Buoyancy-Generating Agents for Stomach-Specific Drug Delivery: An Overview with Special Emphasis on Floating Behavior

Rania A. H. Ishak

Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Ain Shams University, Monazamet El Wehda El Afrikeya street, Abbassiah, Cairo, Egypt.

ABSTRACT - Gastric retentive drug delivery provides a promising technology exhibiting an extended gastric residence and a drug release independent of patient related variables. It is usually useful in improving local gastric treatment as well as overcoming drug-related problems .i.e. drugs having narrow absorption window, short half-life or low intestinal solubility. Buoyancy is considered one of the most promising approaches for gastro-retention of dosage forms. Floating drug delivery systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach causing an increase in gastric residence time. The buoyancy of these systems is attained by the aid of substances responsible to generate the low density. Various agents with different mechanisms were adopted either gas-generating agents, air entrapping swellable polymers, inherent low density substances, porous excipients, hollow/porous particles inducing preparation techniques or sublimating agents. Therefore, this review gives an exclusive descriptive classification of the different categories of these buoyancy-generating agents while representing the related research works. An overview is also conducted to describe relevant techniques assessing the floating behavior of such dosage forms either in vitro or in vivo. Finally, a collection representing FDA-approved floating pharmaceutical products is adopted with emphasis on the buoyancy-generating agent type used in each product.

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INTRODUCTION

The stomach is the most proximal organ of the gastro-intestinal (GI) tract (GIT) after the oesophagus. It has several functions; temporary storage of food input, mechanical breakdown of food into smaller particles; chemical digestion with breakdown of proteins and regulation of output of chyme into the duodenum (1).

Gastric emptying results from the net effects of propulsive forces within the stomach and the resistance to flow offered by the pyloric sphincter (2). Under fasting conditions, the GI motility is associated with some cyclic contractile events known as migrating myoelectric complex (MMC) that occurs every 1.5 to 2 h. Therefore; the gastric residence time (GRT) of any undigested material can be expected to be short. However, in the fed state, the cycle MMC is disrupted and delayed causing a prolongation in GRT (3).

After ingestion, liquids are rapidly distributed throughout the entire stomach. They empty from the stomach according to first-order kinetics; i.e., proportional to the volume present in the stomach. The gastric emptying rate of solids shows a biphasic pattern: a lag phase during which little emptying occurs, followed by a linear emptying phase during which solid particles empty from the stomach by mainly zero-order kinetics, that is, independent of gastric volume (2, 4). The stomach empties solids completely over approximately 3 to 4 h (5). Therefore the speed of emptying liquids, or contents consisting of smaller particles, is faster than that of solids.

The chemical composition of the chyme entering the duodenum also affects the rate of gastric emptying. If the chyme is too acidic, fatty or proteinaeous, gastric emptying is delayed (1).

Gastric retentive drug delivery (GRDD) provides a promising technology exhibiting an extended GI residence and a drug release independent of patient related variables (6). It is usually useful in overcoming drug-related problems .i.e. drugs having narrow absorption window, short half-life or low intestinal solubility (7). Moreover, this delivery type has the tendency to maximize drug concentrations within gastric mucosa for better local treatment.

Corresponding Author - Rania A. H. Ishak; Faculty of Pharmacy, Ain Shams University, Monazamet El Wehda El Afrikeya street, Abbassiah, Cairo, Egypt. raniaaziz@pharma.asu.edu.eg

There are three main gastro-retention approaches (7): mucoadhesion, where the dosage form adheres to the stomach walls (8-10); expansion, where the dosage form becomes too large to pass through the pyloric sphincter (11, 12); and floatation, where the dosage form floats on the stomach contents due to its low density (13-17).

However, the mucoadhesive drug delivery systems suffer from inconsistent and unpredictable gastric transit time due to continuous mucus turnover (18), in addition to the inherent risk of esophageal adherence resulting in drug-induced injuries (19). On the other hand, the gastro-retention of expandable dosage forms is enhanced by the combination of its substantial dimensions with the high rigidity to withstand the peristalsis and mechanical contractility of the stomach. These systems are sometimes referred to plug type systems because they may clog the pyloric sphincter preventing the exit of stomach contents (20).

Floating drug delivery systems (FDDS) have a bulk density lower than that of gastric fluids ($\rho \approx 1$ g/cm^3) and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time causing an increase in GRT (6). The buoyancy of these dosage forms is obtained by the inclusion of substances or agents responsible to generate the system low density. Therefore, this review gives an exclusive detailed description of the different types of these buoyancy-generating agents with presenting the related formulation approaches. Moreover, a report is conducted to illuminate different techniques studying the floating behavior of such buoyant dosage forms either *in vitro* or *in vivo*. An overview is also presented summarizing the buoyancy-generating agents in FDA-approved products that rely on floatation.

METHODS USED TO ASSESS THE FLOATING BEHAVIOR OF GASTRO-RETENTIVE DOSAGE FORMS IN VITRO

For monolithic dosage forms
Buoyancy study
The floating property of the monolithic systems is determined by visual observation. The floating lag time (FLT) and the total floating time are determined in the USP dissolution apparatus or in a beaker containing simulated gastric fluid SGF (pH 1.2, maintained at $37 \pm 0.5\ °C$). The time required for the tablet to rise to the surface of the medium and float is considered as FLT. The duration of time the dosage form remained

constantly on the surface of medium is considered as the total floating time (21, 22).

Alternating Current Biosusceptometry (ACB) is a magnetically novel method used to characterize FLT and the tablet hydration rate. It is composed of an automated ACB sensor used to acquire magnetic images of floating tablets containing ferrite as a magnetic marker (23).

Determination of the floating strength
The floating strength of developed systems is an important parameter to be measured. As the presence of food in the stomach might increase the viscosity heavily, higher floating forces is needed to increase the probability of the tablet to remain afloat, reducing food effects on tablet retention (24). The floating strength of monolithic systems is determined *in vitro* by monitoring the total vertical force *F* working on an immersed object, an experimental setup using an apparatus and methodology based on Timmermanns and Moës **(Fig. 1)** (15, 25-27). As the force *F* determines the resultant weight of the floating tablet, it may be used to quantify and thus to further characterize floating behavior. The magnitude and direction of force *F* and thus the resultant weight of the floating object is determined by the vectorial sum of the gravity (F_{grav}) and buoyancy (F_{buoy}) forces acting on the tablet as presented in Eq. 1.

$$F = F_{buoy} - F_{grav}$$
$$= d_f gV - d_s gV = (d_f - d_s)gV$$
$$= (d_f - m / V)gV \quad (Eq.\ 1)$$

where *F* is the total vertical force, *g* is the acceleration of gravity, d_f is the density of the fluid, d_s is the density of the tablet, *m* is the tablet mass and *V* is the tablet volume.

The instrument **(Fig. 1)** used to determine the floating strength of the tablet samples measures the force equivalent to *F* required to maintain the tablet totally submerged into the dissolution medium (15). According to **Fig. 1**, a test object **(2)** holder (either needle-like or mesh-like) **(6)** is connected to a metal base placed on an analytical balance **(5)** via a linear force transmitter **(1)** having a double role in maintaining the sample in the medium **(3)** and in transmitting the reaction force F of either upward or downward direction **(4)** to the balance (15). For the performance of floating strength experiments the tablets are placed in a beaker with SGF 0.1 N HCl, so that the sample holding device is covered with

dissolution medium. After the positioning of the tablet in the dissolution medium and subsequent taring of the analytical balance the sample is shifted under the sample holder. The floating strength is then determined as the weight diminution on the analytical balance over time (24).

Determination of dosage form density and porosity

For calculating the apparent densities of the tablets, their volumes and masses are determined. The height and diameter of the prepared tablets are measured using a micrometer and then used for the calculation of the volume of the cylindrical devices (28). The true density of the matrix devices is determined using a helium pycnometer (28, 29).

The porosity ε of the samples is then calculated using Eq. 2:

$$\varepsilon = 1 - (\rho_a / \rho_t) \qquad \text{(Eq. 2)}$$

where ρ_a represents the apparent density and ρ_t the true density of the dosage forms (28).

According to Sauzet et al. (29), the apparent density of the tablets ρ_a is also determined using the apparatus according to Timmermanns and Moës (15, 25-27), based on an immersed beam measuring the buoyancy force. The apparatus is made of a transparent parallelepipedic box filled with a liquid with a known density, which is SGF 0.1 N HCl pH 1.2. A thin flexible polymethyl methacrylate (PMMA) beam is immersed in the bath and is equipped with a sample holder made with metal wires **(Fig. 2)** at its free extremity while the other extremity is held firmly (29).

