Expert Opinion

Gastroretentive drug delivery systems

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A controlled drug delivery system with prolonged residence time in the stomach is of particular interest for drugs that i) are locally active in the stomach, ii) have an absorption window in the stomach or in the upper small intestine, iii) are unstable in the intestinal or colonic environment, or iv) exhibit low solubility at high pH values. This article gives an overview of the parameters affecting gastric emptying in humans as well as on the main concepts used to design pharmaceutical dosage forms with prolonged gastric residence times. In particular, bioadhesive, size-increasing and floating drug delivery systems are presented and their major advantages and shortcomings are discussed. Both single- and multiple-unit dosage forms are reviewed and, if available, results from *in vivo* trials are reported.

Keywords: bioadhesion, controlled drug release, floating system, gastric retention

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1. Introduction

The main function of the stomach is to temporarily store food, start its digestion and to release the resulting chyme slowly through the pylorus into the duodenum. Because of the small surface area of the stomach, absorption into the systemic circulation is restricted. The jejunum and ileum are the most important sites for absorption of nutrients and drugs. In the colon, mainly water and ions are absorbed, as well as certain drugs (that show significant absorption due to the long residence time in the colon).

The process of gastric emptying is characterised by a distinct cycle of electromechanical activity known as the interdigestive migrating myoelectric complex. This series of events that cycle through the stomach and small intestine every 1.5 – 2 h is divided into four consecutive phases [1]:

- Phase I (45 – 60 min), the most quiescent, develops few or no contractions;
- Phase II (30 – 45 min) consists of intermittent action potentials and contractions, which gradually increase in intensity and frequency as the phase progresses;
- Phase III (5 – 15 min) is a short period of intense contractions and peristaltic waves, involving both the proximal and distal gastric regions ('housekeeper waves'). In this phase, indigestible solids are removed from the fasted stomach;
- Phase IV (0 – 5 min) is a transition period of decreasing activity until the next cycle begins.

In order to study the parameters affecting the process of gastric emptying, various methods have been applied, such as γ-scintigraphy, radiography, endoscopy, radiotelemetry and magnetic-marker monitoring [2-5]. Furthermore, indirect information on gastric emptying could be gained by comparing the pharmacokinetics of drugs administered in oral dosage forms of different size. Factors affecting the gastric emptying and, hence, the gastric retention time of oral dosage forms include:

- density, size and shape of the dosage form [6-9];
- concomitant ingestion of food and its nature, caloric content and frequency of intake [10-16];

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- (simultaneous) administration of drugs acting as anticholinergic agents (e.g., atropine, propantheline), opiates (e.g., codeine) and prokinetic agents (e.g., metoclopramide, cisapride) [17];
- biological factors, such as gender, posture, age, sleep, body mass index, physical activity and disease states (e.g., diabetes, Crohn's disease) [18-21].

The therapeutic interest to prolong the gastric residence time of a pharmaceutical dosage form with time-controlled release kinetics can be significant, especially in the case of drugs, which:

- are locally active in the stomach (e.g., misoprostol [22], antacids [23] and antibiotics against *Helicobacter pylori* [24-26]);
- have an absorption window in the stomach or in the upper small intestine (e.g., L-DOPA [27,28], *p*-aminobenzoic acid [29], furosemide [30,31] and riboflavin [32,33]);
- are unstable in the intestinal or colonic environment (e.g., captopril [34]); or
- exhibit low solubility at high pH values (e.g., diazepam, chlordiazepoxide [35] and verapamil HCl [36-38]).

Furthermore, as the total gastrointestinal transit time of the dosage form is increased by prolonging the gastric residence time, these systems can also be used as extended release devices with a reduced frequency of administration and, thus, improved patient compliance [39].

In contrast, a prolonged residence time in the stomach is not desirable for drugs that:

- cause gastric lesions (e.g., NSAIDs);
- are unstable in the acidic pH of the stomach; or
- undergo a significant first-pass effect (i.e., metabolism in the liver prior to entering the systemic circulation; e.g., nifedipine).

Most gastroretentive drug delivery systems are single-unit dosage forms [40-42], which have in common the risk of losing their effect too early due to their all-or-nothing emptying from the stomach. To overcome this restriction, multiple-unit floating or bioadhesive systems have been proposed [43,44]. These distribute uniformly within the gastric content and gradually empty from the stomach, possibly resulting in longer-lasting effects and reduced intersubject variabilities.

The main approaches used to increase the gastric residence time of pharmaceutical dosage forms include:

- bioadhesive delivery systems, which adhere to mucosal surfaces [45];
- delivery systems that rapidly increase in size once they are in the stomach to slow the passage through the pylorus [201];
- density-controlled delivery systems, which either float or sink in gastric fluids [46,47].

The major advantages and shortcomings of these concepts will be reviewed in the following sections.

2. Bioadhesive drug delivery systems

Various types of polymers have been studied for their bioadhesive properties and several excellent review articles have been published on the fundamental aspects and potential applications of bioadhesive dosage forms [48-52]. Bioadhesive polymers are usually macromolecular, hydrophilic gelling substances with numerous hydrogen-bond forming groups, such as carboxyl, hydroxyl, amide and sulfate groups (e.g., crosslinked polyacrylic acids, sodium carboxymethyl cellulose, sodium alginate and carrageenan). In addition to hydrogen bondings, covalent and electrostatic interactions are known to be of importance. Although the exact mechanisms of bioadhesion are not yet completely understood, certain elements of the process are known to be of significance, such as spreading the bioadhesive over the substrate to increase the surface area of contact; diffusion/penetration of polymer chains of the bioadhesive into the substrate; and domination of the attractive forces over the repulsive ones.

Several types of dosage forms have been proposed to allow prolonged residence within the stomach based on bioadhesive polymers. For example, Akiyama and Nagahara [44] developed mucoadhesive microspheres consisting of a drug and Carbopol® 934P (Noveon, Inc.; polyacrylic acid, polymerised in benzene, highly crosslinked with allyl sucrose) being dispersed within a waxy matrix of polyglycerol esters of fatty acids. These systems were reported to adhere to the stomach mucosa in rats and Mongolian gerbils, and to prolong the gastrointestinal residence of the drug after oral administration. The adherence can probably be explained by the hydration and swelling of the Carbopol in the microspheres on contact with water. Importantly, parts of the polymer remained within the microspheres, whereas the rest was 'anchored' within the mucus layer. When furosemide (showing an absorption window in the upper intestine) was administered to rats (and riboflavin to human volunteers incorporated in these microspheres), enhanced absorption was observed compared with the administration of the respective furosemide/riboflavin suspensions. Furthermore, amoxicillin-loaded microspheres of this type showed higher anti-*H. pylori* activity in the Mongolian gerbil stomach compared with an amoxicillin suspension. Thus, this principle seems to work *in vivo* as well.

Microparticles consisting of amoxicillin-loaded ion-exchange resin, encapsulated in mucoadhesive polymers (polycarbophil and Carbopol 934) were prepared by a modified oil-in-oil solvent evaporation technique, aiming to increase the efficacy of amoxicillin in the treatment of peptic ulcers [53]. The *in vitro* release of the drug was rapid in the presence and absence of the polymer coating. Interestingly, the gastric residence time in rats was longer, and the distribution of the microparticles on the mucosa apparently superior in the case of uncoated systems. The authors concluded that the proposed system failed to prolong the residence in the stomach.

