefore a high fat meal will strongly increase the GRT. Other delayed gastric emptying approaches of interest include sham feeding of indigestible polymers or fatty acid salts that change the motility pattern of the stomach to a fed state, thereby decreasing the gastric emptying rate and permitting considerable prolongation of drug release [19,20].

Independent from the composition of the food itself, the frequency of the intake will significantly increase the GRT because of lower MCC overall activity.

3.2 The pylorus limitation

During the digestion the pylorus size is about 2 – 3 mm, while during the inert-digestive phasis its diameter is about 12.8 ± 7.0 mm [21]. Therefore, all particles which have a diameter inferior to 5 mm can pass through the pylorus to duodenum [6,7]. The gastric peristaltism exerts forces which are able to disintegrate dosage forms of sufficient size having hardness inferior or equal to 1.89 Newton [22].

3.3 Gender, posture and age

Generally stomach emptying is slower in women compared to men, regardless of weight, height, body surface area and even when the hormonal changes due to the menstrual cycle were normalized [23].

Bennett *et al.* [24] have also demonstrated the role of posture in gastric emptying. They observed that an alginate raft emptied faster than food in subjects lying on their left side because the raft was presented to the pylorus ahead of the meal and so emptied faster. One can think that Romans had done some first trials according to this observation. Elderly people generally show extended GRT independent from posture or gender.

For the functional factors of the GRDF technology, main parameters are:

3.4 Size and Shape of monolithic dosage form

The bigger the dosage form, the greater the GRT. Floating dosage forms are less concerned by this basic concept. Different Shapes have been proposed (**Figure 1**), Ring-shaped and Tetrahedron-shaped devices are reported to have better GRT compared with other shapes [25-27].

3.5 Monolithic vs multiple unit system

As claimed for classical extended release, multiple units exhibit a better predictable release and regarding specificity of GRDF, they avoid the possible "all or nothing" effect. "All or nothing" in this context means that a monolithic dosage form may eventually exit the stomach before the gastroretentional properties become functional due to a combination of the lag time and the gastric emptying process.

Within the field of GRDF, a lot of different technologies (**Table 1**) have been investigated, published or patented, but only few of them have actually reached the market (**Table 2**).

4. Technologies for GRDF achievements

The technologies can be classified according to the main property responsible for the gastric retention (**Figure 2**). As most of the systems combine different concepts, this approach is not sufficient to establish an exhaustive classification.

Several approaches are available to achieve a gastro retentive system, one possible classification according to their *in-situ* behaviour can be as follows (**Figure 3**):

- High density system
  - Unfolding system [28,29]
  - Expandable [30,31]
  - High density excipient
  - Magnetic system
- Low density system
  - Intrinsic low density due to porosity
  - Low density due to gas generating
  - Low density due to expandable excipient
- Muco adhesive system

The high density approach is based on three different ways (Right part of **Figure 3**):

- A form size superior to pylorus diameter 12.8 ± 7.0 mm [21] during the gastric emptying, this group comprising expandable, and unfolding system.
- Gastric media have a density close to the density of water: 1.004 g/cm^3, so for this development way the particles density must be superior to 1 g/cm^3 in order to be entrapped into the gastric antrum to achieve gastric retention.
- This method can be reinforced by the use of a magnet.

The low density approach is based on different points of view (Left part of **Figure 3**):

- The intrinsic low density which is function of porosity, the porosity can be due to a porous carrier for active pharmaceutical ingredient [32], or due to solvent evaporation like water [34] or organic solvent [35].
- Low density obtained by a gas generating reaction, the air produced is entrapped in a kind of gel forming matrix [36].
- Low density reached by swelling of polymer excipient [37].

4.1 Systems based on high density

4.1.1 High density system

These systems are generally based on formulations containing high density inert materials such as Barium sulfate, Zinc Oxide. They typically need a density close to 2.5 g/cm^3 to achieve a significant retention in the lower part of the stomach [38]. Rouge *et al*. performed a comparative pharmacokinetic study on floating and sinking multiple unit dosage forms containing Atenolol. No significant differences were detected between the two systems [40].

Simoni *et al*. [41] have compared enteric-coated ursodeoxycholic acid for sinking and floating systems and found a higher AUC for the sinking system. They speculate that the sinking tablet is expelled in the latter phase of gastric emptying along with the solid content at a higher pH leading to better absorption.

These systems seem to be less effective in human beings, therefore, no such system is available on the market.

4.1.2 Magnetic system

For magnetic retention in the stomach, a small magnet is contained in the center of a matrix tablet. After administration, an external magnet outside of the body can be used to keep the tablet in the stomach if it is placed in the correct position. Gröning *et al*. [42] have developed Acyclovir tablets using this technology and found increased plasma levels in a pharmacokinetic study when an external magnet was used to keep the tablets in the stomach. The difficulty of positioning the external magnet coupled with the inability to hold it in place throughout the AP release make this treatment very unpleasant for the patient.

4.1.3 Expandable systems

The expandable GRDF are usually based on three configurations: a small ('collapsed') configuration which enables convenient oral intake; expanded form that is achieved in the stomach and thus prevents passage through the pyloric sphincter; and finally another small form that is achieved in the stomach when retention is no longer required i.e., after the GRDF has fully released its active ingredient, thereby enabling evacuation [43]. The expansion can be achieved by swelling or by unfolding in the stomach [53].

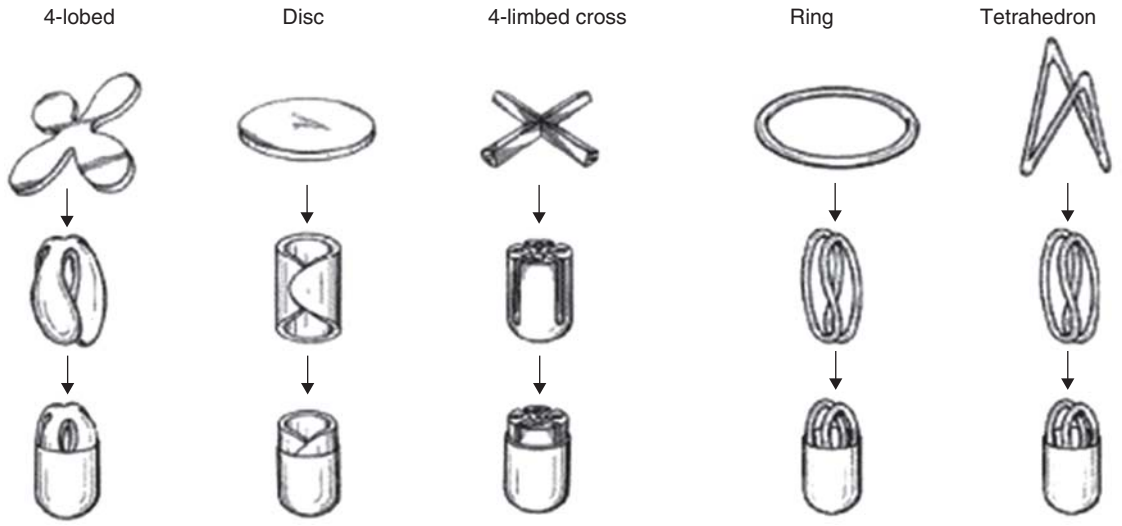

Figure 1. Different geometric forms of unfoldable systems proposed by Caldwell *et al.* [26,27].
Illustration adapted with permission of Bardonnet *et al.* [5].

Table 1. Listing of different platform technologies for gastric retention.

