Expert Opinion

In vitro and *in vivo* techniques to assess the performance of gastro-retentive drug delivery systems: a review

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Background: Interest in gastro-retentive drug delivery systems (GRDDS) can be attributed to the desire for increased patient convenience (once daily dosing) and to increase the therapeutic index (reduced C_{max}, increased C_{min}). A range of evaluation techniques for GRDDS exist for *in vitro* and *in vivo* evaluation. *Objective*: The aim of the present review is to describe the methodologies used for *in vitro* and *in vivo* evaluations of GRDDS. *Methods*: The proposed critical parameters for floating and swelling types of GRDDS are discussed. Modifications in dissolution testing and improved biorelevant testing methods are also described. The *in vivo* techniques for measuring gastro-retentive performance are also summarised. *Conclusion*: The described methods can be used as assessment techniques for the evaluation and development of GRDDS. With these techniques, it is possible (with appropriate controls) to determine if a GRDDS provides hope for advantages of extended residence time in the stomach.

Keywords: floating system, gastro-retention, *in vitro* dissolution, *in vivo* testing, swelling system

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1. Introduction

The short residence time of oral controlled release dosage forms (CRDF) in the stomach leads to problems with bioavailability for certain classes of drugs. Increased interest in the novel drug delivery systems that are retained in the stomach for a longer period of time can be attributed to the enormous scientific and patent literature [1-16]. Such dosage forms are usually referred to as gastro-retentive drug delivery systems (GRDDS) and are advantageous for a variety of drugs. Unlike conventional CRDF, which release the drug in a controlled manner throughout the entire gastrointestinal tract, GRDDS retains in the stomach for an extended period of time and releases the drug in a controlled fashion. The rationale for the selection of active pharmaceutical ingredients for fabrication as a GRDDS is described in **Table 1**.

The stomach is a dynamic organ of the body and the residence time of the dosage form is affected by various physiological as well as pharmaceutical factors. Various platform technologies and the marketed products are outlined in **Table 2**. The evidence of the need for and success of GRDDS in the healthcare system is presented in **Table 3**.

To ensure drug release in the stomach from GRDDS, the dosage form requires thorough and meticulous evaluation for optimum gastro-retentive performance, which can be assessed directly by *in vivo* imaging technologies or indirectly by the measurement of various parameters which are believed to be linked to

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Table 1. Rationale for gastro-retention of drugs.

Rationale for gastro-retention	Name of drug
Narrow absorption window at upper part of gastrointestinal tract	Levodopa Riboflavin Calcium Repaglinide Atenolol Theophylline Diltiazem Risedronate
pH-dependant absorption from stomach (acidic drugs)	Furosemide
Degradation at higher pH (higher stability at lower pH)	Captopril
Degradation in intestine or colon	Ranitidine
Higher solubility at lower pH or weakly basic drugs	Cinnarizine Diazepam Verapamil Cefpodoxime proxetil Dipyridamole Rosiglitazone maleate
Drugs for local action – antacids, anti-ulcer drugs, antibacterials for *H. pylori* infection	Acetohydroxamic acid Misoprostol Amoxicillin Clarithromycin Metronidazole

Table 2. Platform technologies for GRDDS.

Company	Platform technology	Type of technology
Depomed	AcuForm	Polymer-based technology
Intec Pharma	Accordion Pill	Expandable film, filled in capsule
Sun Pharma	Gastro Retentive Innovative Device (GRID)	Coated multilayer floating and swelling system
Merrion Pharma	Gastrointestinal Retention System (GIRES)	Gas generating inflatable pouch in capsule
Flamel	Micropump	Gastro-retention with osmotic system
Roche	Hydrodynamically Balanced System (HBS)	Matrix forming polymer-based floating system

gastric retention. However, in many cases of purported gastro-retention, clarity regarding the effectiveness of the GRDDS has been limited by a lack of high quality evaluation technology and limited use of appropriate controls. Scientists have formulated GRDDS using various approaches, which are briefly mentioned in **Table 4**. The evaluation parameters for optimisation of GRDDS formulations depend on the type of GRDDS. Mucoadhesive systems have not been preferred for GRDDS owing to the high turnover rate of mucoadhesive site, that is the mucus lining of the stomach wall. The evaluation techniques used for the assessment of bioadhesive or mucoadhesive dosage forms have been described in detail by Mathiowitz *et al.* [17]. The current review deals with various *in vitro* and *in vivo* techniques for the evaluation of gastro-retentive performance of floating and expandable types of GRDDS.

2. Evaluation parameters for gastro-retentive performance

2.1 Floating dosage forms

Floating dosage forms, also referred to as low density systems, remain buoyant in the gastric fluid for an extended period of time. Floating systems may be inherent low density type systems or may achieve their low density after coming into contact with the dissolution media. *In vitro* parameters that could be linked to *in vivo* gastro-retentive performance of the floating systems include lag time, density (porosity) and floating time.

2.1.1 Floating lag time

The lag time for the floating dosage form is the time required by the dosage forms to emerge on the surface of the dissolution medium after placing it into the dissolution medium [18,19]. For liquid dosage forms like *in situ* gel forming formulations or raft, a small Petri dish (4.5 mm diameter) containing the required dose of liquid is put carefully into the dissolution vessel and the time required by the formulation to emerge on the surface is determined [20,21]. Irrespective of the drug, the ideal dissolution medium for evaluation of GRDDS is 0.1 N HCl or simulated gastric fluid (SGF) to mimic the *in vivo* conditions, while other media have not been defined for the more relevant fed condition, since floating GRDDS are only purported to be effective in the fed state. The lag time is an important parameter to compare batch-to-batch formulation. It is an essential parameter for the dosage form, where density is reduced upon coming into contact with the dissolution medium (i.e., *in situ* gas generating effervescent dosage forms). Essentially, lag time is the time required for a reaction between the gas forming agent like bicarbonates and the acidic dissolution medium, so that it reduces the density of the dosage form and moves it upwards to the surface of the dissolution medium. Dosage forms having intrinsic low density, for example hollow microspheres, microballoons, foam particles, etc, may exhibit a negligible lag time as no reaction is initiated for their floating properties. Larger values of lag time are undesirable as the housekeeper waves of the stomach may sweep out the dosage form into the intestine prior to its buoyancy.