Jackson *et al.* [54] observed extended gastric residence times of the positively charged ion-exchange resin colestyramine. In

addition, this substance had the ability to coat the gastric mucosa uniformly. The adherent behaviour was considered to be responsible for the prolonged gastric residence. As the oppositely charged ion-exchange resin Amberlite IRP-69 did not possess the same characteristics, and as the coating of the colestyramine with ethylcellulose (EC) reduced the effects, the surface charge of the resin obviously plays a significant role in mucoadhesion and subsequent retention. These findings indicate that colestyramine has an interesting potential for the design of drug delivery systems aimed to topically treat the gastric mucosa.

Hejazi and Amiji [55] prepared tetracycline-loaded chitosan microspheres by ionic precipitation with sodium sulfate. Spherical particles with an average diameter of 2.0 – 3.0 µm were formed. Depending on the preparation method, 8 – 69% drug could be incorporated. However, the entire amount of tetracycline was instantaneously released at pH 1.2 and 2.0 due to the dissolution of the microspheres. At pH 3.5 and 5.0, ~ 70 and 90% of the drug was released after 3 and 8 h, respectively. The same authors studied the gastric residence of chitosan-based microspheres and the local tetracycline concentrations following oral administration in gerbils [56]. Of the administered drug dose, ~ 10% remained within the fasted stomach after 2 h. Most of the microspheres were found in the colon 6 h after administration. Furthermore, the gastric residence time of the chitosan-based microspheres was found to be independent of the gastric pH within the range of 1.0 – 4.5. However, the tetracycline concentration profile in the stomach, following administration in the microsphere formulation, was similar to that of an aqueous solution. The drug was predominantly found in the colon and urine 6 h after administration. Again, there was no significant difference in the tetracycline concentration profile when the gastric pH varied in the range of 1.0 – 4.5.

Recently, chitosan-based microspheres with 85% tetracycline loading were prepared by ionic precipitation followed by chemical crosslinking with glyoxal [57]. Importantly, increased residence times in the fasted gerbil stomach were observed with these systems, compared with both tetracycline solutions and non-crosslinked microspheres. After 2 h, 17% of the crosslinked microspheres remained in the fasted stomach, whereas only 10% of the non-crosslinked systems were retained. Furthermore, the tetracycline concentration in the stomach was higher in the case of crosslinked microspheres, compared with oral solutions and non-crosslinked chitosan-based systems at all investigated time points during 10 h. After 6 h, tetracycline could be detected in the stomach, the colon and the urine.

Higo *et al.* [58] prepared a tetracycline–sucralfate complex under acidic conditions and evaluated its mucoadhesive properties both *in vitro* and *in vivo*. For this purpose, a novel *in vitro* gastric mucoadhesion test using *ex vivo* rat stomach was developed. Excellent mucoadhesive properties of the tetracycline–sucralfate complex were demonstrated. Importantly, higher amounts of the complex were retained on the gastric mucosa compared with the physical mixtures of tetracycline and sucralfate (50 – 60 versus 25% after 3 h). The results of this *in vitro* study supported the observations *in vivo*.

Schmitz *et al.* [59] developed a stomach-targeted oral delivery system for low molecular-weight heparin based on minitablets. Thiolated polycarbophil was used as the mucoadhesive carrier material and was compared with hydroxyethylcellulose (HEC) as a non-mucoadhesive control. The *in vitro* drug release profiles were similar, and near constant release rates were observed during 4 h with both polymers. In a gastric transit study in rats, the HEC formulations could not be observed in the gastric lumen at 4 h after administration, in contrast to thiolated polycarbophil-based delivery systems. Further *in vivo* evaluation in rats revealed that the relative bioavailability of oral formulations (compared with subcutaneous administration) was significantly higher in the case of thiolated polycarbophil compared with HEC.

Although the concept of bioadhesion gains increasing interest in alternative routes of administration (e.g., nasal, buccal, ocular, vaginal and rectal), only a few successful approaches to develop bioadhesive systems with prolonged residence time in the stomach have been reported. The major challenge for such systems is the high turnover rate of the gastric mucus and the resulting limited retention times. Furthermore, it is difficult to specifically target the gastric mucus with bioadhesive polymers. For example, polycarbophil and Carbopol stick to the various surfaces they come into contact with [60]. An advantage of mucoadhesive dosage forms in the stomach (and in general) is the intimate contact with the mucosa leading to short pathways for locally acting drugs, such as antibiotics against *H. pylori*.

3. Size-increasing drug delivery systems

Another approach to retain a dosage form in the stomach is by increasing its size above the diameter of the pylorus, even in the widest state during the housekeeper wave. Due to significant inter-individual variations, the cutoff size cannot be given exactly. Approximately, the dosage form should be > 13 mm; however, even bigger units have been observed to be emptied from the stomach. In order to facilitate swallowing, it is highly desirable to design dosage forms with an initially small size, which, once they are in the stomach, significantly increase in size. The expanded state should be achieved fairly quickly, in order to prevent premature emptying through the pylorus. On the other hand, the systems should also guarantee their clearance from the stomach after predetermined time intervals, in order to avoid accumulation following multiple administrations. Other characteristics of an optimal size-increasing drug delivery system include: no effect on gastric motility and emptying pattern, no other local adverse effects (e.g., on the gastrointestinal wall), and inexpensive industrial manufacture [61].

The increase in the system size can be based on several principles, including unfolding in the stomach (to complex

geometric shapes); expanding due to swellable excipients; and expanding due to gas generation.

3.1 Systems unfolding in the stomach

Several geometric shapes, such as tetrahedron, ring, cloverleaf, disk, string and pellet/sphere, which can be packed tightly into a gelatin capsule and unfold after dissolution of the capsule shell, have been patented by Caldwell *et al.* [202-205]. These systems consist of at least one erodible polymer (e.g., hydroxypropyl cellulose, Eudragit® E; Röhm Pharma GmbH), one nonerodible polymer (e.g., polyolefins, polyamides, polyurethanes), and a drug that is dispersed within the polymer matrix. The importance of the physical characteristics of this type of systems, such as size, shape and flexibility on the resulting gastric emptying was studied in beagle dogs [62]. Cloverleaf, disk, string and pellet shapes were moulded from silastic elastomer. Tetrahedron and rigid-ring shapes were fabricated from blends of low-density polyethylene and ethylene:vinyl acetate copolymer. Furthermore, the devices contained barium sulfate in order to monitor their location by X-ray. These were folded, placed within gelatin capsules and administered to dogs. Interestingly, the tetrahedron-shaped devices remained in the stomach for longer periods of time than the other tested shapes (of similar size). The gastric retention of rigid rings was significantly affected by their size. Disk- and cloverleaf-shaped systems showed only poor gastric retention. In addition, strings and pellets were eliminated fairly rapidly. Erodible tetrahedron-shaped devices consisting of rods ('arms'; made of poly[ortho ester]/polyethylene blends) and 'corners' (based on silastic elastomer; Figure 1) showed prolonged gastric residence times in beagle dogs [63]. This could mainly be attributed to the considerable size of the systems (~ 2 cm) on unfolding. A reliable exit from the stomach was ensured by the erosion of the drug-containing arms; the erosion rate being controlled by the polymer-blend ratio. In human volunteers, the gastric residence time of the tetrahedron-shaped dosage forms varied from 0.5 to 6 h [64]. Other types of devices, which can be packed into gelatin capsules and considerably increase in size following unfolding include Y-shaped systems [206] and sheet-like shaped devices [207], optionally with openings to reduce the risk of pylorus obstruction [208].