Company	Platform technology	Mechanism involved
Depomed	AcuForm	Matrix Polymer based technology [30]
Flamel	Micropump	Gastroretentive osmotic system
Glaxo Smith Klein	Gel rafting	Floatation due to a gel forming polymer and effervescence reaction
Intec Pharma	Accordion Pill	Unfolding film, embedded in capsule [63,108]
Merrion	Gastro Intestinal Retention System (GIRES)	Gas generating inflatable pouch in capsule [33]
Ranbaxy	Gastro Retentive	Combination of matrix polymer and gas generating technology [62,109]
Roche	Hydrodynamicaly Balanced System (HBS)	Matrix forming polymer based floating system [78,79,76]
Skye Pharma	Geomatrix	Multilayer tablet with a matrix core
Sun Pharma	Gastro Retentive innovative Device (GRID)	Coated multilayer floating and swelling technology [110]

Unfolding systems might represent one of the best alternatives to resist to the gastric emptying. Indeed the unfolding system is usually introduced through a hard gelatine capsule for an easier intake by the patient. In the stomach the carrier is dissolved due to the action of gastric acid, releasing the GRDF system which unfolds or opens out to achieve its extended configuration. The carrier should maintain unfolded properties for extended time spans [44].

The functionality of these systems is based on dimensions and mechanical shape memory. Many technologies were developed but only few of them reached the market. One can see an interesting system, the "accordion pill" which has been developed by INTEC Pharma and is still not actually marketed.

The dosage form is folded in an accordion-like shape into a hard capsule. After the capsule dissolves in the stomach, the accordion unfolds and can remain in the stomach for approx. 12 h (**Figure 4**).

The accordion is not the only form developed; Curatolo *et al.* [45] have created a spring system stuck by gelatin. The dissolution of gelatin releases the ring. The "Y" system was designed by Sonobe *et al.* [46], the center of this system has a memory, and each portion of "Y" is constituted by an erodible material as drug container (**Figure 5**).

Expandable systems represent an interesting concept and have shown real efficacy but specific attention is needed. Since permanent retention of rigid, large monolithic forms may interfere with gastric motility, causing possible adverse effects such as bowel obstruction, local damage, intestinal adhesion and gastropathy [29]. Finally, this kind of dosage form is probably one of the most difficult to industrialize and might be less cost effective than other forms.

4.1.4 Superporous hydrogels

The superporous hydrogel (SPH) systems represent one of the most investigated [47] and patented systems, their efficacy is mainly governed by polymer formulation and one classification can be established regarding their overall properties. Swelling usually occurs because of osmotic absorption of

Table 2. Listing of some commercialized GRDF products.

Company	Product	Drug
Bayer	Cipro XR	Ciprofloxacin (Ranbaxy)
Bristol Myers Squibb	Kombiglyze XR	Metformin/Saxagliptin
Cipla	Ciplox OD	Ciprofloxacin [39]
Depomed	Glumetza	Metformin
	Proquin XR	Cirpofloxacin
	Gralise	Gabapentin [30]
Fabre	Topalkan	Antacid
Flamel	Coreg CR	carvedilol
GSK	Gaviscon liquid	Antacid
Ranbaxy	Cifran OD	Ciprofloxacin
Roche	Madopar	L-Dopa + Benserazide
	Valrelease	Diazepam
Sanofi	Xatral OD	Alfuzosin (Skye Pharma)

water into the dosage form. The gastric retention is a result of the mechanical properties of the dosage form.

The polymers used in such systems are able to significantly increase the dimensions of the dosage form, in order to be larger than 7 – 12 mm, which represents the pylorus diameter.

Most of the hydrophilic polymers swell by absorption of water, leading to a three dimensional network. Those which are able to swell substantially without disruption of the overall structure are called hydrogels, and if the water content absorbed exceeds 95% of the total weight, this is called a superabsorbent hydrogel.

The water absorption propagates through the spaces in the 3D structure known as the effective pore size which can be from 10 nm to 10 micrometers in diameter, but this process is typically very slow and the dosage form needs some time (a couple of minutes to several hours) to reach the equilibrium. During this time, the dosage form may be evacuated prematurely leading to the all or nothing effect.

Many investigations were performed for hydrogel preparations with the intention to create an effective pore size larger than 10 micrometers in order to speed up the water absorption process.

Different studies are described for superporous hydrogels (SPH) which are intended to swell in less than a minute with improved swelling ratios of more than 100% but these products generally exhibit poor mechanical properties [48-50].

For improved superporous hydrogels, to be useful there is a need to swell fast to a large size and at the same time maintain high mechanical strength. Chen *et al.* [51] have reported that the mechanical strength of the highly swollen SPHs can be increased by adding a composite material during the synthesis.

4.2 Bio adhesive systems

Mucoadhesion of dosage forms to the gastric mucosa has been considered to retain them in the stomach. For instance, mucoadhesive microspheres containing acyclovir have been prepared with chitosan, thiolated chitosan, Carbopol® and methyl cellulose as mucoadhesive polymers [52]. The microspheres containing acyclovir were prepared by an emulsion and a chemical cross-linking technique and then placed into a hard gelatin capsule. These capsules released the microspheres upon dissolution as multiple units, which in turn, released the drug in the stomach over a period of 12 h. Another option included the production of a patch (3 mm in diameter) containing three layers: a water insoluble backing, a model drug (fluorescein, fluorescein isothiocyanate) carrying adhesive layer (dextran and gel forming polymer) and a pH sensitive enteric polymer [54].

A more complex system has been proposed by Lele *et al.* [55] based on formulations containing H-bonded complexes of poly(acrylic acid) or poly(methacrylic acid) with poly(ethylene glycol)–drug (indomethacin) conjugates: the complexes were designed to dissociate as the formulation swelled in contact with the mucosal surfaces at pH 7.4, releasing the PEG-indomethacin conjugate which hydrolysed to release free indomethacin and free polyethylene glycol.

Regarding these studies, even if this approach seems to be effective, the mucosa of the stomach is in a state of constant turnover which makes prediction of the maintenance of adherence quite difficult [56].

4.3 Floating system or low density system

Floating characteristics of a gastric retentive dosage form is assessed by onset of floating, floating duration but also floating strength.

The floating strength has not been quantified extensively. However, it represents an important characteristic as the dosage form has to float *in vivo* even in the presence of food. As higher floating strength increases the probability of the oral dosage form to remain afloat, this attribute plays a major role in reducing food effects on gastric retention.

The determination of Floating strength was investigated by Timmermanns and Moës [57-60] the developed system was based on displacement of sample exercising a pressure on balance measuring this force.

The pellets were placed in a specifically designed basket sample holder, the resultant-weight apparatus enables to monitor *in vitro* the total force F acting vertically on an immersed object and can be used to quantify its floating or non-floating abilities.

Sauzet *et al.* [34] described a new apparatus based on the equipment and methodology designed above.

The apparent density of the tablets ρ_a was determined using a custom apparatus, made of a transparent parallelepiped box filled with a liquid with a known density, based on an immersed beam measuring the buoyancy force. A thin flexible beam was immersed in the bath and was equipped with a sample holder made with metal wires at its free extremity. The other extremity was held firmly (**Figure 6**).

When the solid dosage was placed into the sample holder, it was vertically displaced by the buoyancy force and reached a new steady state once the beam oscillations vanished.

The beam displacement was measured by comparing two digital photographs captured with a webcam Measurement

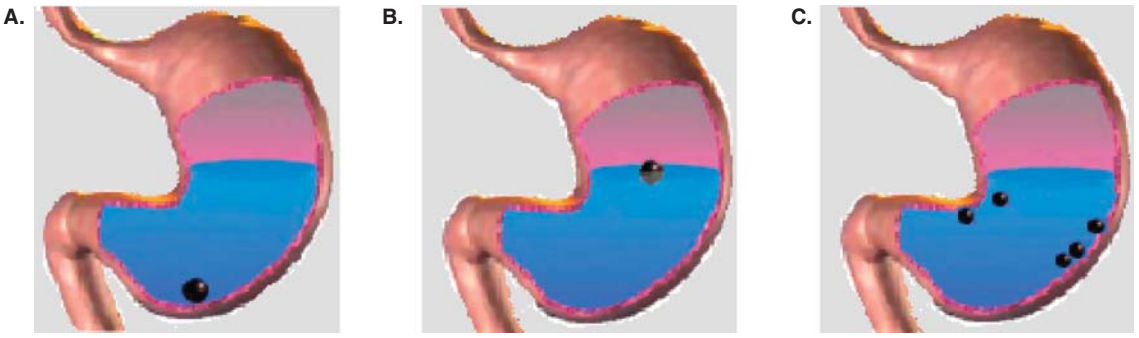

Figure 2. Illustration representing (A): the systems based on High density. **(B)**: the systems based on low density. **(C)**: the mucoadhesive systems.
Illustration adapted with permission of Bardonnet *et al.* [5].

