GASTRORETENTIVE DRUG DELIVERY SYSTEMS: FROM CONCEPTION TO COMMERCIAL SUCCESS

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ABSTRACT

Despite the extensive advancements in the field of drug delivery, the oral route remains the favorable route for administration of therapeutic actives. A success of oral controlled drug delivery systems is associated with reduced dosing frequency, decreased fluctuation in plasma drug concentration profile along with improved patient compliance. However, they are also associated with challenges like shorter gastric residence time, unpredictable gastric emptying and poor bioavailability for some molecules. This has initiated tremendous advancements in the field of gastro-retention to achieve controlled release of drugs along with improved bioavailability of drugs with narrow absorption window as well as localized action in the stomach and upper part of GIT. In present review, efforts have been envisaged to summarize our current understanding in the field of gastro-retention and their \textit{in vitro} as well as \textit{in vivo} characterization. Present review also highlights commercially utilized gastro-retentive technologies and some recently granted US patents in the field of GRDDS.

Keywords: Gastro retentive drug delivery systems (GRDDS), Gastric emptying, Polymers, Bioavailability, Superporous hydrogels, Swellable matrix, Microballoons, Patents

INTRODUCTION

In controlled drug delivery, a given drug needs to be entrapped in a platform, device or any matrix that can later on be released in a controlled way. If the drug is intended to be released at a specific site or organ and taken orally, the whole system is called oral targeted drug delivery system. One of the targets in oral controlled delivery is the stomach area. The stomach can be either a target organ or can serve as a reservoir to release the drug at the specific site. In either case, the drug is required to stay in the stomach area and the challenge will be to find ways to do the task [1].

Main challenges in designing Gastro-retentive dosage forms are shorter gastric residence time and unpredictable gastric emptying times. So before designing any GRDDS, basic understanding regarding anatomy and physiology of GIT is required to modulate gastro-intestinal transit time of drug for better absorption of drugs and site-specific drug delivery [2].

Basic anatomy and physiological aspects of the GIT

The stomach is anatomically divided into three parts: fundus, body and pylorus (pyloric antrum and pyloric sphincter). The proximal stomach, made up of the fundus and body regions, serves as a reservoir for ingested materials while the distal region, pylorus, is the major site for mixing motions, acting as drain pump to the duodenum to accomplish gastric emptying, given in fig.1.

The complex anatomy and physiology of the GIT, including variations in acidity, bile salts, enzyme content, and the mucosal absorptive surface, significantly influence the release, dissolution, and absorption of orally administered dosage forms.

Two distinct patterns of gastrointestinal (GI) motility and secretion exist, corresponding to the fasted and fed states. As a result, the BA of orally administered drugs will vary depending on the state of feeding. The fasted state is associated with various cyclic events which cycle both through the stomach and small intestine every 2-3 h [4], commonly referred to as the interdigestive myoelectric cycle or interdigestive migration myoelectric complex (IMMC), which regulates GI motility patterns. The IMMC is organized into alternating cycles of activity and quiescence and can be subdivided into different phases [5, 6], as depicted in fig. 2.
The performance of oral controlled release drug delivery systems (CRDDS) is also influenced by a phase during which dosage form has been administered.

Approaches for gastric retention

Fig. 3 illustrates various approaches for gastric retention. Various approaches are available to prolong the retention of dosage forms in the stomach. The most common approaches used to increase the gastric residence time of dosage forms include high density systems, floating systems (Effervescent and non-effervescent systems), bioadhesive systems, raft forming systems, low density systems, swelling and expandable systems etc.

High density systems

Dosage forms having density from 1.0 to certain higher values can increase the average GI transit time [7]. Systems having density of ~3.0 g/cm³ are retained in the rugae of stomach and able to withstand its peristaltic movements. However, such type of dosage forms are technically difficult to manufacture with a large amount of drug and to achieve density of 2.4-2.8 g/cm³. Diluents such as barium sulphate, zinc oxide, titanium dioxide can be used to prepare such high density dosage forms [2].

Floating systems

Floating drug delivery systems are having bulk density less than gastric fluids and therefore remain buoyant in the stomach without affecting the gastric emptying rate for extended period of time. When the system is floating on the gastric contents, the drug is released in controlled manner from the system. After release of drug, the residual system is emptied from the stomach [2].

Floating properties based on the mechanism of buoyancy are divided into:

1) Effervescent systems with low density due to gas generation and entrapment; and
2) Non-effervescent systems with inherent low density or low density due to swelling.