Klausner *et al.* [65] designed unfolding, multilayer, polymeric films based on a drug-containing shellac matrix as the inner layer, covered on both sides with (outer) shielding layers composed of hydrolysed gelatin/Eudragit S (Röhm Pharma GmbH)/glycerine/glutaraldehyde. The system is optionally framed with rigid polymeric strips composed of L-poly(lactic acid)/EC or EC-triethylcitrate. Such dosage forms placed into gelatin capsules were administered to beagle dogs. Two factors were found to influence the *in vivo* gastric retention behaviour: the dimensions and the mechanical properties of the films. With relatively large devices (surface ≥ 2.5 × 2.5 cm) and rigid frames, prolonged residence times and improved absorption properties could be achieved with the model drug riboflavin.

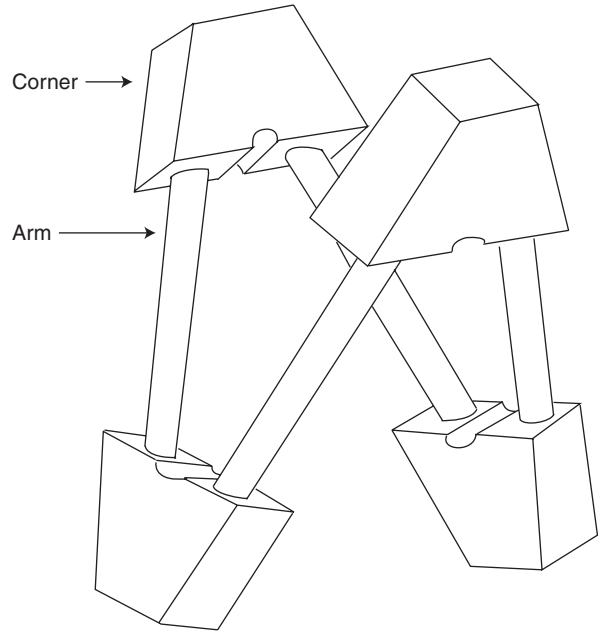

Figure 1. Tetrahedron-shaped drug delivery system formed by assembling two components: silastic corners and erodible arms. Reprinted from CARGILL R, ENGLE K, GARDNER CR, PORTER P, SPARER RV, FIX JA: Controlled gastric emptying. II. *In vitro* erosion and gastric residence times of an erodible device in beagle dogs. *Pharm. Res.* (1989) **6**:506-509 [63], with kind permission of Springer Science and Business Media.

The same group studied the performance of levodopa-containing multilayer films (5.0 × 2.5 cm in size) in beagle dogs [66]. The systems consisted of an inner, drug-containing film layer (EC-levodopa, 1:1), covered on both sides by (outer) shielding layers of enzymatically hydrolysed gelatin/Eudragit S/glycerine/glutaraldehyde blends (48:30:20:2), and a frame of rigid polymeric strips (L-poly[lactic acid]/EC, 9:1). Importantly, therapeutic levodopa concentrations (> 500 ng/ml) could be maintained over 9 h following the administration of one single film. The mean absorption time of the drug was significantly extended in comparison to non-gastroretentive controlled-release particles and oral solutions. The performance of levodopa-containing, multilayer films was also studied in humans [67]. Prolonged gastroretentivity (≥ 5 h) could be achieved due to the rigidity and size of the dosage forms. The films rapidly unfolded and maintained their mechanical integrity. The absorption period of the drug was significantly prolonged in comparison to a non-gastroretentive controlled-release tablet.

A tablet-shaped system with retention arms has been patented by Curatolo and Lo [209,210]. The retention arms are initially folded (e.g., fixed by a gelatin band), in order to facilitate swallowing. Once in contact with gastric fluids, they expand and, thus, prevent rapid emptying through the pylorus.

The major disadvantage of most systems that are unfolding in the stomach is their complex shape, making them difficult

to produce, and cost intensive on a larger scale. Furthermore, their geometries could lead to mucosa irritation.

3.2 Systems expanding due to swellable excipients

The significant swelling of this type of drug delivery system is generally due to the presence of specific hydrogel formers, which drastically increase in size following contact with aqueous media. Several devices based on this concept have been patented [211-217].

Urquhart and Theeuwes [218] described a tablet-shaped system consisting of a plurality of small, drug-containing pellets dispersed within a hydrogel-forming polymer matrix. This device swelled 2- to 50-fold in the stomach, thus, potentially providing extended gastric residence times. The pellets were subsequently released from the system following the erosion of the polymer matrix and the drug was released from the pellets for gastric or intestinal absorption.

Deshpande *et al.* [68] developed a controlled-release gastric retention system based on: i) a swellable core, consisting of the drug (chlorphenamine maleate or riboflavin 5′ phosphate) and the expanding agents polyvinyl pyrrolidone XL, Carbopol 934P and calcium carbonate, and ii) a permeable coating, consisting of blends of Eudragit RL 30D and NE 30D (Röhm Pharma GmbH) at different ratios. The tablets swelled in ~ 10 – 15 min to 2- to 4-times their original volume, and drug release occurred during 15 – 18 h. The coating ensured the integrity of the tablet during the initial swelling phase and subsequently controlled the release rate of the drug (the polymer-blend ratio and coating level being the most important parameters). The optimal ratio of Eudragit RL 30D to NE 30D was found to be 70:30. The authors concluded that this combination provides sufficient elasticity to withstand the pressure of expansion during the initial swelling phase, and at the same time allows the breakdown of the device following exhaustion of the drug [69].

A gastroretentive dosage form based on a bilayer tablet consisting of a collagen sponge, which is compressed onto a drug-containing polymer layer with controlled-release properties, was developed by Cloer and Gröning [70]. Following contact with aqueous fluids, the collagen sponge expanded to a length of 5 cm, which was assumed to be sufficient to prevent direct emptying through the pylorus. Drug release from this system could be controlled by the composition of the second layer. A related device consisted of a three-layer tablet with two sustained-release layers at the top and one compressed collagen sponge at the bottom.

Park and colleagues described interesting enzyme-digestible hydrogels consisting of poly(vinyl pyrrolidone) crosslinked with albumin [71-73]. These hydrogels, which were especially designed for gastroretentive dosage forms, swelled to a significant extent (which was affected by the albumin content and degree of albumin alkylation). The hydrogels were degraded in the presence of pepsin either by bulk or by surface degradation. With increasing albumin alkylation, pepsin digestion was diminished and bulk degradation was the predominant release mechanism. The gastric residence time in dogs exceeded 24 h, even under fasted conditions. Such an enzyme-digestible, swelling-hydrogel formulation was used to deliver flavin mononucleotide, which is known to be absorbed only from the upper small intestine. Importantly, the drug could be detected up to 50 h after administration in the blood, indicating the gastric retention of the hydrogel in the stomach. The same group described a further, very promising, size-increasing gastroretentive drug delivery system [74-77] based on superporous hydrogels with rapid swelling kinetics and superabsorbent properties. Equilibrium swelling with these devices is attained in < 1 min. The swelling ratio (volume of the swollen gel:volume of the dried form) can exceed 1000 in some cases. The mechanical strength of the highly swollen, superporous hydrogels was increased by adding a composite material, such as croscarmellose sodium, which forms a dispersed phase within the continuous polymer matrix during the synthesis (superporous hydrogel composites). Gastric retention experiments in dogs showed promising results. The devices were placed in hard gelatin capsules for oral administration. Even when the dog was maintained in the fasted condition for 36 h before the experiment, the superporous hydrogel composites remained in the stomach for 2 – 3 h (after which they broke into pieces and emptied into the intestine). On the other hand, when the initial fed state was maintained for the first few hours, the superporous hydrogel composites stayed in the stomach for > 24 h. Figure 2 shows the concept of the gastric retention of such a system. The superporous hydrogel composite swells to a few hundred times of the original volume in a few minutes (Figure 2A). The gastric contraction, which initially pushes the hydrogel to the pylorus (Figure 2B – D) slips over the surface of the system (Figure 2E) and pushes the hydrogel back into the body of the stomach (Figure 2F). This process is repeated until the superporous hydrogel composite breaks into smaller pieces. Recent advances in the field led to so-called superporous hydrogel hybrids, which are prepared by adding a water-soluble or water-dispersible polymer that can be crosslinked after the superporous hydrogel is formed [78]. Examples for hybrid agents are polysaccharides, including sodium alginate, pectin, chitosan or synthetic water-soluble hydrophilic polymers, such as poly(vinyl alcohol). Compared with conventional superporous hydrogels and superporous hydrogel composites, superporous hydrogel hybrids are not easily breakable when stretched because they possess highly elastic properties in the swollen state, which can be very useful for the development of gastrointestinal devices.