Table 3. Marketed products based on GRDDS.

Marketed product	Drug	Company
Glumetza®	Metformin	Depomed
ProQuin®	Ciprofloxacin	Depomed
Gabapentin GR® (in Phase III clinical trials)	Gabapentin	Depomed
Baclofen ER®	Baclofen	Sun Pharma
Cifran OD® (outlicenced to Bayer)	Ciprofloxacin	Ranbaxy
Coreg CR®	Carvedilol	Flamel
Madopar HBS®	L-Dopa + Benserazide	Roche
Valrelease®	Diazepam	Roche
Liquid Gaviscon®	Antacid	Glaxo Smith Klein

2.1.2 *Density/specific gravity of the dosage form*

For a floating dosage form, density is an important parameter to predict its floatability. Tablet density [22,23] is the ratio of tablet weight (w) to tablet volume (v). Tablet volume is calculated by measuring tablet height (h) and diameter (m) using a micrometer gauge.

For the multiple units such as microspheres, density may be calculated by determining mass volume of known mass weight of microspheres [24-27]. The mass volume can be determined by the photographic counting method where photographs of microspheres are captured. Diameters of microspheres are measured with an image analyser from the photographs and the mass volume may be calculated using equation 1.

$$\sum^{n} V = (\pi/6)\sum^{n} d^3 \quad (1)$$

Another approach is to determine specific gravity using the liquid displacement method [28-31], where a known mass of solid is filled into the pycnometer, followed by a liquid filling; and by using the value of specific gravity of the liquid, the volume of liquid displaced by solid is to be determined for calculating the specific gravity of the solid. Water, Benzene or n-Hexane may be used as solvent for displacing the medium.

2.1.3 *Porosity*

Porosity plays an important role for GRDDS based on porous carriers or hollow microspheres [32]. Porosity may be calculated by measuring true density (ρ_t) and particle density (ρ_p) as per the following equation:

$$\varepsilon = \left(1 - \frac{\rho_p}{\rho_t}\right) \times 100 \quad (2)$$

True density may be determined using helium–air pycnometer [24], nitrogen adsorption method [33] or mercury porosimetry [34,35]. Sher *et al.* [36] determined pore size and pore volume using a mercury porosimeter for microporous particles of Accurel MP® (Membrana GmbH, Obernbury, Germany), where the sample is loaded in a cell under vacuum and then exposed to mercury under high pressure up to 33,000 psi absolute.

2.1.4 *Floating time/buoyancy time*

Floating time, also referred to as buoyancy time, may be defined as the total time period between placing a dosage form in the dissolution medium to the time it remains floating. The test for buoyancy is usually determined in 900 ml of SGF maintained at 37°C using USP dissolution apparatus. Floating time duration could potentially be an indication of the gastric retention time of the dosage form.

Multiple units, such as microspheres, spread over the surface of the dissolution medium. Thus, to estimate the buoyancy time the fraction of microspheres settled down as a function of time are quantified by determining the weight after drying microspheres are collected from the surface of the dissolution medium [37-40]. To simulate gastric motility, El-Gibaly [41] studied the buoyancy of microspheres using a water bath shaker with a shaking speed of 100 o.p.m. (oscillations per minute) at 37°C by soaking 50 microspheres in 100 ml of SGF.

In another approach studied by Ichikawa *et al.* [42], the known quantity of pills were immersed in 70 ml of dissolution medium in a 100 ml beaker maintained at 37°C. The beaker vibrated horizontally at a speed of 100 r.p.m. in an incubator at 37°C. The percentage of floating pills was calculated by determining the number of floating pills by photographing the monolayer of floating pills on the surface of the dissolution medium at regular time intervals.

Recently, a novel method was developed by Shah [43] for the continuous evaluation of the percentage of floating microspheres as a function of time. A known weight of microspheres was placed in SGF filled in a glass percolator and the microspheres that settled down in the percolator were collected at regular time intervals, and were dried and weighed to calculate the percentage of floating microspheres. The continuous collection of non-floating microspheres from the bottom of the percolator without disturbing the buoyancy of the microspheres is the unique feature of the method.

2.1.5 *Resultant weight*

The lag time, density and floating time are now considered as essential parameters for the majority of evaluations describing the floating capability of dosage forms. However, although the density value may indicate whether an object will float or not, it does not reflect the magnitude of floating force produced by the object. The changes in weight and volume of dosage form due to the dissolution of drug and swelling and erosion of polymer as

Table 4. Approaches to formulate GRDDS.

Low density approach (floating systems)	
Floating – non-gas generating system	
Monolithic systems	**Multiple units**
Hydrogel matrix systems	Calcium alginate/pectinate gel beads
HBS™ capsule	Alginate beads with air compartment
Tablet – single layer and bilayer	Oil entrapped gel beads
Matrix tablet with foam	Casein–gelatin beads
Matrix tablet with lipid	Hollow microspheres
Tablet with agar and oil	Microballoons
Tablets in hollow cylinder	Microparticles with foam
Coated hollow globular shell	Floating powder
Porous reservoir with floating chamber	Granules with calcium silicate
Multilayer flexible film	Gelucire® granules
Floating – gas generating system	
Monolithic systems	**Multiple units**
Hydrogel matrix tablet with bicarbonates	Ion exchange resin beads
HPMC matrix tablet with carbopol	Floating pills
Coated effervescent core	Porous alginate beads
Programmable capsule with spring	
Multiple films	
System with inflatable chamber	
Expandable approach (plug-in systems)	
Swelling systems	**Unfolding systems**
Superporous hydrogel	Obstructing means
Polymeric envelope	Multilayer polymeric sheets
Matrix tablets with thiolated gelatin	Geometric configurations (with and without receptacle means)
Compressed collagen sponge	
Bioadhesive/mucoadhesive approach	
Bioadhesive tablets, films, microspheres	
High density approach	
Incorporation of iron powder, zinc oxide or TiO_2 (inert material with high density)	

a function of time yields continuous variation in density of the dosage form, which affects the floating capability and thus cannot be predicted by a single determination of density.