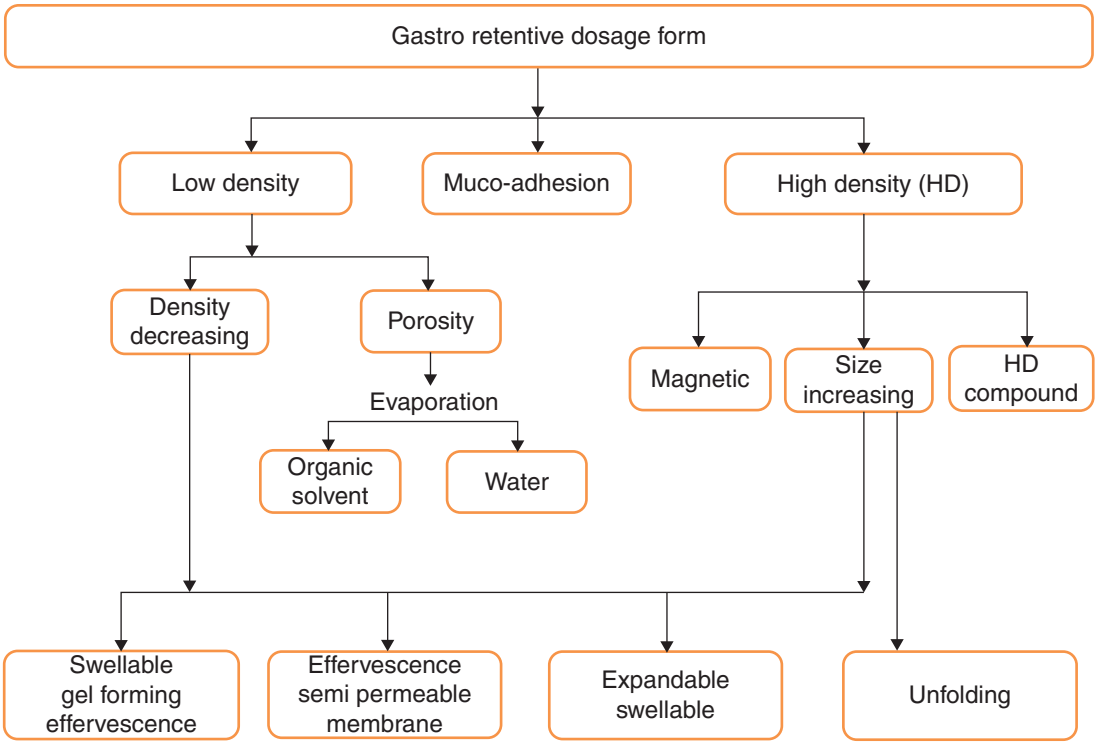

Figure 3. The three mechanisms classification of gastro retentive dosage form achievement focused on high and low density aspect.

of the induced deviation allows the calculation of its density according to the Equation 1:

$$\rho a = \frac{\rho f}{1 - \frac{Ewh^3 \delta c}{4gL^3 mc}}$$

Equation 1: calculation of the apparent density of the tablet.

Where

- ρ_f is the liquid density,
- mc is the tablet weight,
- *g* the acceleration of gravity,
- *h, w and L are respectively the thickness, the width and the length of the beam.*
- δc is the displacement of the beam and
- E is the elastic modulus of beam material (Young's modulus).

The monitoring of the orally ingested floating gastric retentive dosage forms under physiologic conditions has been considered. For instance, magnetic resonance imaging of tablets loaded with magnetic Fe_3O_4 particles has been used to identify the position and residence time of such

Figure 4. An unfolding GRDF: the accordion pill.
Reproduced with permission of IntecPharma [111].

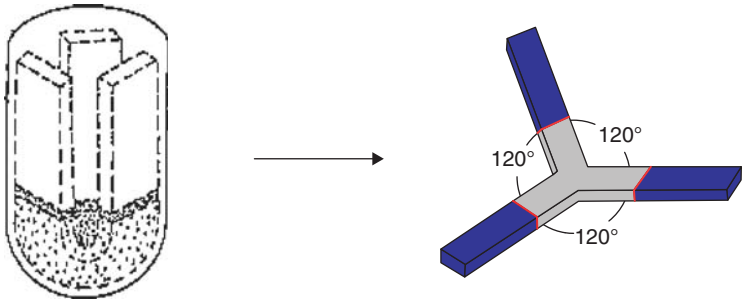

Figure 5. Unfolding dosage form.
Adapted from Sonobe *et al.* [46].

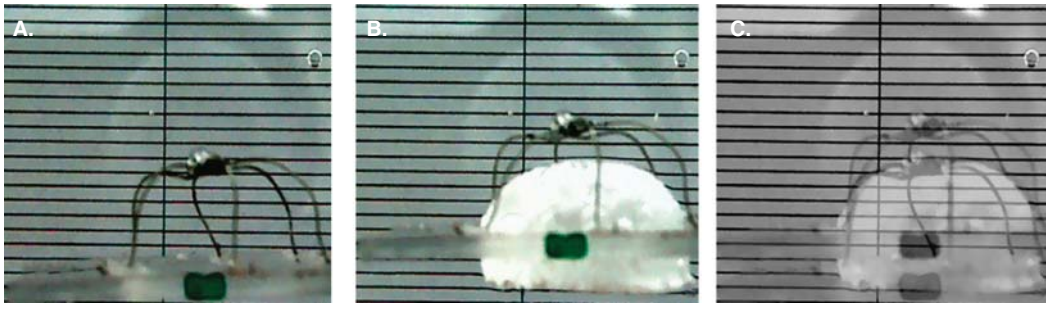

Figure 6. Determination of the apparent density (A): image of the beam extremity with the sample holder. **(B)**: Due to the buoyant force of the tablet, the beam is lifted vertically. **(C)**: Difference between photographs A and B showing the displacement δc. The millimetre scale is seen in the back.
Reproduced with permission of Sauzet *et al.* [34].

tablets in the stomach of seated human volunteers. The study also included the use of gadolinium chelates to assess the relative position of the tablet to the intra gastric meal level: the distribution was about 20% at a proximal position and 36% at a distal position [61].

Several approaches of non-effervescent and effervescent formulation technologies have been patented, published and used in order to customize gastric residence time of the GRDF [30,62,63,45,46]. Therefore floating systems can be classified regarding their effervescence behavior.

4.3.1 *Effervescent system*

The use of a gas to decrease the density of the dosage form is an interesting alternative. Floating of dosage forms can be achieved by the inclusion of a gas generator agent in an inert matrix [64].

The rafting system, a liquid based formulation which forms a viscous cohesive gel containing entrapped CO_2 bubbles on contact with gastric fluid. Washington *et al.* [65] compared four formulations of liquid Gaviscon, a well-known rafting system used in the gastro-esophageal reflux and heartburn. Regarding the composition, adding antacid compounds enhance the neutralization properties but decreases the raft breaking strength leading to partial gastroretentive properties. It is important to notice that such systems represent an interesting vehicle for taking gastroretentive solid dosage forms as suspensions.