Effervescent floating drug delivery systems

This approach provides floating drug delivery systems based on the formation of CO₂ gas. It utilizes effervescent components such as sodium bicarbonate (NaHCO₃) or sodium carbonate, and optionally citric or tartaric acid. Upon contact with the acidic environment, a gas is liberated, which produces an upward motion of the dosage form and maintains its buoyancy. A decrease in specific gravity causes the dosage form to float on the chyme. Such effervescent system is often combined with swellable and rate controlling polymers like hypromellose and polyethylene oxide. Such combined system provides additional buoyancy and increased gastro retention through expanding mechanism and low density.

Zou et al. [8] developed a floating pulsatile drug delivery (FPRT) system of Verapamil HCl using dry coating technique. The tablet consists of bilayer tablet in which one layer is buoyant layer and other layer is composed of dry coated tablet containing drug-containing core, coated by a hydrophilic polymer which is responsible for a lag phase in the onset of pulsatile drug release. The buoyant layer, prepared with Methocel® K4M, Carbopol® 934P and sodium bicarbonate, provides buoyancy to increase the retention of the oral dosage form in the stomach. The results exhibited a certain lag time before the drug release is mainly due to the erosion of the dry coated polymer layer. Floating time was manoeuvred by the quantity and composition of the buoyant layer.

Ravi Kumar et al [9] prepared floating effervescent tablets of Famotidine utilizing hydrocolloids like various grades of HPMC and Carbopol® 934P and gas-forming agents like sodium bicarbonate and citric acid. The optimized formulation was subjected to various kinetic release investigations and it was found that the mechanism of drug release was predominantly diffusion with polymeric relaxation.

Someshwar et al [10] prepared effervescent floating matrix tablets of Tizanidine hydrochloride using different viscosity grades of HPMC and sodium bicarbonate. Further, tablets were studied for in vitro drug release characteristics for 12 h. Based on the release kinetics, all formulations best fitted the Higuchi, first-order model and non-Fickian as the mechanism of drug release.

Chaitanya et al [11] developed Levodopa effervescent floating tablets by direct compression method using different high molecular weight grades of Polyethylene oxide (Polyox). Among all
formulations studied, formulation containing Polyox WSR 303 in 1:1 drug polymer ratio showed controlled drug release for 12 h.

Non-effervescent floating drug delivery systems

Systems with initially low density are highly desired, since they prevent the risk of premature emptying from the stomach. Inherent low density can be provided by entrapment of air, or by the incorporation of low-density materials, such as fatty substances or oils, or foam powder. The air trapped by the swollen polymer imparts buoyancy to these dosage forms. In addition, the drug is slowly released by controlled diffusion through the gelatious barrier.

Sheth and Tossounion developed hydrodynamically balanced systems (HBS™) containing homogenous mixture of gel-forming hydrocolloids and drug which upon contact with gastric fluid acquired and maintained overall specific gravity less than that of gastric contents (~1.004-1.01),[12]

Kumar et al.[13] has proposed glycerol monooleate (GMO) matrices as gastroretentive carrier systems. The GMO matrices were prepared by melting GMO at 55 °C on a water bath, adding the drug under stirring and pouring the molten mass into cylindrical moulds (8.5 mm inner diameter and 10 mm height) and further frozen at -15 °C. The matrices were equilibrated at room temperature for 24 h before evaluation. The GMO matrices significantly swelled in water and the swollen mass floated at the surface after a certain lag time for 5-6 h.

Yan et al.[14] developed wax based floating sustained release dispersion pellets for a weakly acidic hydrophilic drug protocatechuic acid. This low-density drug delivery system composed of octadecanol/microcrystalline cellulose matrix polymer cores prepared by extrusion-spheronization technique, coated with drug/ethyl cellulose 100cp solid dispersion using single-step fluid-bed coating method. The formulation-optimized pellets could maintain excellent floating state without lag time and sustain the drug release efficiently for 12 h based on non-Fickian transport mechanism.

Non-effervescent floating matrix tablets utilize matrices prepared using swellable and retardant polymers without any effervescent agents.

Oh et al.[15] developed Metformin floating gastroretentive tablets using camphor as sublimation material and PEO as hydrophilic polymer. Floating gastro-retentive tablets have no floating lag time and floated for over 24 h. The mechanism employed for drug release from the GR tablets was diffusion combined with erosion.

Negi et al.[16] prepared floating non-effervescent matrix tablets of Ciprofloxacin HCl using HPMC K4M and Eudrahix ferox seeds powder (EFSP). The floating behaviour of tablets was found to be dependent upon particle size of EFSP. Most of the formulations were best fitted with Korsmeyer-Peppas and zero order release kinetics.