Timmermans *et al.* [44] developed an apparatus for the *in vitro* determination of real floating capabilities in terms of 'resultant weight' as a function of time. As shown in the **Figure 1A**, the resultant weight apparatus consists of a force transmitter device (FTD) connected to a weighing balance. The lower extremity of FTD holds the dosage form into the dissolution medium and transmits reacting force; either upward or downward forces, to the electromagnetic measuring module of a weighing balance. The lower extremity of FTD is interchangeable for different types of floating dosage forms (i.e., needle-like or mesh-like holders).

The resultant weight apparatus operates by measuring the force equivalent to resultant weight F required to maintain the object totally submerged in the fluid. The magnitude and direction of force F corresponds to the vectorial sum of buoyancy force (F_{buoy}) and gravity force (F_{grav}) acting on the dosage form, as shown in equation 3.

(3)

$$F = F_{buoy} - F_{grav} = d_f\, g\, V - d_s\, g\, V = (d_f - d_s) g\, V = (d_f - M/V) g\, V$$

Where F is total vertical force (resultant weight of an object), g is the acceleration gravity, d_f is the fluid density, d_s is the object density, M is the object mass, and V is the volume of the object. The values are used to draw floating curves.

The floating curves are obtained by plotting a continuous resultant weight of the floating dosage form as a function of time. A positive resultant weight signifies that the F is exerted upward and that the object is able to float, whereas a negative value describes downward movement of the object. The crossing of the zero base line by the floating curve from positive towards negative value indicates the transition of the dosage form from floating to non-floating conditions. The intersection of lines on a time axis corresponds to the floating time of the dosage form. Recently some researchers have utilised this apparatus for evaluation and optimisation of various GRDDS [45-48].

2.1.6 *Floating kinetics*

Li *et al.* [49] have developed a continuous floating monitoring system which is based on the method to access the muco-adhesive force measurement. As shown in **Figure 1B**, a floating measuring probe consisting of a stainless steel basket is connected to a metal string, suspended from an electronic balance. The floating dosage form is kept in the basket and immersed at a fixed depth into the dissolution apparatus. The upward force can be measured by the balance and this measure is transmitted to an online computer by RS-232C cable. The data obtained are used to plot a floating kinetic curve where the floating kinetics are plotted against time at each 30 s interval. Researchers have utilised this system to optimise the formulations on the basis of residual floating force (resultant weight) [50,51].

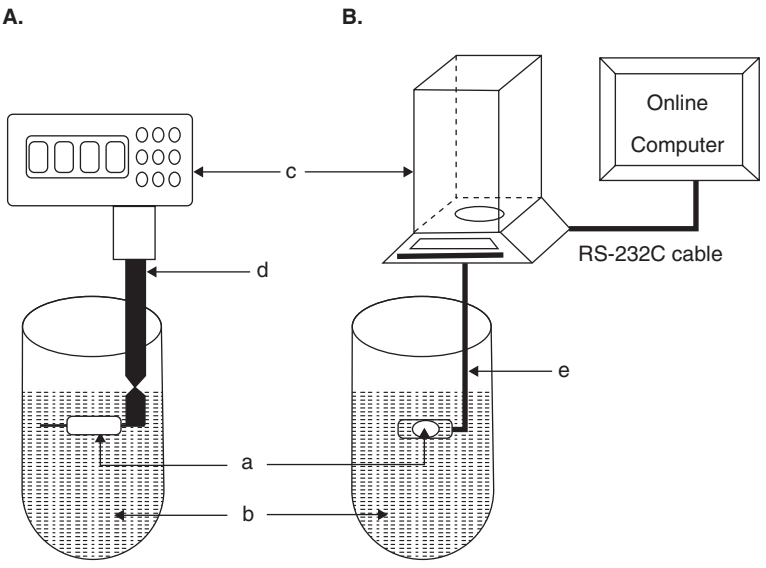

Figure 1. A. Resultant weight apparatus with force transmitter device (FTD). B. Continuous floating monitoring system. a. Floating dosage form, b. dissolution medium, c. electronic weighing balance, d. force transmitter device with holder, e. metal string with basket.

The rate of drug release depends on the rate at which the polymer swells, which in turn depends on the rate of water uptake by the matrix. Hence, one also needs to study the water absorption rate (see Section 2.3.2 below) of the matrix to gain an insight into the release mechanism of the drug from the matrix and predict its release rate.

2.2 Raft characterisation

Raft is an antireflux preparation designed to provide symptomatic relief in gastro-oesophagus reflux disease, by forming a physical barrier on the top of the stomach content in form of a floating gel layer [52]. A raft type of dosage form is generally formulated using alginates and may contain antacids. The indicative parameters for the *in vivo* performance of the raft would be raft strength, buoyancy and resistance to gastric reflux. The raft strength and resistance to reflux gives an indication of the capacity of raft as a physical barrier for prohibiting the transfer of gastric content to the oesophagus and to prevent heart burn. An L-shaped metal wire is held upright in the beaker containing 150 ml of SGF and a sufficient dose of formulation is added. After raft development (about 30 min.) the wire is hooked on the texture analyser (**Figure 2A**) and the force required to pull the wire vertically through the raft is measured as raft strength. To determine the raft resistance to reflux, the raft is carefully transferred to the extrusion cell with an orifice at the base and the force required by a plunger to transfer the content from the orifice is measured using a texture analyser as raft resistance to reflux (**Figure 2B**). Alternatively, a cylindrical rod may also be used to rupture the developed raft. Diameter of the orifice and the cylindrical rod are set to 10 mm for simulating oesophageal sphincter (**Figure 2C**) [53,54].