3.3 Systems expanding due to gas generation

A drug-containing, carbon dioxide-generating, expandable system surrounded by a hydrophilic membrane has been patented by Sinnreich [219]. To provide an adequate control of drug release, a system containing drug-loaded pellets with extended-release surrounded by a polymer membrane (which expands reversibly due to the generation of carbon

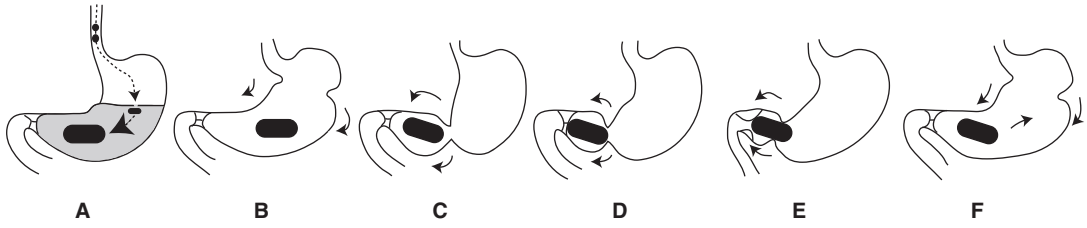

Figure 2. Concept of the gastric retention of a highly swellable, gastroretentive drug delivery system proposed by Park and colleagues. A) The device significantly swells on contact with gastric fluids (to a few hundred times of the original volume); **B – D)** the gastric contraction pushes the hydrogel to the pylorus; **E)** the gastric contraction slips over the surface of the hydrogel; and **F)** the hydrogel is pushed back into the body of the stomach. Reprinted from CHEN J, BLEVINS WE, PARK H, PARK K: Gastric retention properties of superporous hydrogel composites. *J. Control. Release* (2000) **64**:39-51 [76], copyright (2000) with permission of Elsevier.

dioxide following contact with gastric fluid), has been described by Asmussen *et al.* [220]. Intragastric balloon devices, which are deflated when introduced into the stomach via a naso-gastric tube (followed by inflation from outside the body) have been patented for the purposes of appetite control, weight reduction and drug administration [221-223]. However, this is a very inconvenient procedure, which is not suitable for frequent use.

Usually, gas generation and entrapment does not only increase the size of the drug delivery system but also decreases its density, and possibly provides floating properties, thus, presenting a combination of two principles to prolong the gastric residence time. However, the increase in size is the dominant mechanism of gastric retention of the systems discussed in this section, according to the respective authors describing the devices.

Size-increasing systems potentially present the hazard of permanent retention and could lead to serious life-threatening effects after multiple dosing. Consequently, these systems should consist of biodegradable materials or lose integrity after a desired time period. Until this happens, the systems should be sufficiently resistible in order to withstand the powerful waves from the stomach. An important shortcoming of size-increasing systems is the risk to obstruct the pylorus. A major advantage is the independence of their performance on the filling state of the stomach.

4. Density-controlled drug delivery systems

4.1 High-density systems

As pointed out above, the density of a drug delivery system is an important factor influencing the gastric residence time. High-density devices use their weight as a retention mechanism. When the density of the system is larger than that of the gastric juice, the device settles down to the bottom of the stomach, remaining located below the pylorus. However, so far, no successful approach has been described for a gastroretentive system being based only on high density. In contrast, it has been reported that such devices did not significantly extend the gastric residence time [79].

4.2 Floating systems

Floating properties of drug delivery systems can be based on several principles, including: inherent low density; low density due to swelling; and low density due to gas generation and entrapment.

4.2.1 Floating drug delivery systems with inherent low density

It is highly desirable to develop drug delivery systems that float immediately following contact with gastric fluids. This can only be achieved if the low density of the device is provided from the beginning. Compared with systems initially settling down, the risk of premature emptying from the stomach is greatly reduced. Generally, inherent low density is provided by entrapment of air (e.g., hollow chambers [80,224-227]) or by the (additional) incorporation of low-density materials, such as fatty substances or oils [228,229], or foam powder [81-83].

Desai and Bolton [84,230] developed a moulded agar gel tablet with entrapped oil and air, which replaced evaporated water following drying. Interestingly, the amount of agar needed to form the device was remarkably low (2% per tablet). In addition to density reduction, the oil may prevent the air entrapped within the gel matrix from escaping when placed in gastric fluid due to its hydrophobicity. The floating properties of this type of tablet were found to depend on the filling state of the stomach, and relatively constant saliva levels of the model drug theophylline were observed during the 24 h following administration in humans.

Watanabe *et al.* [231] described another single-unit, floating drug delivery system with inherent low density, consisting of a hollow core (empty, hard gelatin capsule or polystyrene foam or pop rice grain) coated with two layers: a subcoat of cellulose acetate phthalate, and an outer drug-containing coating of EC/hydroxypropyl methylcellulose (HPMC). This type of system is very interesting for low-dose drugs but may not be suitable if larger amounts of drug are needed for an effective therapy.

Krögel and Bodmeier [85] proposed a floating device consisting of two drug-loaded HPMC matrix tablets, which were placed within an impermeable, hollow polypropylene cylinder

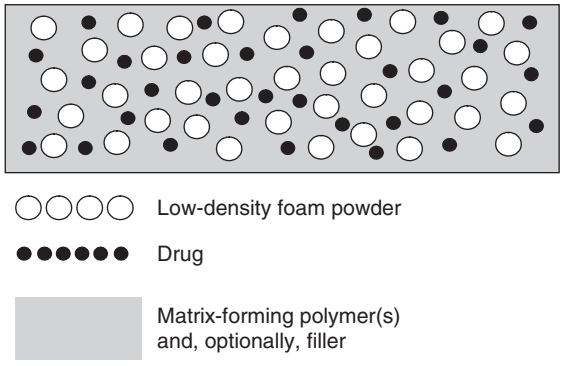

Figure 3. Schematic presentation of the structure of low-density, floating matrix tablets proposed by Streubel *et al.* Reprinted from STREUBEL A, SIEPMANN J, BODMEIER R: Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. *Eur. J. Pharm. Sci.* (2003) **18**:37-45 [81], copyright (2003) with permission of Elsevier.

(open at both ends). Each matrix tablet closes one of the ends of the cylinder so that an air-filled space is created inbetween, providing a low, total-system density. The device remains floating until at least one of the tablets has dissolved.