When the solid dosage is placed into the sample holder, it is vertically displaced by the buoyancy force and reaches a new steady state once the beam oscillations vanish. Measurement of the induced deviation in two dimensions allows the calculation of its density according to the Eq. (4) obtained by combination of the previous Eq. (1) and the following Eq. (3) (29).

The determination of displacement induced by the tablet is given by:

$$\delta_c = 4 \, (L^3 / \, Ewh^3) \, F \qquad \text{(Eq. 3)}$$

where F is the force acting on the free extremity of the beam combining eq. (1) and (3) gives a direct expression for the tablet apparent density:

$$\rho_a = \rho_f / (1 - Ewh^3\delta_c/4gL^3m_c) \quad \text{(Eq. 4)}$$

where ρ_f is the liquid density, m_c is the tablet weight, δ_c is the displacement of the beam and E is the elastic modulus of beam material (Young's modulus). The beam displacement δ_c is measured by comparing two digital photographs captured with a webcam before and after the tablet insertion into the sample holder. The Image software allowed superposing the two images, to calibrate the images and to compute the displacement **(Fig. 2)**. A millimetre scale was placed on the back wall of the tank for image calibration. A standard mass with a known volume was used as internal standard (29).
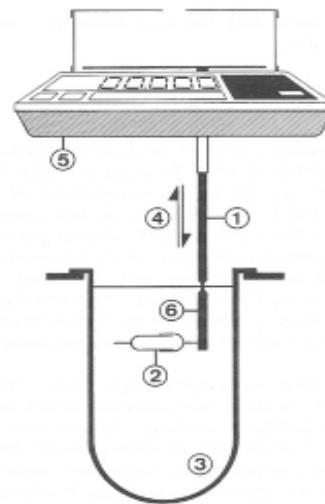

Figure. 1: Partial Schematic View of the Resultant-Weight Measuring System. *Reproduced from ref 15 with permission (15).*

Determination of the swelling index

The swelling index is often calculated in order to find out the swelling ability of the monolithic systems (tablets, capsules) based on swellable hydrophilic polymers. These polymers, upon swelling, entrap air that lowers dosage form density. For calculating the swelling index, the previously weighed dosage forms are placed in a beaker containing SGF, are removed at different time intervals and then re-weighed. The swelling index can be measured by studying its dimensional changes, weight gain, or water uptake (30). Hence swelling index is calculated by the following formula:

$$\text{Swelling index} = (W_t - W_o)/W_o \times 100 \qquad \text{(Eq. 5)}$$

where W_t is the final weight of dosage forms at time "t" and W_o is the initial weight of dosage forms (30).

Benchtop Magnetic Resonance Imaging (MRI) is also used to monitor tablet hydration and swelling characteristics of tablet samples as well as carbon dioxide (CO_2) development inside the polymer shell (24). Tablets are placed in USP dissolution apparatus with SGF 0.1 N HCl and removed for MRI measurements after predefined time intervals. Dark areas in the images are related to dry parts of the tablet or CO_2 development inside the tablet core. Brighter areas of the tablets lead to follow hydration characteristics of the developed systems (24).

For multiple-unit dosage forms
Determination of FLT and buoyancy percentage
Floating properties of the multi-unit dosage forms are studied at 37 ± 0.5 °C. A weighed amount or a specific number of the particles are soaked in a test solution either water or simulated gastric fluid (SGF, pH 1.2) with or without surfactant under stirring conditions at 50 or 100 rpm. The time taken by particles to float on the surface is determined (lag time). The percentage of floating or sinking particles is measured by visual observation (31).

On the other hand, an alternative technique is applied to measure the percentage of buoyancy. After the desired time, the layer of buoyant particles is pipetted and separated by filtration. Particles in the sinking particulate layer are also separated by filtration. Particles of both types are dried in a desiccator until constant weight. Both particle fractions are weighed and buoyancy is determined (Eq. 6) by the weight ratio of floating particles to the sum of floating and sinking particles (32-35).

$$\text{Buoyancy}(\%) = W_f / (W_f + W_s) \times 100 \quad \text{(Eq. 6)}$$

where W_f and W_s are the weights of the floating and settled particles, respectively.

Determination of particle density and porosity
The apparent particle density is determined by the projective image count method (36). Particles are placed on a glass plate. Heywood diameter and particle number are measured by an Image Processing and Analysis System. Subsequently, the apparent particle density is calculated according to Eq. (7).
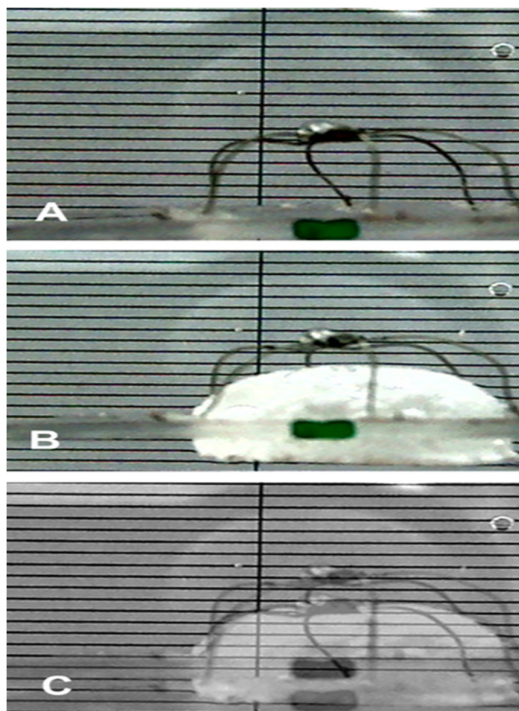

Figure. 2: Experimental Setup for the Determination of the Apparent Density A: image of the beam extremity with the sample holder. B: Due to the buoyant force of the tablet, the beam is lifted vertically. C: Difference between photographs A and B showing the displacement δc. The millimetre scale is seen in the back. *Reproduced from ref 29 with permission (29).*

Apparent particle density = W / V

$$= W / \Sigma (\pi.d^3.n / 6) \qquad (Eq.\ 7) \qquad (36)$$

where W, particles weight; V, particles volume; d, Heywood diameter; and n, number of particles. The true density and porosity of multiple-unit dosage forms are assessed using mercury porosimetry (37). The mercury intrusion data are recorded and plotted against pressure. The porosity of particles is then calculated according to Eq. (8).

$$Particles\ Porosity\ (\%) = (1 - \rho_a / \rho_t)\ X\ 100$$
(Eq. 8)

ρ_a, apparent density of particles; and ρ_t, true density of particles (37).

METHODS USED TO ASSESS THE GASTRO-RETENTION OF DOSAGE FORMS IN VIVO

X-ray radiography
The buoyancy behavior of either monolithic or multiple-unit systems is assayed *in vivo* by administering floating and non-FDDS, loaded with barium sulfate ($BaSO_4$) as radiopaque agent, to human volunteers, beagle/mongrel dogs or albino rabbits. The study is conducted under fed and fasting conditions. The location of either dosage form is then monitored in the gastric region at determined time intervals using X-ray apparatus. Both floating time and GRT of the systems are then noticed and recorded (14, 30, 38-48).

Gamma (ɤ)-scintigraphy:
Dosage forms radiolabelled with [99mTc] or [111In] are first prepared. The labeling efficiency of the process is determined by determining the radioactive counts using ascending ITLC plates. The ɤ-scintigraphy as a non-invasive technique is employed to measure the gastric transit rate with gamma camera. Gastric images of human volunteers or experimental animals using collimator are collected for about 1000 counts per second. The gamma scintigraphic imaging is started just after dosing and is carried out at specified time intervals under the dynamic planer conditions (49-62).