2.3 Expandable dosage forms

Expandable systems increase their size on exposure to gastric fluid and provide a mechanical sensation of fed mode to the stomach for delaying the 'housekeeper waves' generated by stomach motility to transfer the gastric content to the duodenum through the pyloric sphincter, which has a diameter of 12.8 ± 7 mm [6]. Fundamentally, the non-disintegrating expandable system is retropelled back to the stomach by the pyloric sphincter for further digestion and gastric retention time is thus prolonged. Expandable dosage forms work on either swelling or unfolding mechanisms. GRDDS based on the swelling mechanism are formulated using polymer(s) which swell when they come into contact with the dissolution media. Unfolding systems are formulated using polymers with shape memory properties, that is they retain the shape after unfolding [7,55]. Swelling index, water absorption rate and exposed size parameter are essential parameters to predict the gastro-retentive performance of expandable systems.

2.3.1 Swelling index/water uptake

The swelling index represents the swelling capacity of the polymer when it comes into contact with the dissolution media [56-59]. The swelling index or water uptake (Q) of swellable tablets can be determined using equation 4.

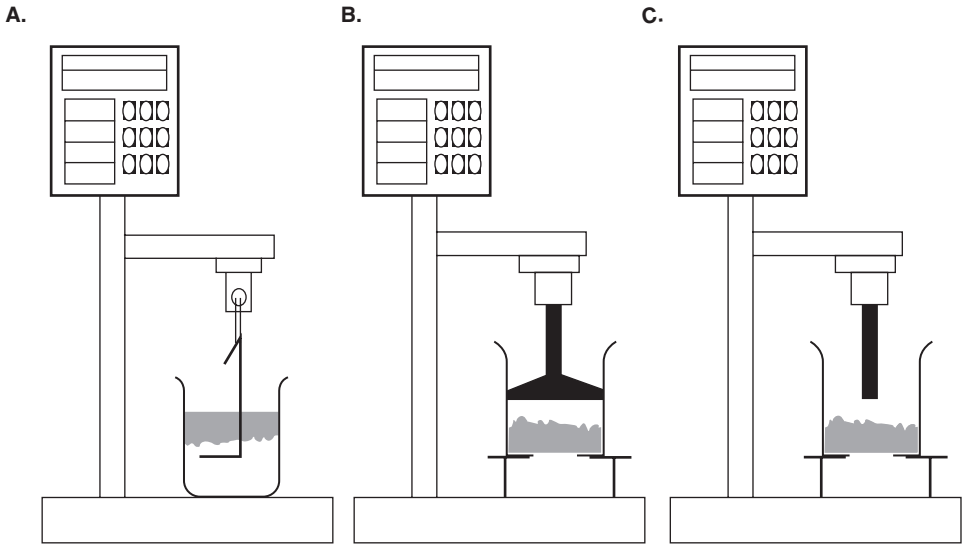

Figure 2. Evaluation of raft system by texture analyser. A. Evaluation of raft strength using hooked wire. **B.** Evaluation of resistance to reflux using extrusion plunger. **C.** Evaluation of resistance to reflux using punch.

$$Q = \left(\frac{W_S - W_D}{W_D}\right) \times 100 \quad (4)$$

Where W_S and W_D represent the weight of the swollen tablet and weight of the dry tablet (initial weight of tablet before swelling), respectively.

The formulator has to design the dosage form by balancing the swallowability by the patient and the gastro-retentive capability. Thus, higher swelling index values are desired for GRDDS based on the swelling system and the expandable type of system. The dosage form developed by Urquhart *et al.* [60] achieves 2 – 50-fold improvement in volume by swelling. This parameter not only reflects the swelling capacity, but also relates to the release of drug from the polymeric matrix.

2.3.2 *Water absorption rate*

While performing the swelling index or water uptake test of swellable dosage forms, according to the present method, one needs to remove the tablet from the dissolution medium at each time interval for measuring weight increase, which damages the gel structure of the swollen polymer. To avoid such problems, Parakh *et al.* [61] have developed a novel method which allows the determination of unidirectional swelling behavior without disturbing the gel layer, and helps in the quantification of the water absorption pattern on the basis of the concentration and viscosity grade of the polymer and the presence of hydrophilic excipients. In this method, concentric circles with a diameter ranging from 7 – 30 mm are drawn on paper, which is laminated to make it hydrophobic. A special arrangement is made for raising and lowering the laminated paper assembly. The tablet is placed on the innermost circle and the assembly is weighed and then kept into a 100 ml beaker containing 35 ml of dissolution media maintained at 37°C. After predetermined time periods, this assembly is raised out of the beaker and reweighed after wiping off the water droplets that adhere to the surface of the assembly. The difference in the weight values can be used to calculate the amount of water absorbed by the matrix. The amount of water absorbed by the matrix can be plotted against the time to determine the water absorption pattern. The average velocity of water penetration front may be determined using equation 5.

$$u = \left(\frac{dWg}{dt}\right) \times \left(\frac{1}{\rho_w \times 2A}\right) \quad (5)$$

Where (dWg/dt) is the weight of water absorbed by the matrix per unit time, ρ_w is the density of water at 37°C, A is the area of the matrix (calculated from circle diameter), and factor 2 accounts for the diffusion taking place through both the faces of the dosage form.