A floating drug delivery system that is less dense than gastric juice due to the incorporation of at least one porous structural element, such as foam or a hollow body, has been patented by Müller and Anders [232]. Different types of dosage forms are described, including tablets. In the latter case, the hollow elements are distributed either within the matrix, compressed as a second layer onto the tablet, or included as a core.

Recently, a single-unit, floating controlled-drug delivery system (tablet) was proposed, consisting of polypropylene foam powder, matrix-forming polymer(s), drug and an optional filler [81]. The structure of this type of tablet is shown schematically in Figure 3. The highly porous foam powder provides a low density and, thus, excellent *in vitro* floating behaviour of the system; all formulations kept floating for at least 8 h in 0.1 N HCl at 37°C. Different types of matrix-forming polymers were studied: HPMC, polyacrylates, sodium alginate, corn starch, carrageenan, gum guar and gum arabic. The tablets eroded on contact with the release medium, and the relative importance of drug diffusion, polymer swelling and tablet erosion for the resulting release patterns varied significantly with the type of matrix-former. Importantly, the release rate could be effectively adjusted by altering the matrix-forming polymer:foam powder ratio, initial drug loading, tablet geometry (radius and height), type of matrix-forming polymer, the use of polymer blends, and the addition of water-soluble or -insoluble fillers (such as lactose or microcrystalline cellulose). Therefore, the floating behaviour of the low-density drug delivery systems could be successfully combined with an accurate control of the drug release patterns.

Furthermore, a novel multiparticulate, gastroretentive drug delivery system based on low-density foam powder has been proposed and its performance demonstrated *in vitro* [82]. Floating microparticles consisting of polypropylene foam powder; verapamil HCl as the model drug; and Eudragit RS (Röhm Pharma GmbH), EC or poly(methyl methacrylate) (PMMA) were prepared with an oil-in-water solvent extraction/evaporation method (Figure 4A). The drug and release-rate controlling polymer were dissolved in methylene chloride. Polypropylene foam powder was then dispersed within this organic phase. The resulting suspension was subsequently emulsified into an external aqueous, polyvinyl alcohol solution (adjusted to pH 12.5) and agitated with a stirrer to allow microparticle formation. The microparticles were separated by sieving, then washed with water and dried in a desiccator. The effects of the various formulation and processing parameters on the internal and external particle morphology, drug loading, *in vitro* floating behaviour, *in vitro* drug-release kinetics, particle-size distribution, and physical state of the incorporated drug were studied. The microparticles were irregular in shape and highly porous. The drug encapsulation efficiency was high and almost independent of the theoretical loading. Encapsulation efficiencies that were close to 100% could be achieved by varying either the amount of ingredients:volume of the organic-phase ratio or the relative amount of Eudragit RS/EC/PMMA. In all cases, good *in vitro* floating behaviour was observed. The release rate of the drug increased with raising drug loading and with decreasing Eudragit RS/EC/PMMA contents. The type of polymer that was used significantly affected the resulting drug-release rate, which increased in the following rank order: PMMA < EC < Eudragit RS. Importantly, a broad spectrum of release patterns could be obtained with the investigated formulations. The size of the microparticles was found to be almost independent of the drug loading, but strongly depended on the relative amount of Eudragit RS/EC/PMMA. Differential scanning calorimetry and X-ray measurements showed that the drug was partly dissolved, and partly in the amorphous form distributed throughout the system.

Further studies focused on the development of a new preparation method for this type of low-density, foam-based, floating microparticles and on the demonstration of the systems' performance *in vitro* [83]. Major advantages of a suggested novel preparation technique include short processing times, no exposure of the ingredients to high temperatures, the possibility to avoid toxic organic solvents, and high encapsulation efficiencies (close to 100%). Floating microparticles consisting of polypropylene foam powder, model drug (chlorphenamine maleate, diltiazem HCl, theophylline or verapamil HCl), and a second polymer (Eudragit RS or PMMA) were prepared by soaking the microporous foam particles with an organic solution of the drug and polymer, and subsequent drying (Figure 4B). The effects of various formulation and processing parameters on the resulting *in vitro* floating behaviour, internal and external particle morphology, drug loading, *in vitro* drug release and physical state of the incorporated drug were studied. Good *in vitro*

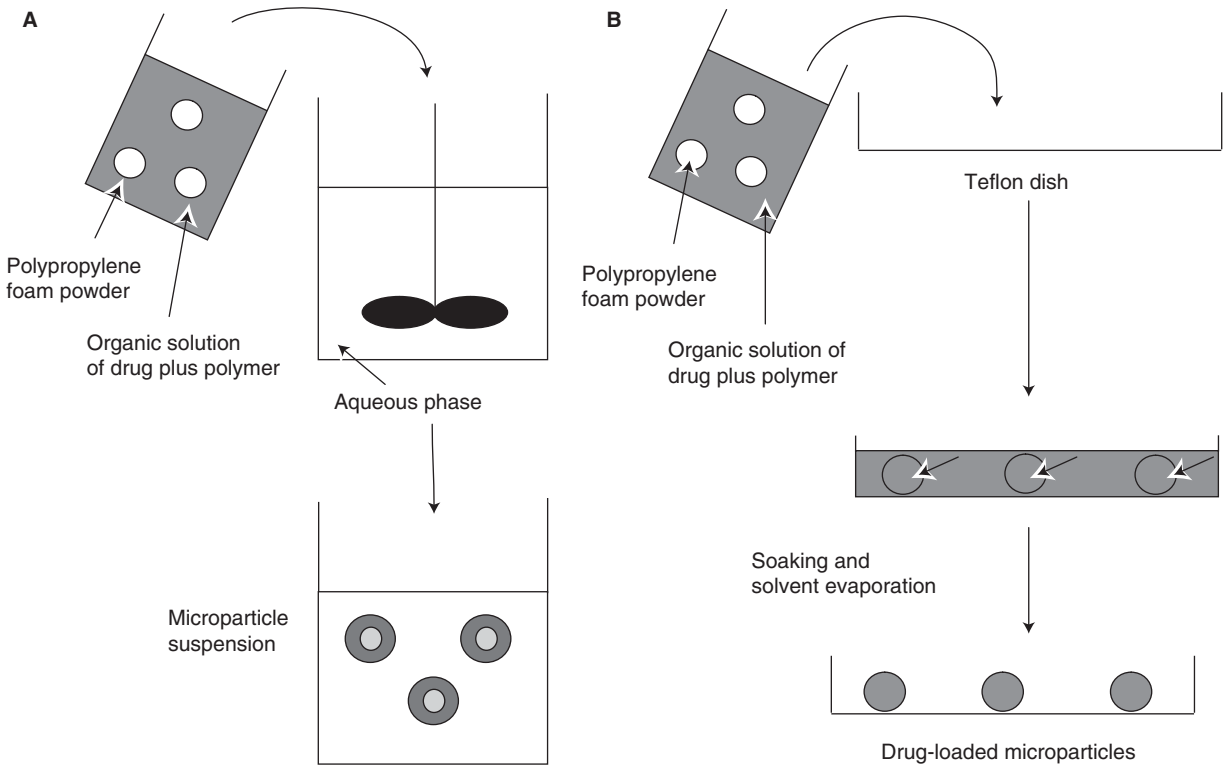

Figure 4. Schematic presentation of the preparation of floating microparticles based on low density foam powder, using: A) a solvent evaporation method; B) a soaking method. Reprinted from [86].

floating behaviour was observed in most cases, and a broad variety of drug release patterns could be achieved by varying the drug loading and type of second polymer. In addition, the low-density microparticles could be compressed into rapidly disintegrating tablets, providing an easily administrable oral dosage form [83].