Table 1: Different approaches utilized for raft based drug delivery systems[19]

| Main approach | Type               | Mechanism                                                                 | Polymers utilized                                                                          |
|---------------|--------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Raft formation based on physical mechanism | Swelling based | Gel formation occurs when liquid effervescent system comes in contact with gastric fluid. | Swellable polymers (like HPMC) absorb water from surrounding fluid and expand at the desired space along with CO₂ formation to float upon gastric fluid. Myverol 18-99 (glycerol mono-oleate), is a polar lipid that undergoes in situ gelling in the presence of divalent/polyvalent cations like Ca²⁺ due to the interaction with gularonic acid block in alginate chains. N-methyl pyrrolidone (NMP) solution. |
| Raft formation based on chemical mechanism | Diffusion | Diffusion of a solvent from polymer solution into surrounding tissue, which further results in precipitation or solidification of polymer matrix. Various ion-sensitive polysaccharides undergo phase transition in presence of various monovalent and divalent cations and cause gelation. | Alginate acid undergoes gelation in the presence of divalent/polyvalent cations like Ca²⁺ due to the interaction with gularonic acid block in alginate chains. K-carrageenan forms rigid, brittle gels in response to small amount of K⁺, i-carrageenan forms elastic gels mainly in the presence of Ca²⁺. Gellan gum (Gelrite®) is an anionic polysaccharide that undergoes in situ gelling in the presence of mono-and di-valent cations. |
Hollow microspheres can be prepared by following techniques: widely distributed in GI tract upon administration and provide more issue, multiple unit floating systems can be designed which can be time, due to its “All or nothing” emptying process. To overcome this unit systems. They are having cons of high variability of the GI transit. Most of the floating drug delivery systems are dominated by single unit systems. Microballoons (Floating microspheres) suitable size hard gelatin capsules for ease of administration. These drug filled SPHCs can also be filled in fashion (see 5). Alternatively, these drug-filled SPHCs can also be filled in the presence of gas bubbles formed by chemical reaction of acid and sodium bicarbonate. This was followed by dehydrating water-swollen hydrogels with ethanol and drying. Equilibrium swelling time can be reduced to less than one minute.[28] Several important properties of SPH such as fast swelling, large swelling ratio and surface slipperiness makes SPH as good candidate material for gastric retention devices.[29] Several superdisintegrants, Ac-Di-Sol®, Primojel®, Epliotab®, and Polyplosdone® were used as model composite materials to promote the swelling speed and to improve the mechanical properties. Ac-Di-Sol® was found to be the best composite material among those excipients. The main role of Ac-Di-Sol® was to increase the physical crosslinking of polymer chains so that the porous structure was maintained during drying of the SPHs.[29]

Superporous Hydrogels

Hydrogels are cross-linked hydrophilic polymers with a network structure. They are able to imbibe large amounts of water and are water insoluble.[20–22] For pharmaceutical applications, they are unique carriers for controlled drug delivery; release control can be governed by both swelling and biodegrading properties. Owing to their high water affinity and biocompatibility, hydrogels based on poly(acrylic acid) and its derivatives[23, 24], Chitosan[25], alginate[26] and collagen[27] have attracted attention.

Chen J et al. prepared a new generation of hydrogels called superporous hydrogel (SPH). They developed super porous hydrogels by crosslinking polymerization of various vinyl monomers in the presence of gas bubbles formed by chemical reaction of acid and sodium bicarbonate. This was followed by dehydrating water-swollen hydrogels with ethanol and drying. Equilibrium swelling time can be reduced to less than one minute.[28] Several important properties of SPH such as fast swelling, large swelling ratio and surface slipperiness makes SPH as good candidate material for gastric retention devices.[29] Several superdisintegrants, Ac-Di-Sol®, Primojel®, Epliotab®, and Polyplosdone® were used as model composite materials to promote the swelling speed and to improve the mechanical properties. Ac-Di-Sol® was found to be the best composite material among those excipients. The main role of Ac-Di-Sol® was to increase the physical crosslinking of polymer chains so that the porous structure was maintained during drying of the SPHs.[29]

Superporous Hydrogel Composites (SPHCs), as the second-generation of SPHs, possess improved mechanical properties over SPHs, with composite agents such as, Chitosan[30, 31] Ac-Di-Sol[32, 33] and Carbopol®[34]. After preparation of these SPHCs, they can be drilled and filled with drug-polymer mixture to provide drug delivery in sustained fashion (see 5). Alternatively, these drug-filled SPHCs can also be filled in suitable size hard gelatin capsules for ease of administration.