The method described above involves removal of the assembly at predetermined time intervals for weighing, which may also lead to disruption of the swollen system while wiping off the droplets. To avoid such inconvenience, Bussemer *et al.* [62] developed a novel apparatus which is schematically shown in **Figure 3A**. In this system the swellable dosage form is kept inside a Plexiglas cylinder on a glass filter of porosity grade #1. A tightly fitting punch of predetermined weight is placed on top of the dosage form. To reduce the friction between the punch and the Plexiglas cylinder, paraffin is applied as a lubricant. The swelling medium at 37°C is added up to the level of

glass filter. All the vessels are covered to avoid water evaporation. Upon penetration of medium through the filter, the dosage form begins to swell and pushes the punch upwards. The swelling medium, which is taken up by the swelling sample, is replaced automatically from the reservoir through the tube. This water flux results in a weight change of the reservoir beaker and can be recorded with a digital balance as a function of time. The water uptake is calculated as shown in equation 4.

The same group of researchers has further modified the apparatus for the evaluation of the swelling force (**Figure 3B**). The dosage form was placed on the glass filter. The punch was then placed on top of the sample and was connected with an Instron-load cell. In contrast to the above, where the punch moves during the swelling process, in the modified apparatus the punch is kept in a fixed position during the test. The swelling medium is added and the swelling force exerted by the dosage form is recorded as a function of time.

2.3.3 *Exposed size parameter*

The folded or coiled unit of an unfolding type of expandable system is filled into a capsule and on release the system unfolds to its maximum size to achieve gastro-retention [63]. Thus, the *in vivo* capability to unfold and the preservation of the shape and size as a function of time are the critical parameters to optimise the formulation for gastro-retention, which can be determined by 'exposed size parameter'. The X-ray contrast aluminium threads obtained from surgical gauze pads are incorporated in the formulation of unfolding GRDDS, generally on the periphery of the dosage form. The X-ray photographs are taken at regular time intervals and percentage exposed size parameter (% ESP) are calculated using equation 6.

$$\%ESP = \left(\frac{L_S \times L_L}{S}\right) \times 100 \quad (6)$$

Where L_S and L_L are the average length between parallel contrast threads in the shorter and longer dimensions, respectively. S is the maximum surface area of GRDDS before folding or coiling.

3. *In vitro* drug release

GRDDS are intended to remain in the stomach and release the drug in the gastric fluid. Consequently, the *in vitro* drug release from GRDDS should be studied in SGF or in acidic media. The majority of researchers use USP dissolution apparatus I or II, depending upon the type of dosage form. SGF or 0.1 N hydrochloric acid (pH 1.2), with or without enzymes and surfactants, have been used as a dissolution media for GRDDS. The traditional dissolution method for floating and/or swelling dosage forms is associated with a number of drawbacks such as the possibility of adherence of the dosage form to the paddle shaft, incomplete exposure to the dissolution medium and failure to mimic *in vivo* conditions. The floating system remains buoyant over the surface of the dissolution media, which may not rotate under the influence of the paddle in the USP dissolution method, where paddle is located at a lower part of the dissolution vessel (**Figure 4A**). Moreover, the drug that is released makes a surface film over the dissolution medium and does not mix uniformly, resulting in poor *in vivo–in vitro* correlation (IVIVC).

For breaking the surface film in the dissolution vessel formed by floating dosage forms, Burns *et al.* [64] modified the USP dissolution method, where the paddle blade is rotated at the surface of the dissolution media, rather than at the lower part (**Figure 4B**). This modified method exhibited more reliable dissolution data and could also distinguish between acceptable and unacceptable floating formulations.

The dissolution profile of a swellable–floating type of gastro-retentive system is highly sensitive to its position in the dissolution vessel and to the hydrodynamic conditions in the vessel. The USP dissolution apparatus I (basket apparatus) is better suited to ensure the full exposure of all surfaces of the hydrophilic swelling tablets (**Figure 4C**). However, it has been observed that after few hours the tablet swells to the extent that it completely constricts the radius of the basket and thus impedes further swelling and drug release [65].

To allow maximum exposure of floating dosage forms to the dissolution media, it can be fully submerged by use of a helical wire sinker (**Figure 4D**) [66,67], as recommended by the USP. However, application of the helical wire sinker to the swellable floatable system appears to inhibit the three-dimensional swelling process of the dosage form and consequently suppresses drug release from the formulations.

Alternatively, a ring mesh assembly has been used to retain the floating dosage form to be submerged. Pillay *et al.* [66] studied the dissolution of swellable–floating systems by placing them beneath the ring/mesh assembly (**Figure 4E**). Durig *et al.* [65] evaluated floating and sticking extended release systems using a double ring mesh assembly. As depicted in **Figure 4F**, two stainless steel meshes are kept at a height difference of 3.5 cm and the dosage form is placed in the compartment of the double ring mesh assembly.

Burns *et al.* [68] modified the dissolution apparatus by the insertion of a moulded and indented continuous glass shoulder, 72 mm from the base, upon which a circular stainless steel mesh of similar diameter is kept (**Figure 4G**). The mesh effectively divides the vessel in the lower third. A floating dosage form is placed under the inserted mesh, where it is retained in the lower portion of the vessel and prevented from floating freely to the surface. A USP paddle is rotated immediately above the mesh to cause rotation of the dosage form. The major objective of the various approaches mentioned above is that results are obtained in