Hollow microspheres (microballoons) consisting of Eudragit S (an enteric polymer) containing the drug in the polymeric shell were developed by Kawashima *et al.* [87-89]. The preparation procedure and mechanism of microballoon formation is schematically illustrated in Figure 5. A solution of polymer and drug in ethanol/methylene chloride is poured into an agitated aqueous solution of polyvinyl alcohol. The ethanol rapidly partitions into the external aqueous phase and the polymer precipitates around the methylene chloride droplets. The subsequent evaporation of the entrapped methylene chloride leads to the formation of internal cavities within the microparticles. However, according to Lee *et al.* [90], many drugs are not released in significant amounts from this type of microparticles at the pH of gastric fluids. Modifications of this system consisted of the addition of nonvolatile oil to the dispersed phase [91] or the use of Eudragit S/RL mixtures [92]. The group of Kawashima also prepared hollow microspheres using mixtures of Eudragit S and other hydrophilic or hydrophobic polymers (such as Eudragit L [Röhm Pharma GmbH], hydroxypropyl methylcellulose phthalate, HPMC or EC) [93]. The incorporation of HPMC within the outer shell showed promising results concerning the control of drug release from the system at the pH of gastric fluids. With increasing HPMC contents the amount of riboflavin released also increased; however, the floating properties of the microspheres decreased. The performance of these riboflavin-containing microballoons was also studied *in vivo* [94,95]. After oral administration to healthy volunteers, the intra-gastric behaviour was investigated by γ-scintigraphy and the urinary excretion of riboflavin was followed. In the fed state, microballoons were retained in the stomach for up to 5 h (Figure 6). In this experiment, each volunteer was given an aqueous solution of indium-111 chloride prior to administration of ^{99m}Tc-labelled samples for the purpose of outlining the stomach, and a measure of inherent gastric emptying of liquid. Importantly, the bioavailability of riboflavin was significantly higher compared with a non-floating control formulation. Interestingly, microspheres with good floating properties but low *in vitro* drug-release rates showed lower urinary excretion of riboflavin in the time period of 4 – 8 h after dosing, compared with microspheres with worse floating properties and high *in vitro* drug release rates. Thus, it is important to select an appropriate balance between the floating properties and drug-release rates with this type of system.

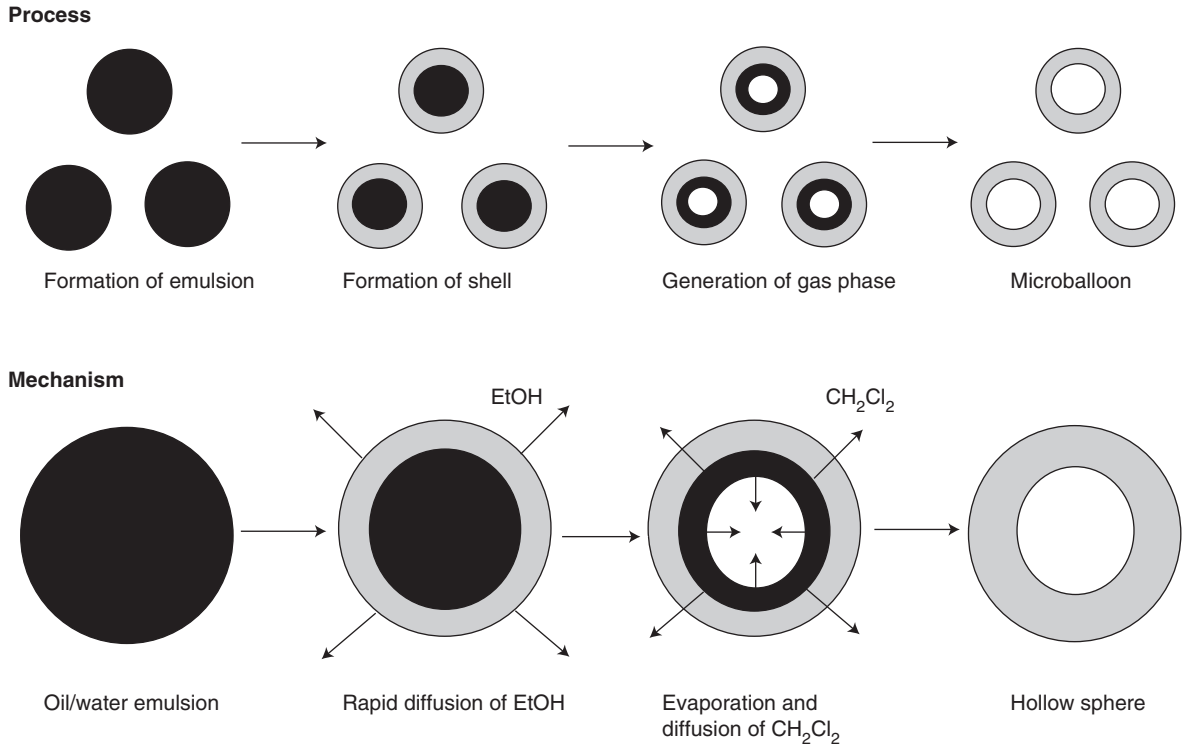

Figure 5. Preparation procedure (emulsion-solvent diffusion method) and mechanism of microballoon formation proposed by Kawashima *et al.* Reprinted from KAWASHIMA Y, NIWA T, TAKEUCHI H, HINO T, ITO Y: Hollow microspheres for use as a floating controlled drug delivery system in the stomach. *J. Pharm. Sci.* (1992) **81**:135-140 [88] with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

Another method for the preparation of hollow microspheres has been reported by Stithit *et al.* [96], which is based on a modified solvent evaporation method. Theophylline powder is dispersed into a solution of cellulose acetate butyrate and Eudragit RL 100 (1:1) in acetone. This dispersion is pressurised under carbon dioxide gas, which dissolves and forms bubbles following the release of pressure. Immediately after the onset of bubble formation, the system is emulsified into an external oil phase. Some of the generated carbon dioxide bubbles are entrapped within the dispersed drug–polymer droplets and lead to the formation of internal cavities within the hardened microspheres.

Thanoo *et al.* [97] prepared hollow polycarbonate microspheres using a solvent evaporation technique, which are capable of floating on the gastric fluid. A solution of the polymer in methylene chloride was mixed with micronised drug and introduced as a pasty mass into an outer aqueous phase containing sodium chloride, polyvinyl alcohol and methanol. High-drug loadings (> 50%) were achieved by this process. Recently, piroxicam was incorporated into this type of hollow polycarbonate microspheres with encapsulation efficiencies > 95% [98]. *In vitro* drug release in simulated gastric fluid showed no significant burst effect. The system was also evaluated *in vivo* in rabbits and was found to provide sustained drug delivery during prolonged time periods, with an increased bioavailability compared with the free drug.