Indirect methods
Pharmacokinetics study
The bioavailability of some drugs as ofloxacin (63) and ciprofloxacin HCl (64) is strongly dependent on the local physiology in the GI tract and preferably is absorbed in the higher sections of the intestine. These drugs are readily soluble in the acidic environment of the stomach. In the intestine, where neutral to slightly alkaline pH conditions prevail; however, precipitation of the active compounds occurs, which adversely affects absorption in the lower sections of the intestine. Other drugs like furosemide (65), riboflavin (59, 66), ranitidine HCl (67), dipyridamole (68), famotidine HCl (69), norfloxacin (70), verapamil (71), repaglinide (61) and levodopa (62) suffer from poor bioavailability due to the presence of a narrow absorption window in the upper GIT. Therefore, the design and development of GRDDS for such drugs is beneficial. Pharmacokinetics study is performed from blood sampling estimating C_{max}, t_{max} and AUC from the observed mean drug plasma concentration against time profile. K_{el} and $t_{1/2}$ are also computed. The extent of absorption from the prepared test formulation relative to the marketed or non-floating one is calculated as the relative bioavailability. Also, drug concentrations could be determined in urine samples at scheduled time intervals following administration. Subsequently, cumulative amount of excreted drug in urine as a function of time is measured (66).

Microbiological assay
H. pylori causing peptic ulcer resides mainly in the gastric mucosa or at the interface between the mucous layer and the epithelial cells of the antral region of the stomach (72). Most antibacterial agents as amoxicillin (73), metronidazole (74), clarithromycin (75) and acetohydroxamic acid (76) have low minimum inhibitory concentrations (MIC) against *H. pylori* in culture due to the low concentration of the antibiotic reaching the bacteria under the mucosa, instability of the drug in the low pH of gastric fluid and short residence time of the antibiotic in the stomach (77). To improve the efficacy in eradicating the infection is to deliver the antibiotic locally in the stomach through FDDS (77, 78). Longer residence time will allow more of the antibiotic to penetrate through the gastric mucus layer to act on *H. pylori* (79). The efficacy of antibiotic-containing floating delivery system to eradicate *H. pylori* is assessed by microbiological assay. Animals are inoculated with *H. pylori* culture broth containing known bacterial colony forming unit (CFU) via intra-gastric gavage. Fourteen days after infection, the drug was orally administered at different doses in the form of either floating or suspension. Placebo FDDS, used as a control, are

administered in the same manner. One day after administration of the dose, the animals are killed and the stomachs are removed. Each stomach is homogenized and then plated on modified Skirrow's medium. The viable cell counts for each stomach are calculated by counting the number of colonies on the agar plates. The colonies are identified as *H. pylori* by morphology and urease activity. The number of colonies per plate is counted and expressed as log CFU per gastric wall (73-76).

Determination of the pharmacological effect
The gastro-protective effect of anti-ulcer agents as DA-6034, a new flavonoid derivative (80) or nizatidine (81), formulated in FDFs, are evaluated in experimental animals with gastric ulcers. The ulcers are induced either with biopsy forceps (80) or ethanol (81). Floating or control systems are orally administered for several days. The ulcer healing effects are evaluated using a gastric endoscope for several days after administration. Ulcer healing effects are estimated by grade ulcers from 0 to 5, where '0' indicated a normal gastric wall, '1' a scar with similar to normal gastric wall, '2' insignificant erosion with flare, '3' severe erosion with flare and swelling, '4' a gastric ulcer with a blood spot, and grade '5' a bleeding gastric ulcer (80). Additionally, the ulcer protection index could be compared to control group (81).

Pharmacodynamic study
Metformin HCl is a glucose lowering agent with narrow absorption window. The effectiveness of the antidiabetic drug containing floating formulations was evaluated *in vivo* by measuring its hypoglycemic response in both normal and diabetic albino rats (82).

The *in vivo* antiulcer property of famotidine in FDDS was investigated using pyloric ligation method. The mean volume of gastric secretion, mean pH and mean total acid for formulation and control treated rat groups were calculated (83).

Anti-tumor Activity
The anticancer drug, 5-fluorouracil (5-FU), was formulated into FDF in order to prolong GRT, target stomach cancer, and increase drug bioavailability according to Shishu et al. (84). The therapeutic efficacy of FDFs containing 5-FU was checked against benzo(α)pyrene-induced stomach tumors in albino female mice (Balb/C strain). The tumor incidence in mice with FDF was recorded and compared with the conventional tablet dosage form (84).

DIFFERENT CATEGORIES OF BUOYANCY-GENERATING AGENTS

The general structure of different floating systems using versatile buoyancy mechanisms is illustrated in a schematic diagram **(Fig. 3).**

Table 1. Summarizes the different parameters affecting the floating behavior of dosage forms based on the type of buoyancy-generating agents.

Gas-generating agents
The gas entrapped in the dosage form achieves the low density required for buoyancy. Carbonate or bicarbonate salts as sodium bicarbonate ($NaHCO_3$) and calcium carbonate ($CaCO_3$) are usually incorporated in the formulation alone or blended with organic acids like citric and tartaric acid and then dispersed in the polymeric matrix. This mixture was found to be appropriate for achieving desired buoyancy characteristics. Upon immersion, carbonate or bicarbonate ions start the reaction immediately *in vitro* with the acidic dissolution media or *in vivo* with the gastric HCl and the added organic acids, if present. This reaction generates sufficient amount of CO_2 which get entrapped and protected within the gel layer formed by hydrophilic polymer hydration. This leads to decreased density of the tablet (below 1 g/cm^3), as a result of which the tablet becomes buoyant. Furthermore, since the pH of the stomach is elevated under fed state (~3.5), citric or tartaric acid incorporated in the formulation was found to provide sufficiently acidic medium for the salts to react. This will allow the system to float independent of the pH of the medium (22, 30, 85). Based on this approach, many research works have formulated gastro-retentive dosage forms either as monolithic or multiparticulate systems. Based on GRDDS research, various factors were proven to influence the buoyancy behavior of gas-generating agents containing systems.

Factors affecting system floatation based on gas generation approach
The percent of gas-generating agents
The proportion of gas-generating agents was considered an important factor that should be adjusted to get the least possible lag time with an extended floating duration. Goole et al. (86) confirmed that FLT decreased as the proportion of effervescent agents increased. It was also reported that the gas-generating blend decreases the lag time by accelerating the hydration of the swelling
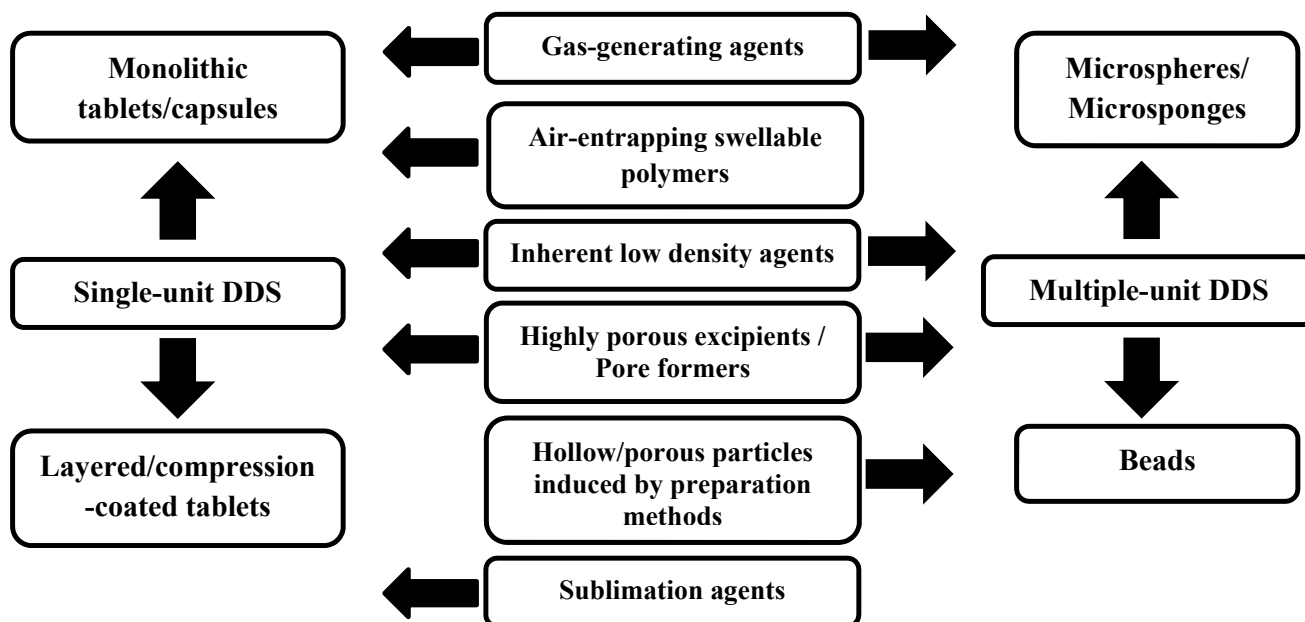
Figure. 3: Schematic diagram showing the general structure of different FDDS using versatile buoyancy mechanisms

polymer, thus allowing a higher floating duration because of the constant generation and subsequent trapping of CO_2 (87). Nama et al. (88) prepared an optimized hydrodynamically balanced system (HBS) by adjusting the weight percentage of $NaHCO_3$ used at about 8% along with hydroxypropyl methyl cellulose (HPMC) K4M polymer. The latter formula gave an *in vitro* FLT of less than 3 min with a floating duration extended for 12 h. *In vivo* X-ray radiographic studies showed the enhanced GRT of the tablet to 220 min (88). Tadros (45) also developed promising systems exhibiting excellent floating properties with the aid of either $NaHCO_3$ or $CaCO_3$ at 20% (w/w) along with HPMC K15M and Na alginate (Na alg). Abdominal X-ray imaging of formula containing $NaHCO_3$, loaded with $BaSO_4$, in six healthy volunteers revealed a mean gastric retention period of 5.5 h (45). Another floating system was prepared based on both citric acid and $NaHCO_3$ at 3.75 and 18.75% w/w , respectively, as the effervescent base, dicalcium phosphate and HPMC K15M as drug release retardants (89). The formulations were found to have FLT less than 1min.