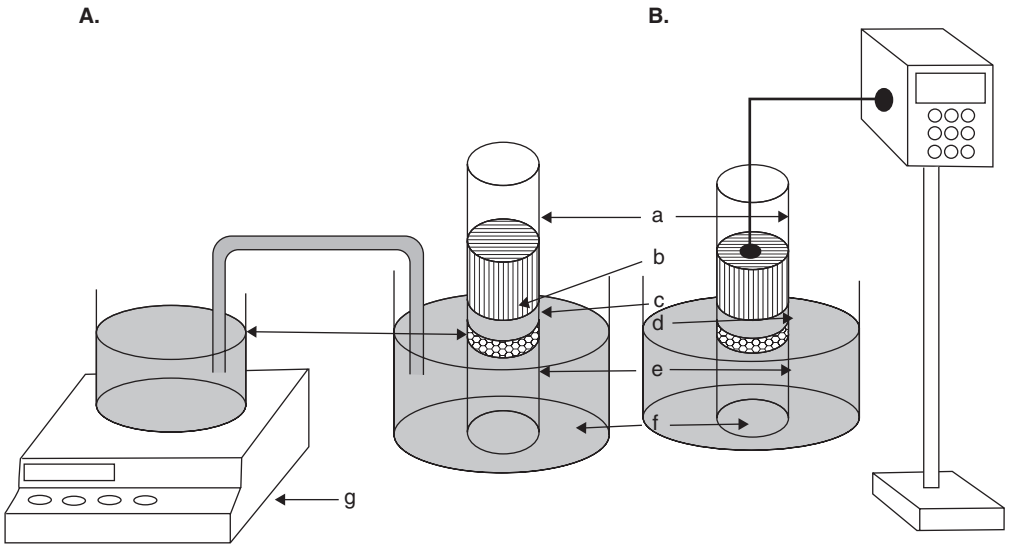

Figure 3. A. Assembly for continuous water uptake study. B. Apparatus for swelling force study. a. Cylinder, b. movable punch, c. immovable punch, d. swelling system, e. glass filter, f. dissolution medium, g. electronic weighing balance.

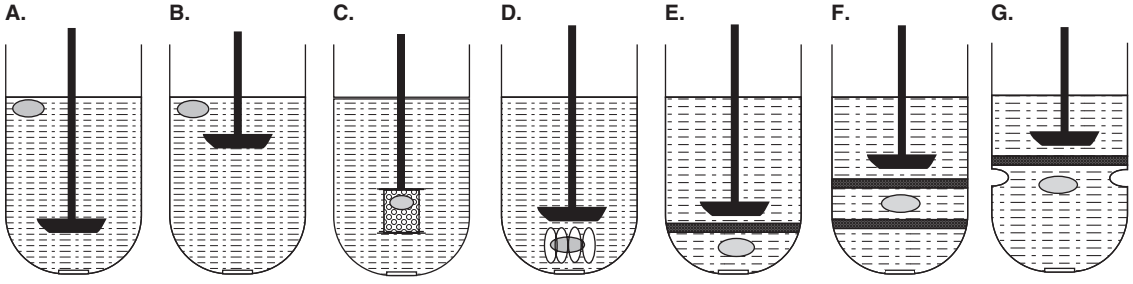

Figure 4. *In vitro* dissolution study apparatus and modifications. A. USP apparatus II (paddle method), **B.** paddle over surface, **C**. USP apparatus I (basket method), **D.** use of helical wire sinker, **E.** paddle over ring mesh, **F.** double ring mesh assembly, **G.** mesh mounted on indented glass shoulder.

reliable and reproducible dissolution profiles, which also exhibit good correlation with the *in vivo* data.

Although the various modifications mentioned above improve the dissolution profile of floating dosage forms, they do not mimic the *in vivo* conditions of the stomach. One approach for mimicking the *in vivo* stomach condition was adopted by Nakagawa *et al.* [69], where the floating tablet was evaluated according to the paddle–beads method. To receive the mechanical impact force as experienced in the stomach, 1500 polystyrene beads (diameter, 6.35 mm; specific gravity, 1.05 g/cm^3) were added to the dissolution media (300 ml) and the paddle was rotated at 75 r.p.m.

Another attempt was made by Gohel *et al.* [70] to mimic the *in vivo* conditions of gastric volume, gastric emptying and gastric secretion rate, which is essentially a modification of the Rossett–Rice method used for antacid evaluation. As schematically described in **Figure 5A**, a 100 ml glass beaker is modified by adding a side arm at the bottom of the beaker so that the beaker can hold 70 ml of 0.1 N HCl dissolution medium, which is comparable to the *in vivo* gastric volume. A burette is mounted above the beaker to deliver the dissolution medium at a flow rate of 2 ml/min to mimic the gastric acid secretion rate. The side arm is used not only for maintaining a constant level of dissolution media, but also for providing sink conditions and which may also be used for the sampling purposes. The use of a magnetic stirrer in the beaker allows free rotation of the floating dosage form without allowing it to stick. Due to the improved *in vivo* mimicking property of this method, it is proposed to give better IVIVC.

For drugs with good absorption in the stomach but which are degraded in acidic conditions, the drug release rate from the dosage form and rate of absorption in body can be balanced so that the drug has minimum exposure time to the acidic media. The use of classical apparatus, where the released drug remains in the acidic

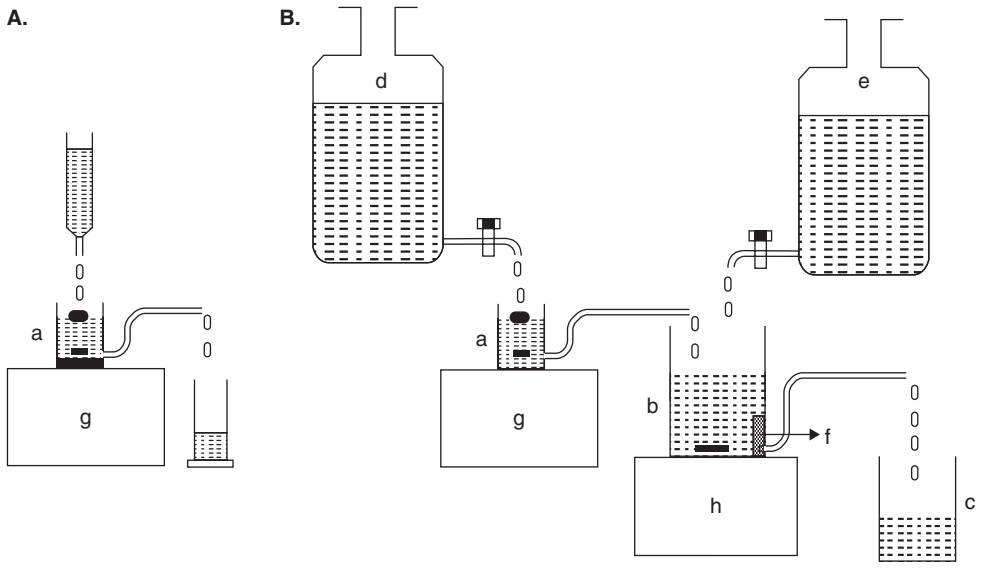

Figure 5. A. Modified Rossett–Rice apparatus. B. Biorelevant multicompartment dissolution apparatus. a. Gastric compartment, b. intestinal compartment, c. absorption compartment, d. gastric reservoir, e. intestinal reservoir, f. filter, g. and h. magnetic stirrers with heater.