Another multiple-unit gastroretentive drug delivery system containing air compartments was described by Iannuccelli *et al.* [99,100]. In this system, each single unit consists of a calcium alginate core, which is separated by an air compartment from a calcium alginate or calcium alginate/polyvinyl alcohol membrane. As shown in Figure 7, the air compartment is formed during a drying step, which causes the shrinkage of the hydrated core. Good *in vitro* and *in vivo* floating behaviour of drug-free systems was demonstrated. Furosemide was incorporated into the units [101]; however, only 20% of the dose was released after 8 h. In order to optimise the *in vitro* drug-release patterns, a solid dispersion of furosemide/polyvinylpyrrolidone was prepared by dissolving both components in methanol and subsequent solvent removal. Loading both the core and the membrane of the units with this solid dispersion meant that more adequate drug release rates could be obtained (~ 65% furosemide was released after 8 h). Furthermore, the release characteristics and pharmacokinetics of riboflavin (exhibiting an absorption window in the upper small intestine) administered with this type of drug delivery system were monitored, and the effects of different feeding conditions before and after dosing on the urinary excretion of the

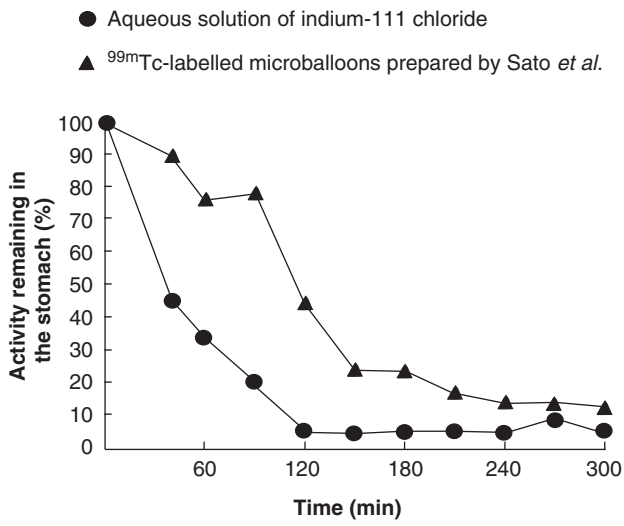

Figure 6. Gastric emptying profiles in a human volunteer (fed state). Reprinted from SATO Y, KAWASHIMA Y, TAKEUCHI H, YAMAMOTO H, FUJIBAYASHI Y: Pharmacoscintigraphic evaluation of riboflavin-containing microballoons for a floating controlled drug delivery system in healthy humans. *J. Control. Release* (2004) **98**:75-85 [94], copyright (2004), with permission of Elsevier.

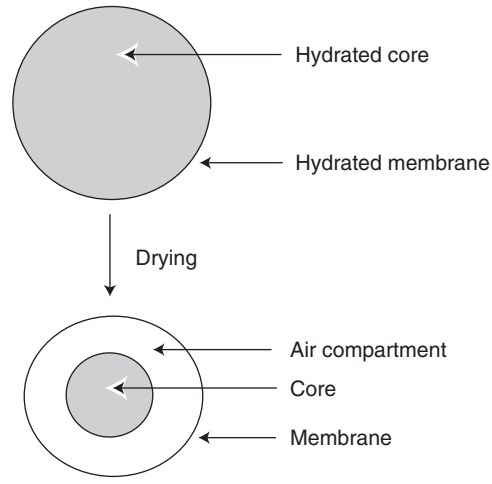

Figure 7. Schematic presentation of the air compartment formation in multiple unit gastroretentive drug delivery systems proposed by Iannuccelli *et al.* Reprinted from IANNUCCELLI V, COPPI G, BERNABEI MT, CAMERONI R: Air compartment multiple-unit system for prolonged gastric residence. Part I. Formulation study. *Int. J. Pharm.* (1998) **174**:47-54 [99], copyright (1998), with permission of Elsevier.

drug were investigated [102]. As expected, increased drug bioavailabilities were obtained when prolonging the gastric residence time. Dosing after a light or a heavy meal, or feeding after dosing, enhanced the urinary excretion of riboflavin.

Another type of bead formulation containing air compartments was described by Bulgarelli *et al.* [103]. An aqueous solution of casein and gelatin was added to an outer mineral oil phase and stirred with a paddle stirrer. Foam was developed and stabilised by the emulsifying properties of casein. The dispersed phase was solidified by cooling, leading to air bubble incorporation and the formation of large holes in the beads.

Talukder and Fassihi [104] prepared beads of low methoxylated pectin and, optionally, sodium alginate crosslinked with calcium chloride. The floating properties of the devices strongly depended on the subsequent drying process. Oven-dried beads did not float, whereas freeze-dried beads remained floating for > 12 h in hydrochloride buffer pH 1.5 due to the presence of air-filled hollow spaces within the system.

4.2.2 Floating drug delivery systems with low density due to swelling

A floating single-unit dosage form with sustained drug release consisting of a capsule, which contains a mixture of drug and hydrocolloids, has been described by Sheth and Tossounian [233]. Following contact with gastric fluid, the capsule shell dissolves and a mucous body with a bulk density of < 1 is formed. Based on this principle, pharmaceutical products have been developed containing L-DOPA, combined with a decarboxylase inhibitor [234] and diazepam [235]. A comparative study of the properties of different polymers that could be useful for the preparation of floating capsules has been carried out by Dorozynski *et al.* [105]. The floating properties of the dosage forms depended on the type of polymer used. Capsules filled with chitosans showed the lowest densities; the highest ones were observed with sodium alginate-containing capsules. The maximum floating force for capsules (size 0) ranged from 26.7 (sodium alginate) to 64.7 mN (chitosan).

In addition, floating tablets with sustained release containing a mixture of drug and hydrocolloids and remaining in the stomach for an extended period of time, have been described [236,237]. Matrix tablets based on HPMC K4M have been developed by Baumgartner *et al.* [106]. Following contact with gastric fluid, the systems take up water and swell. As the increase in volume is more important than the increase in mass during swelling, the densities of these devices decrease, acquiring a value of < 1. Thus, after a certain lag time the systems start to float. The influence of several processing and formulation parameters on the floating properties of this type of matrix tablet has been studied by different research groups [107-110]. Reduced floating lag times could be provided by decreasing the compression forces (thus, increasing tablet porosities), increasing polymer molecular weights, and increasing particle sizes of the matrix-forming polymer. Floating mini-tablets based on hydrophilic cellulosic polymers were prepared by Rouge *et al.* [111]. However, these tablets (which were filled into gelatin capsules) tended to stick together during the dissolution process. To prevent the tablet sticking, either a coating (with the flexible polymer Eudragit NE 30D) or an antiadhesive filler was added.

A glycerol monooleate (GMO) matrix was recently proposed as a gastroretentive carrier system [112]. The devices were prepared by melting GMO at 55°C in a water bath, adding the drug under stirring and pouring the molten mass into cylindrical moulds with an inner diameter of 8.5 mm. The GMO matrices significantly swelled in water and the swollen masses floated at the surface after a certain lag time.

4.2.3 *Floating drug delivery systems with low density due to gas generation*

A further interesting approach to provide low-density, floating drug delivery systems is based on the formation of carbon dioxide within the device following contact with body fluids. For example, multi-layer matrix tablets have been proposed containing an effervescent layer loaded with carbonate and optionally citric acid [113-115,238]. After contact with acidic aqueous media, carbon dioxide is generated and entrapped within the gelling hydrocolloid, causing the system to float. In addition, capsules containing such an effervescent mixture have been prepared and the effects of different formulation variables on drug release and floating behaviour were studied [116]. HPMC of different viscosity grades and Carbopol 934P were used as hydrocolloids. It was found that the HPMC viscosity, the presence of Carbopol and the polymer–polymer interactions had significant impact on the release and floating properties of the delivery systems.

Timmermans and Moës developed an interesting *in vitro* method to measure the floating forces of dosage forms, considering their weight and volume variations after immersion into a fluid [117,118]. With the proposed method, resultant weight versus time curves were obtained, providing information about the stability and durability of the floating properties. The floating capabilities of different matrix systems based on swellable polymers (including gas-generating systems) were quantified [119]. However, long-term floating behaviour was not observed with any of the investigated formulations.