Moreover, the gas-generating agents could be also added in a separate layer providing system floatation. Recently, tri-layered floating tablets were also prepared using polyethylene oxide (PEO) polymer with middle layer consisting of drug and polymer while outer layers consisted of polymer with $NaHCO_3$. With an increase in the amount of $NaHCO_3$, faster buoyancy was achieved due to the increased CO_2 gas formation. The optimized formula exhibited FLT of 3-4 min (90).

Based on gas generation approach, multiple-unit FDDS were also prepared. According to Choi et al. (91), the floating calcium alginate beads were prepared by ionotropic gelation of Na alg with Ca^{2+} ions, and CO_2 was developed from the reaction of $CaCO_3$ or $NaHCO_3$ with acid. The evolving gas permeated through the alginate matrix, leaving gas bubbles or pores, which provided the beads buoyancy. The effects of gas-forming agents on bead size and floating properties were investigated. As gas-forming agents increased, the size and floating properties increased. Shishu et al. (84) also demonstrated that the beads containing higher amounts of $CaCO_3$ demonstrated instantaneous, complete, and excellent floating ability over a period of 24 h.

Gellan polysaccharide was also investigated by Rajinikanth and Mishra (44, 76) preparing floating $CaCO_3$-based bead systems. $CaCO_3$ reacts with acidic medium releasing CO_2 and Ca^{2+} ions. The released CO_2 was entrapped in the gel network producing buoyant beads. Ca^{2+} ions produced either from $CaCO_3$ or $CaCl_2$ reacted with gellan producing a cross-linked three-dimensional gel network that restricted

further diffusion of CO_2 drug resulting in an extended period of floating. Increasing both $CaCO_3$ and gellan concentrations significantly reduced FLT. The control beads (without $CaCO_3$) sank uniformly in the medium. While those containing 0.5-2% $CaCO_3$ along with 0.25-1% gellan showed 71-100% floatation with 4-10 min FLT for more than 8 h in simulated gastric fluid pH 1.2 and for at least 6 h in rabbits' stomach detected by X-ray radiological method (44, 76).

Therefore, it could be concluded that increasing concentration of gas-generating agents to a certain limit reduces significantly the system FLT and extends as well buoyancy duration. While excessive addition of these agents might cause a disruption in dosage form integrity and hence complete loss of floatation capability.

The type of carbonate salts

According to Choi et al. (91), alginate floating beads containing either $CaCO_3$ or $NaHCO_3$ as gas-forming agents showed different porosity degrees, bead gel strengths and hence altered buoyancy behaviors. Application of $NaHCO_3$ significantly increased porosity and pore diameter in comparison to $CaCO_3$. Incorporation of $CaCO_3$ resulted in smoother beads of higher gel strength than those produced with $NaHCO_3$. This indicated that $CaCO_3$ is superior to $NaHCO_3$ as a gas forming agent in alginate bead preparations (91).

Furthermore, calcium pectinate gel (CaPG) beads containing different carbonate salts types, i.e., $NaHCO_3$, $CaCO_3$, K_2CO_3 or Na_2CO_3, as a gas-forming agent, showed different floating properties according to Sriamornsak et al. (92). The CaPG beads containing NaHCO3 or CaCO3 were produced instantaneously by ionotropic gelation in which intermolecular cross-links were formed between the divalent calcium ions and the negatively charged carboxyl groups of the pectin molecules. The CaPG beads containing K_2CO_3 and Na_2CO_3 could not be produced as a viscous gel was formed before extrusion through needle. Incorporation of $NaHCO_3$ resulted in porous structured beads, as $NaHCO_3$ can dissociate in neutral medium and readily produce the CO_2 gas. While the beads containing $CaCO_3$ showed a dense, non-porous structure due to the insolubility of $CaCO_3$ in neutral medium. Acidification of gelation medium by HCl increased the pores in the structure of beads containing $CaCO_3$. This was explained by dissociation potency of $CaCO_3$ in acidic medium, i.e., $CaCO_3$ dissociates to release divalent calcium cations contributing to more homogenous CaPG

bead formation and CO_2 gas that could be entrapped in the matrix gel beads (92).

The polymer type used

The choice of the polymeric matrix, needed to retain CO_2 gas generated after acid-base interaction, was found to play a role in controlling both FLT and duration. Asnaashari et al. (93) studied the effect of different polymers in preparing floating tablets. $NaHCO_3$ was added as a gas-forming agent along with HPMC, psyllium and carbopol in different concentrations as floating agents that retain the produced gas. These hydrocolloids become hydrated and form a colloid gel barrier around its surface with thickness growing by time. With increasing volume due to hydration, the system shows bulk density less than 1 g/cm^3 and then remains buoyant in the fluid. It was observed that formulae containing HPMC showed prolonged lag times for buoyancy. Adding psyllium to these formulations reduced relative lag times, and kept their proper buoyancy duration times. This could be due to psyllium intrinsic high tendency for gel formation (higher than HPMC). The study also showed that carbopol regardless of the short lag time for floating, could not prepare good buoyancy attributed to rapid hydration, gel formation and erosion rate of carbopol (93).

Moreover, Patel et al. (94) observed that the type of filler and the ratio of Gelucire 43/01, as a hydrophobic meltable binder, to HPMC K4M had significant influence on buoyancy lag time. Recently, Rao and Lakshmi (21) designed a floating system using three polymers xanthan gum, HPMC K15M and HPMC K4M, and $NaHCO_3$ as the gas-generating agent. Based on the results, tablets prepared by xanthan gum was the best formulation with an *in vitro* FLT less than 1 min and buoyancy was extended for more than 12 h. This was attributed to the swelling behavior of the prepared formulae based on the formation of hydrogel by the hydrophilic polymers used, their concentrations and molecular weights (21).

The type and level of polymeric coating

Floating drug delivery systems, consisting of gas-generating agent within the core and covered by polymeric film coat, showed variable buoyancy behaviors depending on the type and concentration of polymer in coat. Blends of a water-insoluble polymer and a hydrophilic polymer at different ratios were tried (28). The addition of soluble polymers, such as HPMC, polyethylene glycol (PEG) 6000, PEG 600, and

Kollicoat® IR, greatly increased the water uptake ability of the insoluble polymers (Eudragit® NE, RS, and RL; Surelease®; and Kollicoat® SR) and caused them to immediately initiate the effervescent reaction and float, but the hydrated films should also be impermeable to the generated CO_2 to maintain floatation and sufficiently flexible to withstand the pressure of CO_2 to avoid rupturing (95). The increased amount of a gas forming agent did not affect time to float while increasing coating level of gas-entrapped membrane increased FLT (96).

The compression pressure

Jiménez-Martínez et al. (97) showed that Metolose SH 4000 SR matrices compacted at 55 MPa float in the dissolution medium for more than 8 h while those compacted at 165 MPa float only when $NaHCO_3$ is included in the formulation due to increase in the matrix hydration volume. The matrix density was lower when compacted at 55 MPa.

The method of preparation

A study investigated the physicochemical properties of hot-melt extruded (HME) and directly-compressed tablets containing a blend of Eudragit® RS PO and $NaHCO_3$ (98). The cross-sectional morphology of the HME tablets showed a porous structure since CO_2 gas was generated due to the thermal decomposition of $NaHCO_3$ in the softened acrylic polymers at elevated temperature during the extrusion process. The HME tablets floated on the surface of the media for 24 h while directly-compressed tablets showed no buoyancy in the dissolution media (98).