Sustained release verapamil hydrochloride has been delivered as floating tablets produced from granules containing mixtures of a forming matrix (hydroxypropyl methylcellulose, hydroxypropyl cellulose, ethyl cellulose or Carbopol®) together with sodium bicarbonate and anhydrous citric acid. *In vivo* X-ray imaging experiments were conducted on fasted beagle dogs in order to abolish the effect of food, showing that the gastric emptying time of the floating tablets could be more than 4 h and less than 5 h [66].

Multi-unit tablets containing furosemide have been formulated and processed as follows: a core containing a solid dispersion of furosemide in polyvinyl pyrrolidone with other excipients prepared by direct compression; the core is then first coated with an effervescent layer (mainly sodium bicarbonate) and a second coat with polymethacrylates (Eudragit® RL30D, the most promising). The time to float decreased as the amount of the effervescent agent increased and the coating level of the polymer decreased. The minitablets remained in the stomach for about 6 h, as observed in radiograms [67].

Krogel and Bodmeier [68] have designed a floating system with pulsatile drug delivery. In this example a core with the drug contained the effervescent material. The core was coated with a polymeric material of either acrylic (Eudragit® R, RS, RL or NE) or cellulosic (cellulose acetate, ethyl cellulose) polymers. The authors found that a coat with high elongation value and high water and low CO_2 permeabilities (e.g., Eudragit® RL with acetyltributyl citrate) show the best results for the effervescent reaction (floating process), whereas a weak semipermeable film which ruptured after a lag-time (ethylcellulose with dibutylsebacate) was the best for the pulsatile drug delivery component. The drug was released from the first component by addition of cellulose acetate or hydroxypropyl methylcellulose. Floatation time could be controlled by the composition (type of polymer and plasticizer) or processing (thickness of the coating or hardness of the core).

A more complex preparation was suggested by Kawashima *et al.* [35,69]. The authors suggested the preparation of hollow microspheres loaded with Ibuprofen in their outer polymer shells. The microspheres were prepared by a novel emulsion solvent diffusion method, whereby the ethanol–dichloromethane solution of a drug and an enteric acrylic polymer were poured into an agitated aqueous solution of polyvinyl alcohol at 40°C. The gaseous phase in the dispersed polymer droplet was generated by the evaporation of the dichloromethane forming an internal cavity in the microsphere of the polymer with the drug. The microballoons floated continuously over the surface of acidic dissolution media with surfactant.

A multi-layer system comprising a Sustained Release core, an inner effervescent layer containing both sodium bicarbonate and tartaric acid, and an outer layer as a swellable membrane was investigated by Ichikawa *et al.* [70]. The outer layer contained polyvinyl acetate and shellac, whereas the inner layer was subdivided in 2 layers in order to avoid direct contact between effervescent substances. When immersed, water diffusion through outer membrane allows neutralization of inner effervescent layers with CO_2 production. The system was then able to float approximately during 5 h.

Sungthongjeen *et al.* [71] developed a floating multiple units system using an extrusion spheronization, based on this multi-layer system but carbon dioxide becomes entrapped in a polymeric membrane of aqueous colloidal polymer dispersion (Eudragit® RL 30D, RS 30D, NE 30D). The optimum system (Eudragit® RL 30D) could float completely within 3 min and maintained the buoyancy over a period of 24 h. The drug release was sustained and linear with the square root of time.

Hamdani *et al.* [72] developed a melt pelletized floating multi units system manufactured in a high shear mixer. Formulations were based on a mixture of Compritol® and Precirol® as lipidic binders and sodium bicarbonate as a gas-generating agent. Floating pellets with high theophylline content were investigated. Such pellets released approximately 50% of theophylline after 8 h and 75% of the pellets were still floating after 23 h.

Fukuda *et al.* [73] compared tablets containing Eudragit® RS PO and sodium bicarbonate made by hot-melt extrusion (HME) to corresponding tablets manufactured by direct compression (DC). Only the HME tablets exhibited sustained release properties and floated for 24 h. This is attributed to the porous structure formed from CO_2 gas was generated due to the thermal decomposition of sodium bicarbonate in the softened acrylic polymer at elevated temperature during the extrusion process.

Other approaches [74,75] are based on ion exchange resin beads which are loaded with bicarbonate and coated with a semi permeable membrane. These beads exhibit prolonged gastric residence due to the release of carbon dioxide which is trapped inside the coating of the beads.

4.3.2 Non Effervescent system

Such systems are generally prepared from one or more matrix-forming polymers chosen from polycarbonates, polyacrylates, polymethacrylates, or polystyrene together with a second gel-forming, highly swellable hydrocolloid component, which is typically a cellulose compound or a polysaccharide.

Upon contact with gastric fluids, the polymer is hydrated and a colloidal gel network is formed which is directly responsible for the drug release. The release of hydrophilic

drugs is mainly governed by diffusion mechanisms while hydrophobic drugs are released by erosion of the external surface of the dosage form. The air trapped within the swollen polymer allows the buoyancy of the dosage form.

Seth & Tossounian [76] were the first to develop the Hydrodynamically Balanced Systems (HBS) in a capsule containing a drug embedded in a gel-forming hydrocolloid matrix [77]. This single unit dosage form swells upon contact with gastric fluid to form a gel which remains buoyant for an extended period of time. Based on the same concept, they developed HBS floating tablets [78,79] comprising at least 20% of one or more hydrocolloids such as Hydroxypropyl methylcellulose (HPMC), hydroxethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC). Both the desired period for floating and drug release can be adapted by variation of the hydrocolloid formulation. If these systems are designed for sustained release until complete erosion; their floating behavior may change with time following increased hydration of the polymer. Low density is generally a result of volume increase during swelling, while water uptake will increase both the tablet mass and the erosion. This complex mechanism leads to floating strength variations during the sustained release.

USHIMARU [80] developed another floating sustained-release dosage form containing a mixture of a cellulose/starch derivative and a higher fatty acid glyceride which is solid at room temperature. The powder blend is filled into capsules and the capsules are heated to a temperature above the melting point of the fatty acid component. After cooling down to room temperature, floating sustained release capsules are obtained.

Mitra [81] developed a sustained release oral medicinal delivery device as a flexible sheet-like system. The device is a multilayer composite comprising a water-insoluble polymer containing the drug and a barrier film overlaying the carrier film. The barrier film comprises a mixture of a water insoluble polymer another copolymer which is permeable for both water and the drug. Both layers are sealed in a way to entrap small air pockets, contributing to the buoyancy of such system.

A new interesting gastroretentive platform is the module assemblage or dome Matrix® technology, introduced by Colombo *et al.* [82] which is based on release units or modules made by hydrophilic polymers (matrix) having the shape of a disc with one convex and one concave base respectively male and female, in order to facilitate their assemblage.

By sticking two of the modules concave base against concave base, a system with an internal void space is formed. This assembly, named void configuration, is characterized by an immediate floatation of the system when plunged in water (**Figure 7**) [83].

Recently, Casas *et al.* [84] studied Riboflavin release from such systems using tapioca starch copolymers in "void configuration", a system with an internal void space (**Figure 7**).

Combination of floatation capability of the assembled modules and the prolonged drug release provided by the graft copolymers make these assembled modules candidates as controlled release gastro-retentive dosage forms.

As discussed previously, it is of importance to develop a platform which is able to float immediately, especially for monolithic dosage forms. Therefore another approach remains the formulation of intrinsic low density dosage forms.

Streubel *et al.* [85,86] developed microparticles containing polypropylene foam powder, Verapamil and different polymers (Eudragit® RS, ethylcellulose, polymethyl methacrylate) by the use of an oil in water solvent evaporation method: All formulations studied showed good floating behaviour and a broad spectrum of dissolution profiles could be obtained. They also developed a monolithic floating drug delivery system based on highly porous polypropylene and matrix-forming polymers. The highly porous foam powder provided low density tablets which were able to float for at least 8 h in 0.1 N HCl at 37°C. Drug release characteristics were modified according to the ratio of matrix-forming polymer and foam powder and were also strongly related to drug chemistry [87].