dissolution media and degrades continuously, may give an inaccurate estimate for the absorption of the drug from modified released formulations. To overcome this problem, researchers have further modified the method by collecting the dissolution medium eluted out from the side arm of a beaker into chloroform for the extraction of the drug to prevent further degradation of the released drug (i.e., mimicking absorption of the drug) [71].

Bajpai *et al.* [72] proposed a dissolution test with refreshing medium (DTRM) apparatus, which works on a similar principle to that of the modified Rossett–Rice apparatus. The separating funnel was modified to prepare the diffusion cell for mimicking gastric conditions.

Specifically for floating dosage forms containing poorly soluble weakly basic drugs, further improvement to the modified Rossett–Rice apparatus was carried out by Parikh *et al.* [73]. Poorly soluble weakly basic drug have higher solubility in acidic conditions (i.e., the stomach) and lower solubility but higher absorption (according to pH partition theory) in alkaline conditions (i.e., the intestine). Thus it is expected that the drug released in the acidic media would ideally be absorbed from the intestine. As described in **Figure 5B**, the novel multi-compartment dissolution apparatus consists of gastric, intestinal and absorption compartments in series. The volume of each compartment and the transfer rate of media to and from each compartment were set to mimic the *in vivo* conditions. The floating dosage form remains buoyant in the gastric compartment where the drug is released in the acidic media, transferred through an S-shaped side arm into the intestinal compartment where the drug is exposed to alkaline conditions. Due to the change in pH, a fraction of the drug may precipitate and the remaining soluble form of the drug is transferred to the absorption compartment via a filter. Essentially, this novel method is more biorelevant, as it predicts absorption of only the soluble fraction of the drug from the intestine, and improvement in the IVIVC may be expected.

4. *In vivo* evaluation of gastro-retention

Although various *in vitro* techniques are available to evaluate the gastro-retentive performance of dosage forms, *in vivo* evaluation techniques are considered to be the most reliable. Additionally, *in vivo* evaluation data would improve the prospects of obtaining a patent or filing a FDA registration of any novel GRDDS. Therefore, various *in vivo* techniques to study the gastro-retentive performance of dosage forms are mentioned.

4.1 Roentgenography

X-ray technique is the most widely used method for examination of internal body systems [74]. It is the simplest and cheapest compared to other methods for studying the gastro-retentive behaviour of dosage forms *in vivo*. Barium sulfate is a widely used radio opaque marker, which is incorporated within the dosage form, and X-ray images may be taken at various intervals to view the positioning of gastro-retentive dosage form *in vivo* conditions. For better exemplification of GRDDS by radiology, a high concentration of barium sulfate (40% or more)

is required, which would require changes in the formulation of GRDDS [75]. This problem can be overcome by incorporation of radio-contrast aluminium threads obtained from surgical gauze pads [63]. The major drawback of this technique is the amount of exposure of human volunteers to X-rays, which depends on exposure time, frequency and repetitions required to assess the efficacy. Higher exposures to X-rays lead to a hazardous risk to the human body.

4.2 γ-Scintigraphy

Similar to X-ray technique, γ-emitting materials may also be incorporated into the dosage form, where images may be captured using scintigraphy [76-80]. The widely used γ-emitting materials are ^{111}In (Indium) and ^{99m}Tc (Technetium). Recently this technique has gained importance because it is a highly sensitive method and uses lower doses of radiation, thus leading to less health hazards to the human volunteers. The method requires minor changes in the formulation, which is a unique feature compared to other marker-based techniques.

4.3 Gastroscopy

Gastroscopy is a peroral endoscopy technique used with fibre optics or video systems [81,82]. Gastroscopy is used to inspect visually the effect of prolongation of the dosage form in the stomach. It can also allow the withdrawal of the GRDDS from the stomach for thorough evaluation. GRDDS are intended to remain in the stomach for about 8 – 12 h; in order to assess the gastro-retentive performance by peroral endoscopy, the video system has to enter into the body of the volunteer at regular time intervals, making the procedure inconvenient to the volunteer, as well as necessitating the presence of a gastroenterologist for the entire evaluation study. These factors have lead to the limited use of gastroscopy.

4.4 Magnetic marker monitoring

In this technique, the dosage forms are magnetically marked by incorporating iron powder within the dosage forms. Images can then be captured by very sensitive biomagnetic measurement equipments [83-85]. The method does not involve the use of any radiation, thus it is less hazardous than the previous methods. However, the technique is not widely used because it requires formulative changes, that is incorporation of iron powder, which has higher density and may affect the performance of GRDDS.

4.5 Ultrasonography

In this technique, ultrasonic waves are reflected at substantially different acoustic impedances across an interface, enabling the imaging [86]. By transmission of ultrasonic waves, the acoustic mismatch is traced out across the interface between dosage form and physiological surface. However, this method is not popular due to lack of ultrasound traceability at the intestine. Another drawback of this method is some of the dosage forms may not exhibit a sharp acoustic mismatch.