Sriamornsak et al. (92) prepared CaPG beads containing carbonate salts showed different floating properties depending on the drying method. Incorporation of $NaHCO_3$ resulted in porous structured beads while the beads containing $CaCO_3$ showed the dense, non-porous structure if the beads were air-dried. Freeze-dried beads demonstrated more porous structure and hence higher floating ability than that of air-dried beads.

Combinatorial factors

Krögel and Bodmeier (125) were the first adopting a floating drug delivery system based on a reservoir system consisting of a drug-containing effervescent core and a polymeric coating. The time to flotation could be controlled by several factors; the composition (type of filler, concentration of effervescent agents), hardness of the tablet core, and the composition (type of

polymer and plasticizer) and thickness of the coating layer (125). The influence of three commonly used fillers, microcrystalline cellulose, dibasic calcium phosphate and lactose, on the floating behavior of the coated tablets was investigated. Tablets containing lactose floated earlier than tablets prepared with the inorganic filler dibasic calcium phosphate. This could be explained by the different densities. In addition, lactose has a higher water solubility and thus osmotic activity, resulting in a faster uptake of the medium into the core by diffusion through the coating. Microcrystalline cellulose, an insoluble filler with a high water uptake and disintegration capability, resulted in the rupturing of the coating and disintegration of the tablet. CO_2 did not accumulate under the coating and escaped through the ruptured films, floating was therefore not achieved. Therefore, lactose was the filler of choice. The higher amount of effervescent agent caused faster and higher CO_2 generation. However, at very high concentrations of the effervescent agents, the coating was less stable due to the increased inner pressure, and the risk of rupturing of the polymeric coating was higher. Moreover, increasing the hardness of the tablet core from 30 to 130 N resulted in an increase in the time to flotation. A lower hardness resulted in tablets with a higher porosity, which facilitated the water penetration and therefore the effervescent reaction. A polymer coating with a high elongation value and high water- and low CO_2 permeability was selected (Eudragit® RL/acetyltributyl citrate) in order to initiate the effervescent reaction and the floating process rapidly. With increasing the level of the outer polymeric coating, the floating started later due to the delayed water penetration through the thicker coating (40, 126).

Additionally, Khan et al. (127) have designed a novel floating elementary osmotic pump tablet (FEOPT). The FEOPT consisted of an osmotic core (drug, mannitol, and hydrophilic polymers) coated with a semipermeable layer (cellulose acetate) and a gas-generating gelling layer ($NaHCO_3$ with hydrophilic polymers) followed by a polymeric film (Eudragit RL 30D). The effect of formulation variables such as concentration of polymers, type of diluents, and coat thickness of semipermeable membrane was evaluated in terms of FLT and duration of floatation. All the developed FEOPT showed FLT of less than 8 min and floating duration of 24 h (127).

Air-entrapping swellable polymers
One of the approaches to formulate FDDS involves intimate mixing of drug with a gel-forming hydrocolloid. Buoyancy of the dosage form is governed by the swelling (hydration) of the hydrocolloid particles on the system surface when it contacts the gastric fluids, resulting in an increase in the bulk volume. Moreover, the presence of internal voids in the dry center (porosity) affects the system floatation. These two factors are essential for the dosage form to trap air and hence to acquire bulk density less than 1 and so remain buoyant on the gastric fluid (128). In addition, the gel structure acts as a reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier (6, 129). Among the variables affecting the floating pattern of systems containing these gel-forming hydrocolloids; the type of polymer, drug and other excipients incorporated.

Effect of polymer type on floating behavior
The most commonly used gel-forming or highly swellable polymers are cellulose type hydrocolloids, polysaccharides, and matrix-forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene (130). Alginate and HPMC were previously reported their ability to float on gastric contents and provided sustained release characteristics (99, 101). Washington et al. (131) suggested that the formulation consisting of a mixture of alginate, forms a gel of alginic acid. The gel becomes buoyant by entrapping the gas bubbles and floats on the gastric contents as a viscous layer. Furthermore, cellulose ether polymers (HPMC) have a bulk density of less than unity in gastric fluids (132, 133).

Alginate and chitosan (Cs) blends were also reported in gelation and air entrapment within the dosage form (16). The buoyancy was not affected neither by the molecular weight or degree of deacetylation of Cs added nor the variation in Cs particle size. Floating was not observed for alginate containing 5% chitin, curdlan, sodium dextran sulfate, pullulan or xylan, instead of Cs (16).

Glyceryl esters of fatty acids such as glyceryl monooleate (GMO) belong to class of polar amphiphilic lipids which swell in water and form various kinds of lyotropic liquid crystals (134). Swelling of GMO matrix system due to water uptake reduces its density and hence assists its floatation for a prolonged period of time (102).

Various grades of swellable polymers (PEO WSR 1105, WSR 301, WSR 303, WSR 60 K, WSR N80 and HPMC K4 M) were used by physical blending with the drug in varying ratios according to Ali et al. (56). From the *in vitro* buoyancy studies it was observed that PEO WSR 60K, PEO WSR 303 and HPMC K4 M containing formulations showed good buoyancy with floatation time up to 12 h. *In vivo* studies using ɤ-scintigraphy showed that the selected HBS formula remained buoyant during 5 h of study in rabbits.

A comprehensive study was conducted to investigate the effects of carrageenans and HPMC on the properties of HBS (135). Matrices based on carrageenans subjected to rapid hydration and erosion, were not able to maintain satisfactory floating properties for a sufficiently long period of time. The application of carrageenans in mixtures with HMC promoted water uptake by HBS formulations (135).

Recently, Dey et al. (100) developed a floating matrix tablet using polymer blend of xanthan gum and guar gum. The optimized formulation containing 20% (w/w) of polymer blend and 50:50 ratio of both gums was able to float more than 12 h. *In vivo* retention studies in rabbit stomach showed the gastric residence of tablet up to 6 h.

Effect of drug and additives on floating behavior
Physiochemical properties of the drug and additives such as PEG 4000, PEG 10000, and stearic acid significantly affected floatability of swellable systems according to Kumar et al. (102). It was observed that the water uptake increases with increase in the loading of polar drug (Chlorpheniramine maleate) and decreases with non-polar drug (Diazepam). Buoyancy lag time was found to increase with increase in stearic acid and PEG amount. Molecular weight of PEG did not significantly affect FLT. The increase in lag time was more in case of stearic acid due to reduction in water uptake caused by hydrophobic nature of stearic acid and hence reduced matrix swelling tendency (102). The effect of PEG on matrix buoyancy could be attributed to the following reasons: (1) at low concentration, PEG as a hydrophilic excipient increases water uptake and forms a porous, non-transparent, low-density matrix, (2) while at higher concentration, erosion of the matrix occurred from the surface, and even breaking of the matrix into small aggregates. The buoyancy is favored by increase in the porosity, whereas opposed by the increase in viscosity of aqueous filled channels. Similar effect was

observed with incorporation of PEG 10000, but the extent of floatation at lower concentrations was comparatively less. It might be attributed to the high molecular weight and less polarity of PEG 10000 yielding the formation of less spongy matrices (102).

Inherent low density agents
Among the agents used to impart the dosage form a low bulk density are the substances characterized by an inherent low density property. The concentration of such substances plays an important factor in buoyancy of the drug delivery system. Murata et al. (16) was among the leading incorporating a low density excipient in a multi-unit floating system. The beads are formed by the ionotropic gelation between alginate and calcium pantothenate in the presence of a vegetable oil (ALGO). The concentration of oil as low density agent used was proven to influence the time to float. The oil-free beads sank in water, physiological saline or HCl solution mimicking gastric juice. However, the ALGO containing 30% olive oil floated in these solutions. ALGO containing 10 or 20% oil firstly sank in water then gradually floated. ALGO containing 40% olive oil was not used because the oil began to leak from the beads at this high concentration (16).