Kawashiwa *et al.* [69] developed microballoons with a hollow structure as a multi-unit floating device by the emulsion-solvent diffusion method. The drug and an acrylic polymer were dissolved in an ethanol-dichloromethane mixture and poured into an aqueous solution of polyvinyl alcohol to form emulsion droplets. Most of the microballoons were floatable *in vitro* even after testing for 12 h, but the *in vivo* radiographical study showed that microballoons were retained in the stomach for only over 3 h.

In order to demonstrate their gastroretentive properties, Sato *et al.* [88] compared microballoons (MB), prepared by the emulsion-solvent diffusion method, to non-floating microspheres (NF). The two dosage forms exhibit similar *in-vitro* Riboflavin dissolution profiles. Riboflavin pharmacokinetics were investigated by analysis of urinary excretion of riboflavin on three healthy volunteers. Urinary excretion of Riboflavin from Microballoons was significantly sustained in comparison to NF in the fed condition and total urinary excretion of riboflavin was higher from MB compared to NF in the fasted and the fed conditions.

Based on this approach some investigations have been reported [89-92], where the polymers are generally chosen from Cellulose acetate, Eudragit® S, Agar and polycarbonate. The resulting multiple unit systems remain promising as they exhibit excellent *in vitro* floatability.

Whitehead *et al.* [93,94] have developed floating freeze-dried calcium alginate multiple-unit dosage forms and have investigated their *in vivo* behavior. The gastric transit was monitored by gamma-scintigraphy and subjects were maintained in the fed state. Prolonged Gastric Retention times (GRT) of over 5.5 h were achieved in all the seven subjects studied. The dosage form remained high up in the stomach for the whole study period.

Shishu *et al.* [95] developed floating calcium alginate beads of 5-fluorouracil (5-FU) and investigated drug loading, drug entrapment efficiency, image, surface topography, buoyancy,

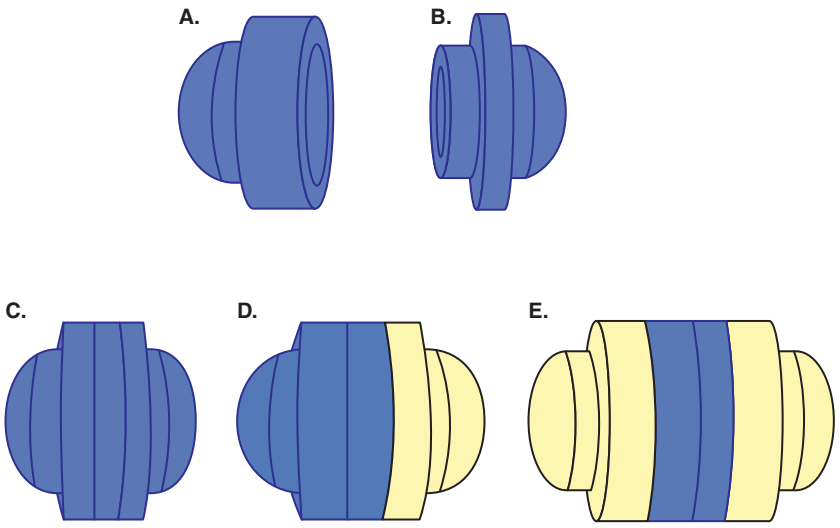

Figure 7. Dome Matrix® modules : Schematic of female module. (A), male module **(B)**, void configuration assembly, made by sticking male and female modules concave base to concave base **(C)**. Assembled systems with additional barrier module to one **(D)** or both **(E)** convex bases of void configuration.
Reproduced with permission from Hascicek [112].

and *in vitro* release. The optimized formulation was subjected to *in vivo* antitumor studies to check the therapeutic efficacy. The multiple unit floating system was found to reduce the gastric tumor incidence in mice by 74%, while the conventional tablet dosage form reduced this incidence by only 25%.

Badve *et al.* [96] developed hollow calcium pectinate beads for floating-pulsatile release of diclofenac sodium for chronopharmacotherapy. The floating beads obtained were porous (34% porosity), hollow with bulk density < 1. *In vivo* studies by gamma scintigraphy determined on rabbits showed gastroretention of beads up to 5 h.

Singh *et al.* [97] developed sterculia-alginate beads to perform a gastric retention by floatation. Such system demonstrated a Fickian mechanism of API release, in function of different parameters (pH, ratio between alginate and sterculia, crosslinker …).

Ishak *et al.* [98] developed floating chitosan treated alginate beads with Metronidazole, a common antibacterial drug used in treatment of H. pylori. The system was then compared to Metronidazole suspension on *H. pylori* infected mice under fed conditions as a single daily dose for 3 successive days. The *H. pylori* clearance tests showed that the floating beads with a dose of 15 mg/kg provided 100% clearance rate whereas the suspension with a dose of 20 mg/kg gave only 33.33%.

Recently, Sauzet *et al.* [34,99] developed a floating monolithic GRDF comprising high dose API (up to 70%) and hydrophobic dusty powder using an experimental design. The manufacturing process is based on aqueous wet granulation. A paste of substantial porosity was obtained by over granulating the initial mixture under high shear conditions. The resulting moulded tablets have shown floatability (app. density: 0.57) and sustained release for 24 h. This system seems promising as it exhibits advantages quite similar to those of hollow spheres (excellent *in vitro* floatability and relatively high loading capacity) but uses water instead of organic solvents within manufacture.

4.3.3 *In situ gelling*

Rajinikanth, *et al.* [100] prepared an intra-gastric floating *in situ* gelling system of an amoxicillin product for the eradication of *H. pylori.* Gellan was used as the gelling polymer and calcium carbonate as the gas-releasing agent. An *in-vivo* study was conducted on Mongolian gerbil, where the required amount of amoxicillin for eradication of *H. pylori* was shown to be 10 times less for the floating system compared to the corresponding amoxicillin suspension.

4.4 Combination of different systems

In practice, even if not explicitly claimed, systems such as the gas-generating devices combine different gastroretentive properties or concepts. They increase in size to prevent transit and at the same time they float due to their low density (as described above). For systems where dual mode of action is explicitly claimed, bioadhesion is often claimed in combination with floating or even swelling behavior.

Some floating-bioadhesive microspheres were prepared with acetohydroxamic acid. This system show a good growth inhibition of H. *pylori* when the acetohydroxamic acid is loaded on the microspheres than the plain aetohydoxamic acid [101].

Another approach, combining the concepts of floating and bioadhesion to provide gastric retention, was described by Jiménez-Castellanos *et al.* [102]. The oral controlled-release system shows, at least *in vitro*, good characteristics on: controlled release of the drug, bioadhesiveness in the

stomach and intestine of rabbits and buoyancy in an acid medium.

Chavanpatil *et al.* [103] developed swellable and bioadhesive tablet of Ofloxacin using HPMC K100 M, psyllium husk and crospovidone. The swelling properties were increased with increasing crospovidone. The bioadhesive property of the developed formulation was found to be significant in combination as compared to HPMC and psyllium husk alone.

Recently, Tadros [104] developed a Ciprofloxacin gastroretentive tablet combining swelling, floating, and adhesive properties. An optimized formulation was then investigated *in-vivo* in six healthy volunteers. The mean gastric retention period was found to be 5.5 h. The first 3 h seemed to be related to the adhesive properties of the form.

Hu *et al.* [105], have recently developed a floating tablet based on gel forming matrix with gas generation, and an enhancer of buoyancy. The enhancer of buoyancy is the hexadecanol whose creates a hydrophobous environment around the tablet, keeps the release medium from enteringtablets and delays the drug release. The reduction of density tablet can be explained by hexadecanol density 0.8176 g/cm^3. However this tablet presents a floating lag time about 3 min, so a prematurate emptying can be occur during the IMMC.