4.6 ^{13}C octanoic acid breath test

Octanoic acid is a medium chain fatty acid absorbed by the upper part of the small intestine, rapidly transported to the liver and immediately oxidised by mitochondria to form CO_2, which is exhaled out in the breath [87-90]. In this method, ^{13}C octanoic acid is incorporated into the GRDDS. The carbon atom of octanoic acid which essentially forms CO_2 is replaced with the ^{13}C isotope. After ingestion of the dosage form, the time duration after which $^{13}CO_2$ gas is observed in the breath indicates the transfer of the dosage form from the stomach to the upper part of the small intestine, which may be considered as the gastric retention time of the dosage form.

5. Conclusion

Various evaluation techniques for an exhaustive study of GRDDS are summarised in this article, along with their advantages and limitations. Researchers may adopt suitable techniques to ensure optimum performance of the gastro-retentive formulation. The applications of biorelevant methods may reduce the risk of formulation failure in clinical trials. Future investigations may concentrate on the development of more biorelevant techniques.

6. Expert opinion

Retaining drugs in the stomach for an extended period of time by formulating GRDDS yields biomedical benefits. To ensure the retention of GRDDS for an intended time period, direct or indirect methods are employed to evaluate various *in vitro* and *in vivo* parameters, depending upon the type of GRDDS.

The floating dosage form should remain buoyant on the gastric fluid under continuous physiological movement of the stomach for a predetermined time period and should deliver the drug in the gastric fluid. Lag time and floating time are the essential parameters to assess the buoyancy. Larger values of lag time may sweep out the dosage form to the intestine, which may lead to the complete failure of the GRDDS. Evaluation of indirect measures such as specific gravity and porosity of the dosage form may support essential evaluation to ensure the buoyancy of floating GRDDS. The precise measurement of such parameters utilising sophisticated equipment facilitates optimisation of the formulation.

The continuous alteration in weight and volume of GRDDS owing to swelling and/or erosion of polymer, entrapment of gas and release of drug from the system affects the specific gravity and therefore buoyancy as a function of time. To assess the buoyancy for the entire floating time period, the 'resultant weight' method and continuous

floating monitoring system are novel sophisticated techniques. Such methods are used to monitor the buoyancy of GRDDS as a function of time and give an indication to researchers for formulative changes. The use of sophisticated techniques ensures the researcher that technologies have been developed successfully and are ready for application.

Raft types of GRDDS were the first to be launched in the market and several marketed antacid rafts are proving therapeutic competence; however, the lack of a thorough evaluation of the system can be observed in various research papers. The function of the raft is not only to retain the system in the stomach for local drug delivery, but also to act as a physical barrier for preventing the transfer of the gastric content to the oesophagus. To act as a barrier, the raft must have physical strength to resist its rupture against stomach motility as well as gastric reflux. The use of sophisticated instruments such as texture analysers for determining various parameters defining the strength of the raft assures the formulators of comprehensive functionality of the raft *in vivo*.

The expandable types of GRDDS are retained in the stomach by *in situ* enlargement of the dosage form either by swelling or unfolding mechanism. The majority of swellable GRDDS are formulated with hydrogels, which swell after coming in contact with the dissolution media and may also float by reducing the specific gravity. The evaluation of indirect parameters like swelling index and water uptake rate gives an idea about the critical properties such as expanding capacity, as well as rate of expansion of GRDDS. The current article summarises the various methods in sequential order, which demonstrates the initiatives taken by scientists for continuous improvisation in evaluation techniques. Magnetic resonance imaging technique may also be employed to monitor the hydration and swelling process of GRDDS [91,92].

Shape memory is the characteristic property of the unfolding type of GRDDS, by which the expanded dosage form resists its transfer through pyloric sphincter. The first step towards gastro-retention prior to shape retention is the complete expansion from the coiled structure, which can be precisely assessed by exposed size parameter.

Despite several demerits, *in vitro* dissolution testing for the majority of GRDDS are carried out by traditional USP dissolution apparatus type I or II. The modifications recommended to conventional methods by various researchers helps to reduce batch-to-batch variability, to enhance reliability and reproducibility of dissolution profiles and to achieve better IVIVC [93]. Reports suggest that increased gastric retention in fed state compared to the fasted condition. Floating systems need the presence of gastric fluid to float on, which is available in the fed state. Expandable systems will also prolong gastric retention time in the presence of a meal. The lack of availability of more biorelevant dissolution media mimicking the *in vivo* physiological condition of the stomach is the current problem for exhaustive evaluation. Although various *in vitro* tests proposed by various scientists recommend an improvement in IVIVC, scientists have been unable to meet this need. Therefore IVIVC testing must be performed for all *in vitro* methods in order to suggest the best technique.

Currently, several pieces of equipment mimicking the gastrointestinal tract have been designed to predict drug absorption [94-99], and are still not used specifically for GRDDS, may be adopted by researchers for in-depth evaluation.

In spite of thorough *in vitro* evaluation of the gastro-retention, one must assess the *in vivo* performance to ensure functionality of GRDDS. Various routinely used techniques for *in vivo* visualisation of GRDDS are described in this review, with their advantages and demerits. None of the methods summarised are as relevant as scintigraphy, owing to their safety, speed and ability to assess the dosage forms without significant modifications. The breath test is a unique class of pathologic test, whereby various physiological parameters are evaluated by assessing the presence of particular chemical or biological substances in the breath. The octanoic acid breath test was used for gastric emptying time for some pathological conditions and the application of such a test for the evaluation of formulation performance opens up a new area for researchers. Other biochemicals used in place of octanoic acid in pathology may also be utilised for GRDDS evaluation [100-102].

In addition, one should not neglect the evaluation of pharmacokinetic parameters for GRDDS compared to conventional CRDF to assure therapeutic improvement.

The summary of techniques mentioned in this article will provide easy access to researchers formulating GRDDS and ensure the success of the dosage form during clinical trials.

Declaration of interest

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

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