Sriamornsak et al. (104, 105) adopted an emulsion-gelation method to prepare oil-entrapped calcium pectinate gel (EMG) beads capable of floating in the gastric condition. The blank and loaded gel beads containing edible oil were prepared by either being gently mixed or homogenized an oil phase and a water phase containing pectin, and then extruded into $CaCl_2$ solution with gentle agitation at room temperature. Pectin helped to emulsify the mixture of water and oil phases during the homogenization process. The prepared emulsion containing pectin was gelled by the action of calcium. The effect of selected factors, such as type of oil (e.g., light mineral, olive, sunflower, peppermint, sesame, rice, soybean and corn oil), percentage of oil (10-30%), and type of pectin based on the degree of esterification on beads morphology and floating properties was investigated. The EMG beads were more spherical and exhibited a smoother surface than conventional calcium pectinate beads. The conventional calcium pectinate beads (with no drug) made of low methoxy pectin did not float in SGF. In contrast, if a sufficient amount of oil was added (i.e. 10% mineral oil, 20% olive oil or peppermint oil), the EMG beads floated immediately and remained floating for 24 h

attributed to the low relative densities of the oils. Drug-loaded EMG beads, containing the same percentage of the latter oils, showed a delay in floatation compared to unloaded beads. However, the beads were then afloat after the drug was released from the beads. The EMG beads treated with glutaraldehyde and contained additives such as PEG 10000, Eudragit® L 100 or glyceryl monostearate showed good *in vitro* floating behavior in SGF (104, 105). Liquid paraffin-entrapped alginate-based floating system was also prepared by Malakar et al. (103) through the same latter method for gastro-retentive delivery. The effect of process variables; drug to polymer ratio by weight, and liquid paraffin to water ratio by volume on beads density and floatation was optimized. The optimized beads showed density of 0.90 g/cm³, with FLT of 8.45 min and floated well over 12 h in simulated gastric fluid (pH 1.2) (103).

Some researchers combined commonly used polysaccharides; either alginate and pectin (136) or alginate and casein (137) in the same oil-entrapped floating microbeads prepared by emulsion gelation method (136, 137). Other authors used a mixture of low density excipients such as isopropyl myristate (oil) and Gelucire® 43/01 (lipid) incorporating in alginate beads (138).

On the other hand, Ishak et al. (74) prepared alginate beads by the aid of the known hydrophobic lubricant magnesium stearate via the ionotropic gelation method. The bead formula containing 5% magnesium stearate showed immediate buoyancy (74).

Furthermore, a developed low-density tablet form using a hydrophobic dusty powder silicon dioxide (Aerosil R972) was prepared by Sauzet et al. (29). The increase of active ingredient percentage led to an increase of the tablet density. While, an increase of Aerosil R972 percentage had a strong influence on decreasing system density (29).

A recently research work adopted by Eberle *et al*. (106) incorporated functionalized $CaCO_3$ (FCC) in a floating gastroretentive drug delivery system (GRDDS). The characteristically low apparent density of the excipient (approx. 0.6 g/cm³) in addition to its inherent high porosity enabled a mechanism of floatation. In SGF, the FCC-based tablets showed instant floatation.

Highly porous excipients / Pore formers
The use of highly porous ingredients in dosage forms was investigated to impart a low density hence floability suitable for gastroretention for the

systems that contain. The addition of pore forming agents was also reported to give the same effect.

In this context, Bulgareli et al. (37) prepared casein–gelatin beads relying on casein emulsifying properties that cause air bubble incorporation and the formation of large pores in the beads. They have been prepared by emulsification extraction method and cross-linked with d,l-glyceraldehyde in an acetone–water mixture 3:1 (v/v). Casein was considered suitable for the formation of an air reservoir for FDDS (37).

Streubel et al. (108) was the first using the highly porous polypropylene foam powder (Accurel® MP 1002 and MP 1000) in floating polymeric microparticles (MPs). The MPs were irregular in shape and highly porous. Good *in vitro* floating behavior was observed as more than 83% of the particles kept floating for at least 8 h. The polymer partially covers the pores and entraps air within the system. Upon exposure to aqueous media the entrapped air is only slowly removed from the system leading to extended floating times (108). Furthermore, the same authors employed the highly porous foam powder in monolithic FDDS with matrix-forming polymers such as HPMC, polyacrylates, Na alg, corn starch, carrageenan, gum guar and gum arabic. All foam powder-containing tablets remained floating for at least 8 h in 0.1 N HCl at 37 °C (107).

Calcium silicate (Florite RE®) as a porous carrier was also used to develop floating microspheres (111). The MPs were prepared by emulsion solvent diffusion technique and Eudragit S as polymer. The MPs were found to be regular in shape and highly porous. All the calcium silicate-based formulations showed good floating ability (84 ± 6.0%). More than 80% of the particles kept floating for at least 10 h (111). Other groups of researchers developed similar floating multiparticulate systems using porous calcium silicate (109, 110).

Furthermore, polyethylene glycol (PEG) is used as pore forming agent that induces buoyancy (112). Floating MPs were prepared by novel solvent evaporation-matrix erosion method using ethyl cellulose (EC) and polyethylene glycol (PEG) blend. When the microspheres are dispersed in SGF, due to high water solubility, PEG goes into solution forming pores on microspheres due to matrix erosion. This phenomenon makes the microspheres to float. The formulated microspheres could float within 5–10 min depending upon the % of PEG present in the microspheres. As the % of PEG increases, floatation time reduces. EC MPs prepared with 20–33.3% of PEG showed floatation for 10 h. The presence of pores on the surface of floating microspheres, due to matrix erosion, are responsible for floating ability (112).

Li et al. (113) recently developed a novel gastro-floating multiparticulate system based on a porous and low-density matrix core with excellent floatability. The porous matrix core was achieved by the complete release of mannitol as bulk water soluble excipient from EC coated beads. The optimized formulation floated on the dissolution medium for at least 12 h without lag time to float (113).

Hollow/porous particles induced by preparation methods

Different formulation techniques of multi-particulate systems were reported to produce hollow or porous particles suitable to be buoyant on dissolution or gastric media.

Emulsion-solvent diffusion method

Microballoons (MB) with hollow structure were firstly prepared by Kawashima et al. (117) as a novel multi-unit floating device by the emulsion-solvent diffusion method. The model drug and an acrylic polymer were dissolved in an ethanol-dichloromethane mixture and then poured into an aqueous solution of polyvinyl alcohol (PVA) with stirring to form emulsion droplets. The use of two solvents (dichloromethane and ethanol) having different rates of diffusion led to the formation of a hollow core responsible for the flotation ability of the microspheres. By changing the polymer concentration and the ratio of ethanol to dichloromethane, different drug contents were embedded in MB shell. With higher polymer ratios, the internal cavity volume of the MB was increased. Most of the MBs were floatable *in vitro* for 12 h when immersed in aqueous media. An *in vivo* radiographical study proved that MBs orally administered to humans were retained in the upper part of the stomach for over 3 h against peristaltic action (117). Similar approach was also developed by El-Kamel et al. (118). Sato et al. (115) found that both the preparation temperature and the MB surface smoothness determined the formation of cavity inside the microsphere and hence its buoyancy. At low temperatures (20 or 30°C), a slow rate of organic solvent evaporation led to formation of porous microspheres as dichloromethane remained in the droplets preventing formation of a hard polymer shell. On the other hand, an increase in evaporation rate of

dichloromethane caused the formation of a large depression within microspheres. Gradual evaporation of dichloromethane at 40°C appeared necessary for cavity formation in MBs (115). The effect of MB size on its *in vivo* buoyancy behavior was also studied by Sato et al. (114) showing that MB with particle size ranged from 500–1000 μm exhibiting high buoyancy compared to MB with particle size <500 μm (114).

Relying on the principle adopted previously by Kawashima et al. (117), Liu et al. (116) developed hollow-bioadhesive microspheres consisted of a mixture of ethylcellulose and Eudragit® EPO and then coated with glyceryl monooleate (GMO) as bioadhesive polymer *in situ.* More than 80% of the hollow microspheres continued to float for at least 10 h *in vitro*. After the hollow microspheres were coated with GMO, the percentage floating at the SGF surface decreased slightly because of some microsphere aggregation, but nevertheless remained high (116).

Ionotropic gelation method
According to El-Gibaly (31), floating microcapsules (MCs) were prepared by the ionic interaction of Cs and a negatively charged surfactant, sodium dioctyl sulfosuccinate (DOS). The use of DOS solution in coagulation of Cs produced well-formed MCs with round hollow core. Most of the hollow MCs tended to float over simulated gastric fluid (SGF) for more than 12 h. The characteristics of floating MCs generated compared with the conventional non-floating microspheres manufactured from Cs and sodium tripolyphosphate (TPP) were also investigated. The use of TPP solution in coagulation of Cs induces the formation of a microsphere structure in which a core is not defined. All TPP/Cs microspheres displayed essentially poor spherical particles with numerous surface cracks and pores compared with DOS/Cs MCs (31).