Desai and Bolton [106] prepared a moulded tablet of an agar gel with air and oil entrapped after water evaporation. The incorporation of oil reduces the apparent density of the tablet and prevents penetration of gastric media into the gel matrix due to the hydrophobicity induced by oil, and the air exit. This tablet can maintain in human stomach in function of the filling state of stomach.

5. GRDF involved in fixed dose combinations (FDC)

These specific systems are actually being used or developed for the diabetes type 2 treatment as a FDC with Metformin XR (GRDF). Metformin XR is combined with a Dipeptidyl peptidase-4 inhibitor (DPP4) drug or with one of the renal sodium-glucose transporter-2 inhibitors (SGLT2). Some of these FDC are still under investigations but some have already shown to be beneficial for patients in the treatment of the diabetes disease. Therefore it can be expected that additional combination producs of this kind will be developed and reach the market in the near future. Actually, because of the high doses of Metformin required in the diabetes therapy, where all currently marketed FDC systems are monolithic, tablet weights are often in excess of 1200 mg. Some of the patients may not be able to swallow such big tablets and this might induces poor treatment compliance.

Furthermore, in a FDC system, only Metformin has to be designed as a gastro retentive system, but not the other drug that is used in the combination. The high dose Metformin is typically included in the core tablet. The gastro retention is achieved as a consequence of the swelling/gelling property of such monolithic matrix system. In order to avoid the sustained delivery of the other drug embedded in the matrix, the drug is applied as an external immediate release layer with coating technique. Another alternative is a bilayer tablet which however represents a less cost effective manufacturing process.

Since in diabetes type 2 therapy, the daily intake of MetforminXR could be as high as 2000 mg, combinations of the above type in the form of multiple units might be an interesting alternative to monolithic forms.

We can expect in the near future more GRS involved in FDC products, examples are:

- for Parkinson disease treatment (combinations of Levodopa/Carbidopa) which might lead to extended coverage above Levodopa's current efficacy threshold and might also extend the time to peak Levodopa concentration relative to the currently available sustained release Levodopa/Carbidopa formulations.
- for pain treatment (acetaminophen/opioids), in which each drug will show both an immediate and a gastric retentive extended release. This could be interesting, especially for acetaminophen, as it could obviate the bioavailability reduction seen in the colon with non-gastric retentive extended release dosage forms.

Especially if the FDC products don't require the same delivery profile for each drug, it will be more convenient to use multiple units instead of a monolithic form as different granule/bead populations can provide for the individual dose and the individual delivery of each drug involved.

6. Expert opinion

According to the review of the scientific literature, after more than three decades of research within the field, the oral gastroretentive dosage forms have been quite extensively investigated, leading to different interesting systems.

As these systems are preferentially to be taken under fed conditions, it remains to be clarified which portion of the retention time in the stomach can be attributed true gastro-retention and which part is taking advantage of the food effect.

Despite the proven advantages of gastroretentive systems for patients, no single system could be identified as the best one for all drug candidates. Each drug candidate or combination has to be assessed on a case by case basis, especially regarding the required dose and the manufacturability. As a matter of fact, the high dose oral systems preferred by the pharmaceutical industry are currently designed as tablets. For tablets containing high doses of API, the polymer selection and formulation of the dosage form are critical for their efficacy and their compressibility. The polymers which are considered the best candidates are those, which show substantial gastric retention (swelling, expanding) even when present in only small amounts in the dosage form. One prominent example is high molecular weight polyethylene oxide (Polyox®) in combination with cellulose derivatives. Other

polymer systems need substantially more excipients leading to increased tablet weights for identical API doses. This is one of the reasons why there are many different marketed formulations of Metformin XR 500 mg but only 2 formulations for the XR1000 mg form.

In conclusion, numerous mechanisms like floating, sinking, effervescence, swelling, bioadhesion, magnetic, etc. have been proposed over the years. While most of the proposed systems show promising dissolution profiles and *in-vitro* retention, only few of them have also shown success *in-vivo*. Currently, the polymeric swelling monolithic systems are the most prominent marketed forms.

Actually one of the well-known Polymeric swelling monolithic systems is AcuForm™ (Depomed, Inc.) [107]. The 2 main advantages of this technology are the possibility to go for relatively high doses of APIs and the use of a classical manufacturing process. At the other end of the spectrum, unfolding systems like the accordion pill (Intec Pharma) [63,108] seem to take less advantage of the food effect but the manufacture could be costly.

It is important to notice that for sustained release, the multiple unit systems are definitely preferred over the monolithic ones; and most of the gastro-retentive marketed products are monolithic. For therapeutic regimes where the maximum doses are in a range of 1000 mg or even more, GRS in the form of multiple units might help to develop more convenient dosage forms. The possibility to combine different mechanisms in order to ensure true gastric retention even in the fasted state should be further investigated.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Kagan L, Hoffman A. Systems for region selective drug delivery in gastrointestinal tract: biopharmaceutical considerations. Expert Opin Drug Deliv 2008;8(6):681-92
2. Bolton S, Desai S. Floating sustained-release therapeutic compositions. US4814179; 1989
3. Hoffman A, Stepensky D. Pharmacodynamic aspects of modes of drug administration for optimization of drug therapy. Crit Rev Ther Drug Carrier Syst 1999;16:571-639
4. Rouge N, Buri P, Doelker E. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. Int J Pharm 1996;136:117-39
5. Bardonnet PL, Faivrea V, Pugh WJ, et al. Gastroretentive dosage forms: overview and special case of Helicobacter pylori. J Control Release 2006;111:1-18
   • **Comprehensive review with the different mechanisms and considerations for Helicobacter Pylori.**
6. Hwang SJ, Park H, Park K. Gastric retentive drug-delivery systems. Ther Drug carrier Syst 1998;15(3):243-84
7. Mayersohn M. In: Banker GS, Rhodes CT, editors, Principles of drug absorption, drugs and the pharmaceutical sciences: modern pharmaceutics. Volume 121. Marcel Dekker, New York; 2002. p. 23-66
8. Russel TL, Berardi RR, Barnett JL, et al. Upper gastrointestinal pH in seventy-nine healthy, elderly, north american man and women. Pharm Res 1993;10:187-96
9. Horter D, Dressman JB. Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract. Adv Drug Del Rev 2001;46:75-87
10. Bannister LH. Alimentary system. In: PL, editor, Churchill Livingstone. Volume XXXVIII. Williams (ed.) Gray's Anatomy, New York; 1995. p. 125-56
11. Minami H, McCallum RW. The physiology and pathophysiology of gastric emptying in humans. Gastroenterology 1984;86:1592-610
12. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery systems. Expert Opin Drug Deliv 2006;3:217-33
    • **Interesting review with details on Floating systems with intrinsic low density.**
13. Moes AJ. Gastroretentive dosage forms. Crit Rev Ther Drug Carrier Syst 1993;10(2):143-95
14. Klausner A, Eyala S, Lavy E, et al. Novel levodopa gastroretentive dosage form: in-vivo evaluation in dogs. J Control Release 2003;88:117-26
15. O'Reilly S, Wilson CG, Hardy JG. The influence of food on the gastric emptying of multiparticulate dosage forms. Int J Pharm 1987;l34:213-16
16. Sangekar S, Vadino WA, Chaudry I, et al. Evaluation of the effect of food and specific gravity of tablets on gastric retention time. Int J Pharm 1987;35:187-97
17. Khosla R, Feely LC, Davis SS. Gastrointestinal transit of non-disintegrating tablets in fed subjects. Int J Pharm 1989;53:107-17
18. Abrahamsson B, Alpsten M, Hugosson M. Absorption, gastrointestinal transit, and tablet erosion of felodipine extended-release (ER) tablets. Pharm Res 1993;10:709-14
19. Singh NB, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release 2000;63:235-59
    • **A good review of floating systems.**
20. Hoener B-A, Benet LZ. In: Banker GS, Rhodes CT, editors, Factors influencing drug absorption and drug availability, drugs and the pharmaceutical sciences: modern pharmaceutics. Volume 121. Marcel Dekker, New York; 2002. p. 93-117
21. Dressman JB, Berardi RR, Dermentzoglou LC, et al. Upper gastrointestinal pH in young, healthy men and women. Pharm Res 1990;7:756-61
22. Kamba M, Seta Y, Kusai A, et al. A unique dosage form to evaluate the mechanical destructive force in the gastrointestinal tract. Int J Pharm 2000;208:61-70