Floating mini-tablets based on HPMC and sodium bicarbonate as the gas generating agent have been developed by Rouge *et al.* [120]. The floating properties of these systems containing either piretanide or atenolol as model drugs could be improved by introducing a wet granulation step. The generated carbon dioxide was entrapped for longer time periods within the tablet matrix when the latter was prepared via granulation compared with direct compression. The observed floating lag times ranged from 1 to 27 min, the floating periods partially exceeded 6 h.

A multiple-unit, oral, floating dosage form that generates carbon dioxide was developed by Ichikawa *et al.* [121,239]. This system has a core-shell structure and the sustained-release core is coated with two different layers: an inner effervescent layer containing both sodium bicarbonate and tartaric acid; and an outer layer of a swellable membrane containing mainly polyvinyl acetate and shellac (Figure 8). Following contact with aqueous media, a balloon-like device is formed due to the generation of carbon dioxide in the effervescent layer and swelling of the outer layer. This very interesting system showed excellent floating abilities. All units floated within ~ 10 min and ~ 80% remained floating over a period of 5 h, irrespective of the pH and viscosity of the release medium.

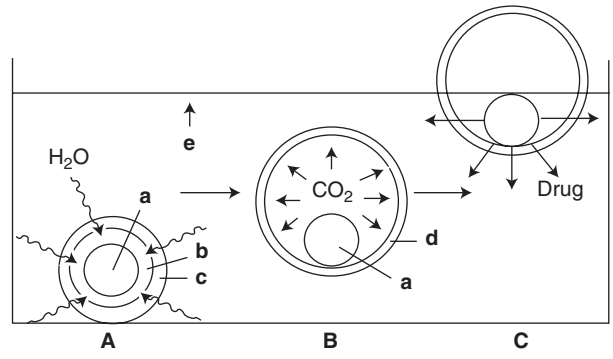

Figure 8. Stages of the floating mechanism of a multiple-unit, oral dosage form described by Ichikawa *et al*.
A) Penetration of water into the device; **B)** generation of carbon dioxide and floating; and **C)** dissolution of the drug.
a) Conventional sustained release core; **b)** effervescent layer; **c)** swellable layer; **d)** expanded swellable membrane layer; **e)** water (37°C) surface in the beaker. Reprinted from ICHIKAWA M, WATANABE S, MIYAKE Y: A new multiple-unit oral floating dosage system. I: Preparation and *in vitro* evaluation of floating and sustained-release characteristics. *J. Pharm. Sci.* (1991) **80**:1062-1066 [121] with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

Another effervescent gastroretentive formulation, which is based on ion-exchange resins has been prepared by Atyabi *et al.* [122,123]. Resin particles are loaded with bicarbonate and coated with a semipermeable membrane. Following exposure to gastric media, exchange of bicarbonate and chloride ions takes place and leads to the formation of carbon dioxide. The gas is trapped within the membrane, causing the particles to float.

Floating minicapsules (0.1 – 2.0 mm in diameter), consisting of a sodium bicarbonate core, which is coated with an inner HPMC layer and an outer pepstatin layer, were developed by Umezawa [240]. On contact with gastric acid, carbon dioxide is generated within the core causing the particles to float. Thus, the release and action of pepstatin within the stomach could be prolonged, and the pepsin activity in patients being treated for gastric and duodenal ulcers was suppressed for prolonged time periods.

Another mechanism of gas generation was described in several patents [241-244]. Gases with a boiling point < 37°C (e.g., cyclopentane, diethyl ether) can be incorporated in solidified or liquefied form into the systems. At physiological temperatures, they evaporate and inflate the device. However, this approach may only be of theoretical interest. Gas removal from these systems and manufacturing of the complex devices may cause significant difficulties.

Generally, effervescent systems suffer from the disadvantage not to float immediately after swallowing because the process of gas generation takes some time. Therefore, they could be cleared from the stomach before becoming effective.

The performance of low-density, floating drug delivery systems is strongly dependent on the filling state of the stomach. Nevertheless, this approach can successfully prolong the gastric retention time [124] and has already led to the production of pharmaceutical products, which are commercially available on the market [125].

5. Drug delivery systems combining different concepts

In practice, various systems combine different gastroretentive concepts, such as the gas-generating devices, which increase in size and float due to their low density (as described above). The concepts of floating and bioadhesion to achieve gastroretention have been combined in tablets consisting of blends of HPMC and Carbopol [126]. Systems loaded with 4 – 5% drug (captopril) were studied. The observed floating behaviour strongly depended on the hardness of the tablets. Only at the lowest level (2 kg/cm^2) the devices floated immediately and kept floating for up to 24 h. At 4 kg/cm^2, the tablets sank for 3 – 4 min before coming up to the surface (and then also remained floating for up to 24 h), whereas at 8 kg/cm^2 no floating was observed at all. Interestingly, this type of tablets, consisting of HPMC-Carbopol blends, had been studied earlier but not in the context of gastroretentive drug delivery [127,128]. The effects of several formulation parameters and of the pH of the release medium on the resulting drug-release kinetics had been investigated. The total amount of polymer was identified to be one of the major factors controlling the release rate of propranolol HCl. Importantly, the pH of the release medium was found to strongly affect the underlying mass transport mechanisms. At pH 1.2, HPMC predominantly controlled the release rate of the drug, whereas at higher pH values, Carbopol became ionised, and interacted with propranolol HCl. Furthermore, the interaction of the two polymers significantly depended on the pH of the release medium.

Another approach, combining the concepts of floating and bioadhesion to provide gastric retention, was described by Jiménez-Castellanos *et al.* [129]. Tablets containing sotalol HCl, sodium carboxymethyl cellulose (as the bioadhesive polymer), hydroxypropyl cellulose (as the matrix-forming polymer) and carbonate (as the gas generator) were prepared. Unfortunately, the observed floating lag times were > 20 min for the investigated tablets, and adhesion seemed to be superior at high pH, compared with low pH.

6. Expert opinion

A controlled drug delivery system with prolonged residence time in the stomach can be of great practical importance for drugs, which are locally active in the stomach; have an absorption window in the stomach or in the upper small intestine; are unstable in the intestinal or colonic environment; or exhibit low solubility at high pH. In these cases, an adequate control of the gastric-residence time combined with time-controlled drug release can significantly improve the efficiency of a pharmacotherapy.

Bioadhesive, size-increasing and floating drug delivery systems show the most promising potential to achieve this goal. The major challenge for bioadhesive systems is the high turnover rate of the gastric mucus. An advantage of mucoadhesive dosage forms is the intimate contact with the mucosa in the stomach, leading to short pathways for locally acting drugs. Combinations of different gastroretentive concepts, such as bioadhesion and low-density floating can be expected to be particularly promising. Recent improvements in the field of size-increasing drug delivery systems resulted in devices that can be easily swallowed, but that rapidly increase in size once they reach the stomach, assuring prolonged gastric-residence times. Importantly, their performance is independent of the filling state of the stomach and, after predetermined time intervals, they break into smaller pieces, guaranteeing their clearance. In contrast, the performance of low-density, floating drug delivery systems is dependent on the filling state of the stomach.

In conclusion, very promising *in vitro* and *in vivo* results have been reported so far with very different types of gastroretentive drug delivery systems. In the future, they can be expected to become of increasing importance, allowing the efficiencies of various types of medical treatments to be improved. The focus will probably be on multiple unit systems, as they permit the reduction of the risk of all-or-nothing effects related with single-unit dosage forms.

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