Solvent evaporation method
Polycarbonate (PC) microspheres were developed by a solvent evaporation technique (119). Drug-loaded microspheres were found to float on SGF. It was shown that the rapid evaporation of dichloromethane from the dispersion produces cavities and pores in the microspheres which render them hollow and floating in nature (119). Joseph et al. (120) prepared similar hollow PC microspheres.

Freeze-drying method
Calcium alginate multiple-unit FDDS was developed by freeze-drying method (121). Spherical beads were prepared by the precipitation of calcium alginate aqueous solution of calcium chloride. The beads are then separated, snap-frozen by liquid nitrogen, and freeze-dried at -40ºC for 24 h. This treatment leads to the formation of a porous system due to the ice crystals, formed by freezing, that sublimate leaving gaps or pores in their place. The *in vivo* behavior of this system compared to a multiple-unit non-FDF prepared from the same material was investigated (52). Prolonged GRTs of over 5.5 h were observed in volunteers taking the radiolabelled floating formulations by ɤ-scintigraphy. In contrast, the non-floating beads displayed short GRTs, with a mean onset emptying time of 1 h (52).

Foam solution-based method
According to Yao et al. (59), a simple and rapid method was established to prepare a novel kind of inner-porous floating beads. The beads were prepared by dripping the foam solution into CaCl₂ solution using disposable syringe needle. The foam solution was consisting of numerous microbubbles with poloxamer 188 as foaming agents and alginate as foaming stabilizer along with the drug. The presence of alginate increased significantly the foamability of poloxamer 188. Addition of the non-ionic surfactant poloxamer 188 leads to the formation of a surfactant–polymer complex through interactions between alginate and surfactant, which contributes to foamability and foam stability. The SEM cross-section pictures of the beads showed that they were inner-porous and composed of bubbles with very thin wall bubbles stacked together. The floating beads showed good buoyancy as most beads could float in the stomach for more than 6 h by ɤ-scintigraphic images (59).

Quasi emulsion-solvent diffusion method
A modified quasi emulsion solvent diffusion method was recently used to prepare floating microsponges by the aid of sodium chloride solution (NaCl) as porogen (122). The organic phase was consisting of polymeric solution of EC and Eudragit S 100 along with the drug in a mixture of ethanol and dichloromethane. The latter organic phase is dispersed into aqueous phase containing PVA, quasi emulsion droplets are formed due to increase in interfacial tension between ethanol and PVA. The diffusion of ethanol from the droplets into the aqueous phase

(PVA) facilitates the counter diffusion of PVA into the droplets, which increases the viscosity of polymeric solution containing EC, Eudragit S 100 and drug within the droplets. Water soluble NaCl effuses into PVA solution leaving polymer matrix behind and the interconnected pores are formed during the formation of microsponges. The microsponges formed with high level of EC and PVA were more buoyant than those with low level. The pharmacokinetic evaluation of the optimized formula in rabbits revealed 10-fold increase in bioavailability as compared to free drug (122).

Electrospray method

A novel low density system of porous Eudragit® RS (ERS) MPs was recently fabricated by Hao et al. via electrospray method (17, 123) . ERS was dissolved in dichloromethane at different concentrations along with the drug. The solution was supplied by a syringe pump for spraying from the grounded nozzle. The nozzle was connected to a positive electrode of a high-voltage power supply helping the smaller sized droplets to break up into micro-sized droplets. Aluminum foil was placed perpendicular to the nozzle as collector. As the solvent of the droplets will evaporate before reaching the collector, thus the solid particles can be obtained directly by electrospray method. The porous MPs would be obtained by electrospray method due to the fast evaporation of solvent. Buoyancy of porous MPs decreased as ERS concentration was increased, which may due to the increase in the density of MPs. More than 85% of porous MPs were floated in all the formulations at 12 h. ɣ-scintigraphy study *in vivo* demonstrated that ^{131}I-labeled MPs retained in stomach for over 8 h, and about 65.50% radioactive counts were finally detected in the gastric region (17).

Sublimation substance

Camphor was used as the sublimation material in a novel floating system as it changed to pores in the tablet during the sublimation process. The GR tablets have a highly porous morphology. The prepared tablets floated for over 24 h and had no FLT. However, as the amount of camphor in the tablet matrix increased, the crushing strength of the tablet decreased after sublimation (124).

Dual floating aids

A number of authors adopted FDDS relying on more than one buoyancy aid; such as air from swellable polymers combined with oil as low density material or with a gas-generating agent. A controlled-release GRDDS was firstly formulated by Desai and Bolton (51) based on both air and oil entrapped in the agar gel network. ɣ-scintigraphic studies for a floating and a heavy non-floating tablet, under fasting and non-fasting conditions, showed that the presence of food significantly increased GRT for both tablets, and tablet density did not surprisingly appear to make a difference in GRT. However, the positions of the floating and non-floating tablets in the stomach were very different (51).

The buoyancy of tablets prepared by Chen et al. (139) was based on both $NaHCO_3$ as gas-generating agent and air entrapped within swellable polymers; hydroxyethyl cellulose (HEC) and sodium carboxymethyl cellulose (NaCMC). An appropriate ratio of HEC to NaCMC, the addition of $NaHCO_3$, as well as compression at lower pressures resulted in the tablets floating over SGF for more than 16 h. The mean bioavailability from the floating tablet was approximately 164% relative to the immediate-release product (139). Similarly, Jagdale et al. (140) formulated floating tablets based on a mixture of $NaHCO_3$ and citric acid combined with a blend of polymers Xanthan gum and Locust bean gum. Floating behavior was achieved due to CO_2 generated from the acid-base interaction in addition to polymer swelling property (140).

Hu et al. developed floating tablets employing hydroxypropyl methylcellulose K4M (HPMC) as hydrophilic gel material, $NaHCO_3$ as gas-generating agent and hexadecanol as floating assistant agent (141). The prepared tablets floated within 3 min and maintained for more than 24 h.

Paula et al. (142) prepared a polymeric floating system composed of Alginate and Cashew gum (CG), loaded with an essential oil (*Lippia sidoides*–Ls) by ionotropic gelation. The beads produced with carbonate and Ls at high level contents exhibited good floatability for up to 5 days (142). Other authors (143, 144) developed oil-entrapped buoyant gellan-based beads. Buoyant beads of gellan were developed by inotropic gelation technique using $CaCO_3$ as gas forming agent and the drug polymer dispersion was emulsified with mineral oil and blended with HPMC or carbopol 934. The beads showed comparatively better residence and higher drug concentration in the gastric mucosa of the treated animals (143, 144).

Another research group developed a dual-mode floating system based on both gas-generating agent and sublimating agent (145) showing instant floatation without lag time *in vitro* (145).

Although the combination of more than one floating aid was predicted to improve buoyancy behavior of different FDDS, yet FLT and duration don't differ significantly compared to a single floating aid. Lack of comparative studies for systems containing single and multiple buoyancy-generating agents might be the reason for inability to conclude the real advantages of dual floating aids.

BUOYANCY-GENERATING AGENTS in MARKETED FDDS

Although floating GR systems have been in focus of interest of many researchers for the last three decades, marketed products are still limited in number. Few marketed FDFs are gas-generating agent-based products. Topalkan® and Liquid Gaviscon ® are well-established marketed antacid floating products produced by Pierre Fabre (France) and Glaxosmithkline (USA), respectively. These products relied on the presence of carbonate and bicarbonate salts in alginate dispersion. The polymer is subjected to *in situ* gelation by the divalent/polyvalent cations present in stomach as well as in formula. Moreover, the interaction of the carbonate and bicarbonate salts with the stomach acid leads to the evolution of CO_2 entrapped within the viscous cohesive gel. The floating polymeric gel sheet formed was usually described as 'raft-forming system' (146).

Furthermore, Baclofen ER® used as muscle relaxant is manufactured as FDF by Sun Pharma Advanced Res Co Ltd. The GR controlled drug delivery system comprises a controlled release core composed of a highly swellable polymer and a gas generating agent capable of swelling and achieving floatation rapidly while maintaining its physical integrity in GIT for prolonged periods in addition to a rapidly releasing coat containing the drug as in the core providing a biphasic drug release in GIT (147) .