23. Mojaverian P, Vlasses PH, Kellner PE, et al. Effects of gender, posture and age on gastric residence time of an indigestible solid: Pharmaceutical considerations. Pharm Res 1988;10:639-44

24. Bennett CE, Hardy JG, Wilson CG. The influence of posture on the gastric emptying of antacid. Int J Pharm 1984;21:341-7

25. Garg S, Sharma S. Gastroretentive drug delivery systems. Business Briefing: Pharmatech; 2003. p. 160-66

26. Caldwell LJ, Gardner CR, Cargill RC. Drug delivery device which can be retained in the stomach for a controlled period of time. US4735804; 1988

27. Caldwell LJ, Gardner CR. Drug delivery device which can be retained in the stomach for a controlled period of time. US4758436; 1988

28. Klausner EA, Eyal S, Lavy E, et al. Novel levodopa gastroretntive dosage form: in-vivo evaluation in dogs. J Control Release 2003;88:117-26

29. Klausner EA, Lavy E, Friedman M, et al. Expandable gastroretentive dosage forms. J Control Release 2003;90:143-62

30. Berner B, Hou Sui Yuen E. A gastric retained dosage form of gabapentin. US20040903879; 2004

31. Markey M, Shell John W. Berner Bret. WO0132217; 2001

32. Jain SK, Agarwal GP, Jain NK. Porous carrier based on floating granular delivery system of repaglinide. Drug Dev Ind Pharm 2007;33:1-34

33. Jagathesan M. EP1648425; 2004

34. Sauzet C, Claeys-Bruno M, Nicolas M, et al. An innovative floating gastro retentive dosage system: formulation and in vitro evaluation. Int J Pharm 2009;378:23-9

• **Investigation of a novel gastroretentive drug delivery system.**

35. Kawashima Y, Niwa T, Takeuchi H, et al. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J Pharm Sci 1992;81:135-40

36. Chaudhari M, Chandwani O, Yelegaonkar R, et al. EP1745775; 2005

37. Timmermans J. Floating hydrophilic matrix dosage forms for oral use: factors controlling their buoyancy and gastric residence capabilities. Ph.D. Thesis. University of Brussels; 1991

38. Clarke GM, Newton JM, Short MB. Comparative gastrointestinal transit of pellet systems of varying density. Int J Pharm 1995;114:1-11

39. Louie-Helm J, Berner B, Fell R, et al. Parmacokinetics of ciprofloxacin gastric retentive tablets in healthy volunteers. Proc Int Symp Control Release Bioact Mater 2001

40. Rouge N, Allemann E, Gex-Fabry M, et al. Comparative pharmacokinetic study of a floating multiple-unit capsule, a high-density multiple-unit capsule and an immediate-release tablet containing 25 mg atenolol. Pharmaceutica Acta Helvetiae 1998;73:81-7

41. Simoni P, Cerre C, Cipolla A, et al. Bioavailability study of a new, sinking, enteric-coated ursodeoxycholic acid formulation. Pharmacol Res 1995;31(2):115-18

42. Groning R, Berntgen M, Georgarakis M. Acyclovir serum concentrations following peroral administration of magnetic depot tablets and the influence of extracorporal magnets to control gastrointestinal transit. Eur J Pharm Biopharm 1998;46:285-91

43. Groning R, Cloer C, Georgarakis M, et al. Compressed collagen sponges as gastroretentive dosage forms: in vitro and in vivo studies. Eur J Pharm Sci 2007;30:1-6

44. Kagan L, Lapidotb N, Afargan M, et al. Gastroretentive accordion pill: enhancement of riboflavin bioavailability in humans. J Control Release 2006;113:208-19

45. Curatolo W, Lo J. Gastric retention system for controlled drug release. US19880200801; 1988

46. Sonobe T, Watanabe S. Gastric retention device. JP19890225245; 1989

47. Omidian H, Rocca JG, Park K. Advances in superporous hydrogels. J Control Release 2005;102:3-12

48. Park H, Park K, Dukjoon K. Preparation and swelling behavior of chitosan-based superporous hydrogels for gastric retention application. J Biomed Mater Res A 2006;76:144-50

49. Torrado S, Prada P, de la Torre PM, et al. Chitosan-poly(acrylic) acid polyionic complex: in vivo study to demonstrate prolonged gastric retention. Biomaterials 2004;25:917-23

50. Chen J, Park K. Synthesis of fast swelling, superporous sucrose hydrogels. Carbohydrate Polymers 2000;41:259-68

51. Chen J, Blevins WE, Park H, et al. Gastric retention properties of superporous hydrogel composites. J Control Release 2000;64:39-51

52. Dhaliwal S, Jain S, Singh HP, et al. Mucoadhesive microspheres for gastroretentive delivery of acyclovir: In vitro and in vivo evaluation. AAPS J 2008;10:322-30

53. Klausner EA, Lavy E, Barta M, et al. Novel gastroretentive dosage forms: evaluation of gastroretentivity and its effect on levodopa absorption in humans. Pharmacol Res 2003;20(9):1466-73

54. Eaimtrakarn S, Prasad YVR, Puthli SP, et al. Possibility of a patch system as a new oral delivery system. Int J Pharm 2003;250:111-17

55. Lele BS, Hoffman AS. Mucoadhesive drug carriers based on complexes of poly (acrylic acid) and PEGylated drugs having hydrolysable PEG-anhydridedrug linkages. J Control Release 2000;69:237-48

56. Chun MK, Sah H, Choi HK. Preparation of mucoadhesive microspheres containing antimicrobial agents for eradication of H. pylori. Int J Pharm 2005;297:172-9

57. Timmermans J, Van Gansbeke B, Moes AJ. Assessing by gamma scintigraphy the in vivo buoyancy of dosage forms having known size and floating force profiles as a function of time. Proc APGI Int Conf Pharm Technol 1989;1:42-51

58. Timmermans J, Moes AJ. How well do floating dosage forms float? Int J Pharm 1990;62:207-16

59. Timmermans J, Moes AJ. Measuring the resultant-weight of an immersed test material: I. Validation of an apparatus and a method dedicated to pharmaceutical applications. Acta Pharm Technol 1990;36:171-5

60. Timmermans J, Moes AJ. Measuring the resultant-weight of an immersed test material: II. Examples of kinetic determination applied to monolithic dosage forms. Acta Pharm technol 1990;36:176-80

61. Steingoetter A, Weishaupt D, Kunz P, et al. Magnetic resonance imaging for the in vivo evaluation of gastric-retentive tablets. Pharm Res 2003;20:2001-7

62. Naresh T, Himadri S. Orally administered controlled drug delivery system providing temporal and spatial control. WO0015198; 2000

63. Afargan M, Kirmayer D. Gastro-Retentive diagnostic assemblies. WO2006072948; 2006

64. Baumgartner S, Kristl J, Vrecer F, et al. Optimisation of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm 2000;195:125-34

65. Washington N, Washington C, Wilson CG, et al. What is "Liquid Gaviscon"? a comparison of four international formulations. Int J Pharm 1986;34(1-2):105-9

66. Elkheshen SA, Yassin AEB, Alsuwayeh S, et al. In vitro and in vivo evaluation of floating controlled release dosage forms of verapamil hydrochloride. Pharmazeutische Ind 2004;66:1364-72

67. Meka L, Kesavan B, Kalamata VN, et al. Design and evaluation of polymeric coated minitablets as multiple unit gastroretentive floating drug delivery systems for furosemide. J Pharm Sci 2009;98:2122-32

68. Krogel I, Bodmeier R. Floating or pulsatile drug delivery systems based on coated effervescent cores. Int J Pharm 1999;187:175-84

69. Kawashiwa Y, Niwa T, Takeuchi H, et al. Preparation of multiple unit hollow microspheres (microballoons) with acrylic resin containing tranilast and their drug release characteristics (in vitro) and floating behavior (in vivo). J Control Release 1991;16:279-90

70. Ichigawa M, Watanabe S, Miyake Y. A new multiple-unit oral floating dosage system. Preparation and in vitro evaluation of floating and sustained-release characteristics. J Pharm Sci 1991;80:1062-6

71. Sungthongjeen S, Paeratakul O, Limmatvapirat S, et al. Preparation and in vitro evaluation of a multiple-unit floating drug delivery system based on gas formation technique. Int J Pharm 2006;324:136-43

72. Hamdani J, Moes AJ, Amighi K. Development and in vitro evaluation of a novel floating multiple unit dosage form obtained by melt pelletization. Int J Pharm 2006;322:96-103

73. Fukuda M, Peppas NA, McGinity JW. Floating hot-melt extruded tablets for gastroretentive controlled drug release system. J Control Release 2006;115:121-9

74. Atyabi F, Sharma HL, Mohammad HAH, et al. Controlled drug release from coated floating ion exchange resin beads. J Control Release 1996;42:25-8

75. Todd RS, Fryers GR. Cholestyramine compositions and method for treating biliary gastritis. US4172120; 1979

76. Seth PR, Tossounian J. The hydrodynamically balanced system (HBSTM): a novel drug delivery system for oral use. Drug Dev Ind Pharm 1984;10:313-39

77. Sheth PR, Tossounian JL. Sustained release pharmaceutical capsules. US4126672; 1978

78. Sheth PR, Tossounian JL. Sustained release tablet formulations. US4140755; 1979

79. Sheth PR, Tossounian JL. Novel sustained release tablet formulations. US4167558; 1979

80. Ushimaru K. Pharmaceutical preparations and a method of manufacturing them. US4702918; 1987

81. Mitra SB. Sustained release oral medicinal delivery device. US4451260; 1984

82. Losi E, Bettinia R, Santi P, et al. Assemblage of novel release modules for the development of adaptable drug delivery systems. J Control Release 2006;11(1-2):212-18

• **Very interesting paper, new flexible gastroretentive system with modules.**

83. Strusi OL, Sonvico F, Bettini R, et al. Module assemblage technology for floating systems: in vitro flotation and in vivo gastro-retention. J Control Release 2008;129:88-92

84. Casas M, Strusi OL, Jiménez-Castellanos R, et al. Tapioca starch graft copolymers and Dome Matrix® modules II. Effect of modules assemblage on Riboflavin release kinetics. Eur J Pharm Biopharm 2011;77:111-15

85. Streubel A, Siepmann J, Bodmeier R. Floating microparticles based on low density foam powder. Int J Pharm 2002;241:279-92

86. Streubel A, Siepmann J, Bodmeier R. Multiple unit gastroretentive drug delivery systems: a new preparation method for low density microparticles. J Microencapsul 2003;20:329-47

87. Streubel A, Siepmann J, Bodmeier R. Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. Eur J Pharm Sci 2003;18:37-45

88. Sato Y, Kawashima Y, Takeuchi H, et al. In vivo evaluation of riboflavin-containing microballoons for floating controlled drug delivery system in healthy human volunteers. J Control Release 2003;93:39-47

89. Soppimath KS, Kulkarni AR, Rudzinski WE, et al. Microspheres as floating drug-delivery systems to increase gastric retention of drugs. Drug Metabolism Review 2001;33:149-60

90. Kawashima Y, Niwa T, Takeuchi H, et al. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J Pharm Sci 1992;81:135-40

91. Sato Y, Kawashima Y, Takeuchi H, et al. In vitro and in vivo evaluation of riboflavin-containing microballoons for a floating controlled drug delivery system in healthy humans. Int J Pharm. 2004;275(1-2):97-107

92. Choudhury PK, Kar M, Chauhan CS. Cellulose acetate microspheres as floating depot system to increase gastric retention of antidiabetic drug: formulation, characteristics and in vitro - in vivo evaluation. Drug Dev Ind Pharm 2008;34:349-54

93. Whitehead L, Fell JT, Collett JH, et al. Floating dosage forms: an in vivo study demonstrating prolonged gastric retention. J Control Release 1998;55:3-12

94. Vanderbist F, Baudier P, Deboeck A, et al. WO2007106960

95. Shishu GN, Aggarwal N. Stomach-specific drug delivery of 5-fluorouracil using floating alginate beads. AAPS Pharm Sci Tech 2007;8: article 48

96. Badve SS, Sher P, Korde A, et al. Development of hollow/porous calcium

pectinate beads for floating-pulsatile drug delivery. Eur J Pharm Biopharm 2007;65:85-9

97. Baljit S, Vikrant S, Dimpal C. Gastroretentive floating sterculia–alginate beads for use in antiulcer drug delivery. Chem Eng Res Des 2010;88:997-1012
98. Ishak RA, Awad GA, Mortada ND, et al. Preparation, in vitro and in vivo evaluation of stomach-specific metronidazole-loaded alginate beads as local anti-Helicobacter pylori therapy. J Control Release 2007;119:207-14
99. Prinderre P, Sauzet C. Process for making gastroretentive dosage forms. EP08290529
100. Rajinikanth PS, Balasubramaniam J, Mishra B. Development and evaluation of a novel floating in situ gelling system of amoxicillin for eradication of Helicobacter pylori. Int J Pharm 2007;335(1-2):114-22
101. Umamaheshwari RB, Jain S, Tripathi PK, et al. Floating bioadhesive microspheres containing acetohydroxamic acid for clearance of Helicobacter pylori. Drug Deliv 2002;9:223-31
102. Jimenez-Castellanos MR, Ziaa H, Rhodes CT, et al. Design and testing in vitro of a bioadhesive and floating drug delivery system for oral application. Int J Pharm 1994;105:65-70
103. Chavanpatil M, Jain P, Chaudhari S, et al. Development of sustained- release gastroretentive drug delivery system for ofloxacin: In vitro and in vivo evaluation. Int J Pharm 2005;304:178-84
104. Tadros MI. Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: development, optimization and in vitro–in vivo evaluation in healthy human volunteers. Eur J Pharm Biopharm 2010;74:332-9
105. Hu L, Li L, Yang X, et al. Floating matrix dosage form for dextromethorphan hydrobromide based on gas forming technique: In vitro and in vivo evaluation in healthy volunteers. Eur J Pharm Sci 2011;42:99-105
106. Desai S, Bolton SA. Floating controlled-release drug delivery systems: in vitro–in vivo evaluation. Pharm Res 1993;10:1321-5
107. Chien-Hsuan H. Gastroretentive drug delivery system: Acuform® Technology, AAPS Modified Release Focus Group; 2010. p. 2-4
108. Tsabari M, Balshey A, Yofe E. US2009304753; 2009
109. Talwar N, Sen H, Staniforth JN. Orally administered controlled drug delivery system providing temporal and spatial control. US6261601; 2001
110. Bhachaland DN, Rupsinh ZY. WO2005101983; 2005
111. IntecPharma. Available from: http://www.intecpharma.com/
112. Hascicek C, Rossi A, Colombo P, et al. Assemblage of drug release modules: effect of module shape and position in the assembled system on floating behavior and release rate. Eur J Pharm Biopharm 2011;77:116-21

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