Almagate Flot-coat® is another marketed antacid product produced by Laboratorios Almirall relying on the inherent low density of a hydrophobic agent. Coating the granulate particles of the antacid product with selected hydrophobic excipients increases the lipophilicity as well as delays reaction with hydrogen ions without altering the intrinsic acid neutralising properties. The prolonged residence time is a function of the lipophilicity of the particles which preferentially adhere to the gastric mucosa or form a layer on the surface of the gastric contents. The antacid is then slowly liberated, reacts with hydrogen ions in the vicinity, protects the mucosa

and its emptying from the stomach is delayed in spite of peristaltic movements (148).

Valrelease® and Madopar® HBS are considered as floating capsules marketed by Hoffmann-LaRoche (USA). The former product contains15 mg diazepam as antianxiety but the latter contains 100 mg L-dopa and 25 mg benserazide used in treatment of Parkinson's disease. The buoyancy of these products is based on air entrapped by swellable polymers providing HBS systems in addition to fatty materials to regulate floatation. These hydrodynamically balanced capsules acquire a density of less than one remaining buoyant on the gastric fluid (101). Cytotec® is another marketed product relying on the same category of buoyancy agents. It is a 100 or 200 µg misoprostol-containing floating SR capsule marketed by G.D. Searle Co. (now Pfizer, USA). The dosage form comprises a non-compressed bi-layer formulation in a capsule; one layer comprising a drug release layer and the other a buoyant layer, providing extended GRT of the dosage form so that substantially all drug is released in the stomach over an extended period. The floating layer includes a polymer having the properties of a gelling agent and which upon contact with gastric fluid hydrates and forms a gelatinous barrier or mass filled with air responsible to decrease the system density. The floating layer provides buoyancy to the dosage form as well as capsule diametric increase as the capsule attains a larger diameter in relation to its original size (149). Moreover, Conviron® is another example of marketed colloidal gel-forming FDDS that contains ferrous sulphate produced by Ranbaxy (India).

Additionally, Depomed, Inc. formulated few products based on patented Acuform® drug delivery technology. This technology depends on a combination of PEO and HPMC as a matrix for a swellable sustained-release tablet providing the ability to swell for GR and to control drug release. The swelling behavior of PEO is retained but balanced against the erosion behavior of HPMC which modulates the extent and progress of swelling (150). Acuform's unique swelling polymers allow the tablet to be retained in the stomach for approximately 8-10 h. Proquin XR® is Depomed's first FDA approved product, and it is a testament to the benefits of GR Acuform drug delivery technology. Proquin XR® is a once-daily extended-release formulation of ciprofloxacin HCl and is intended to treat uncomplicated urinary tract infections.

Acuform technology is also used in the formulation of three additional products marketed

by Depomed's partners: Santarus' Glumetza® (metformin HCl extended release tablets), Merck's Janumet® XR (sitagliptin and metformin HCl extended-release) and Janssen's Nucynta® ER (tapentadol extended-release tablets).

Recently, Depomed apply the same technology in the formulation of once-daily Gralise®(gabapentin) tablets. This is an investigational extended release and gastric retained formulation of gabapentin, an FDA-approved product for the treatment of Postherpetic Neuralgia (PHN). PHN is a persistent neuropathic pain condition caused by nerve damage after a shingles, or herpes zoster, viral infection. The formulation of once- or twice-daily gabapentin is particularly challenging since gabapentin is absorbed through an active transport mechanism which is concentrated in the upper gastrointestinal tract. Therefore a gastric retained formulation of gabapentin may demonstrate an improvement in delivering drug to these active transport sites compared to a more traditional extended release technology (151).

CRITICAL ASSESSMENT

Several approaches have been investigated and developed for GR of dosage forms. This was for purpose of controlling drug delivery, allowing more drug absorption extent for those having narrow therapeutic window, improving local gastric treatment and reducing drug instability/insolubility in high intestinal pH. Buoyancy is one of the promising methods used for stomach specific drug delivery. Various aids were adopted in order to decrease the density of the dosage form hence enhance its floatation. These floating agents were based either on gas generation, air filling, inherent low density, porosity or sublimation. The assessment of the floating behavior for such developed systems is mandatory either *in vitro* or *in vivo* proving their GR tendency by direct or indirect techniques. It is worth to notice that only few of these buoyancy-generating agents provided an instantaneous floatation to the drug delivery system without a delay time; primarily the hollow particles prepared by different formulation techniques. Other floating aids suffered with variable degrees lag time depending on different preparation factors; concentration, type, compression force, additives. Furthermore, the floating duration of all buoyant dosage forms is generally considered unpredictable and inconsistent owing to several technical and physiological influences; mainly the erosion rate of polymer incorporated within the system and the variable gastric emptying rate in fasted and fed state, respectively.

On the other hand, it is perceptible that the majority of marketed GR floating products are monolithic relying on gas-generating agents, swellable polymers or combination of both. In addition, it is well known that the multiparticulate systems are advantageous compared to single-unit ones in; achieving a more predictable drug release profile, preventing all-or-none gastric emptying, allowing co-administration of incompatible actives or units with different release profiles. Despite these, there is no floating multiple-unit GRDDS such as microparticles, minicapsules or beads in the market, yet.

Therefore, future development approaches should focus on:

- A deep *in vivo* study resolving the dilemma of unpredictable gastric emptying of FDDS with reviewing the actual effect of fed and fasted conditions on their GRT.
- Increasing the propensity of the pharmaceutical industry in manufacturing more FDFs especially multiparticulate FDDS in order to solve drug-related problems.

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Table 1: Parameters affecting the floating behavior of FDDS based on the type of buoyancy-generating agents.

Category of Buoyancy-generating agents	Factors influencing buoyancy	Comments	References
Gas-generating agents	The amount of gas-generating agent	↑ Amount → ↓ FLT → ↑ GRT	(44, 45, 76, 84, 86-89)
	The type of carbonate salts e.g. NaHCO$_3$, Na$_2$CO$_3$, CaCO$_3$, K$_2$CO$_3$	CaCO$_3$ and NaHCO$_3$ are better in terms of FLT compared to other salts with the superiority of CaCO3 in enhanced floatation and bead surface smoothness	(91, 92)
	The type of polymer or diluent	Psyllium>HPMC E5>Carbopol Xanthan Gum>HPMC K4M or HPMC K15M	(21, 93, 94) (92)
	The coating type and concentration	Soluble polymers as HPMC, PEG 6000, PEG 600, and Kollicoat® IR increased water uptake ability of insoluble polymers (Eudragit® NE, RS, and RL; Surelease®; and Kollicoat® SR) →↓FLT ↑ coating conc. → ↑FLT	(28, 95, 96)
	The compression pressure	↑compression force → ↑FLT	(97)
	The preparation method	hot-melt extrusion (HME)> direct-compression Freeze-drying>air-drying	(92, 98) (96)
Air-entrapping swellable polymers	The polymer type	Blends of alginate and HPMC, alginate and chitosan, carrageenans and HPMC, xanthan gum and guar gum.	(16, 99-101)
		Glyceryl monooleate (GMO)	(102)
		PEO WSR 60K, PEO WSR 303 and HPMC K4 M	(56)
	The drug or excipients type	↑ polar drug or ↓ non-polar drug amount → ↑ water uptake → ↓ FLT ↑ stearic acid or PEG amount → ↓ water uptake or ↑ viscosity →↑ FLT Mw of PEG did not significantly affect FLT	(102)

Inherent low density agents	The type and concentration of low density excipient	Oils (light mineral, olive, sunflower, peppermint, sesame, rice, soybean and corn oil) (10-30%)	(16, 103-105)
		Magnesium stearate (5%)	(74)
		Silicon dioxide (Aerosil R972)	(29)
		Functionalized $CaCO_3$	(106)
Highly porous excipients or Pore formers	The type of porous or pore forming agents	Casein	(37)
		Polypropylene foam powder (Accurel®)	(107, 108)
		Calcium silicate (Florite RE®)	(109-111)
		PEG	(112)
		Mannitol	(113)
Hollow/porous particles induced by preparation methods	The method of preparation applied	Emulsion-solvent diffusion method	(114-118)
		Ionotropic gelation method	(31)
		Solvent evaporation method	(119, 120)
		Freeze-drying method	(52, 121)
		Foam solution-based method	(59)
		Quasi emulsion-solvent diffusion method	(122)
		Electrospray method	(17, 123)
Sublimation material	The concentration of sublimating substance	↑ amount of camphor in tablet matrix → ↓ tablet crushing strength after sublimation	(124)