**Microballoons (Floating microspheres)**

Most of the floating drug delivery systems are dominated by single unit systems. They have cons of high variability of the GI transit time, due to its “All or nothing” emptying process. To overcome this issue, multiple unit floating systems can be designed which can be widely distributed in GI tract upon administration and provide more reliable and long-lasting drug delivery to stomach[36]. Hollow microspheres can be prepared by following techniques:

| 1. Solvent evaporation technique |
| 2. Emulsion solvent diffusion technique |
| 3. Spray drying method |

These techniques are discussed in detail in following sections:

**Fig. 5: Schematic diagram of SPHC-drug delivery system (Core inside the shuttle system) (Adapted from [31])**

Solvent evaporation technique

There are different methods to use microencapsulation by solvent evaporation technique. The choice of the method that will give rise to an efficient drug encapsulation depends on the hydrophilicity or the hydrophobicity of drug.

For insoluble or poorly water-soluble drugs, the oil-in-water (o/w) method is frequently used. This method is the simplest and the other methods derive from this one. It consists of four major steps[37] (see 6):

1. **Dissolution of the hydrophobic drug in an organic solvent containing the polymer;**
2. **Emulsification of this organic phase (dispersed phase) in an aqueous phase (continuous phase);**
(3) After formation of stable emulsion, evaporation of the solvent from the dispersed phase by increasing temperature or under continuous stirring at room temperature, transforming droplets of dispersed phase into solid particles; and (4) Recovery and drying of microspheres to eliminate the residual solvent.

For hydrophilic drugs, above method is not suitable due to poor solubility of drug in oil phase (dispersed phase). For such water soluble drugs following variants have been proposed by Li et al.[37]:

a) The w/o/w double emulsion method: the aqueous solution of drug is emulsified with organic phase (w/o emulsion) which is further dispersed into a second aqueous solution forming w/o/w double emulsion

b) The o/w co-solvent method: when the drug is not soluble in the main organic solvent, a second solvent called co-solvent is required to solubilize the drug

c) The o/w dispersion method: The drug is dispersed in form of solid powder in organic solution of the polymer

d) The o/o non-aqueous solvent evaporation method: the aqueous phase is replaced by oil such as mineral oil.

Table 2 lists the components used to prepare hollow microspheres by solvent evaporation technique

Solvent evaporation method is simplest method to form microspheres where process can be controlled easily and formed microspheres show good product yield and high encapsulation efficiency. However, this technique possesses limitation like rate of solvent removal which can affect physicochemical properties of formed hollow microspheres.

**Emulsion solvent diffusion technique**

Kawashima et al.[36] prepared hollow microspheres (microballoons) by novel emulsion solvent diffusion technique based on enteric acrylic polymers containing the drug in the polymeric shell. The preparation method and mechanism of microballoon formation is illustrated in 7.

### Table 2: List of components used to prepare hollow microspheres by solvent evaporation technique [37, 38]

| Organic Solvents | Polymers                     | Surfactants                                      |
|------------------|------------------------------|--------------------------------------------------|
| Chloroform       | Ethyl Cellulose              | Non-ionic: Partially hydrolyzed PVA, Tween, Span  |
| Ethyl acetate    | Hypermellose                 | Anionic: sodium dodecyl sulphate (SDS)           |
| Ethyl formate    | Methyl cellulose             | Cationic: Cetyltrimethyl ammonium bromide (CTAB) |
| Dichloromethane  | Cellulose acetate            |                                                  |
|                  | Chitosan                     |                                                  |
|                  | Eudragit® RS 100             |                                                  |
|                  | Eudragit® RL 100             |                                                  |
|                  | Eudragit® S 100              |                                                  |

**Fig. 6: Schematic presentation of microspheres preparation by solvent evaporation technique**

**Fig. 7: Schematic presentation of microballoon preparation by emulsion solvent diffusion technique**
The drug and enteric polymer were dissolved in mixture of ethanol and dichloromethane (1:1) at room temperature. The drug-polymer dispersion was poured into water containing polyvinyl alcohol at 40 °C under agitation. The ethanol rapidly diffuses into aqueous medium, and then the equilibrium concentration of ethanol was retained during the preparation of microbaloons. In contrast, the dichloromethane did not diffuse thoroughly from the droplets into aqueous phase but partly resided in the droplets. During the preparation, the concentration of dichloromethane in the aqueous phase decreased due to evaporation from the system. Evaporation of dichloromethane leaves internal cavities in the microspheres which are useful for buoyancy of the microspheres. Table 3 lists the components used to prepare hollow microspheres by this technique.

Table 3: List of components used to prepare hollow microspheres by emulsion solvent diffusion technique[36, 39–43]

| Organic solvents | Oil | Polymers | Surfactants | Dispersing agent | Stabilizer |
|------------------|-----|----------|-------------|------------------|-----------|
| Ethanol          | Gorn Oil | Eudragit L 100 | Span 80 | Polyvinyl alcohol | Monostearin |
| Dichloromethane  | Ethylcellulose | Eudragit S 100 | Tween 80 |
| Petroleum ether  | Hypromellose | Eudragit L 100 |
| Isopropanol      | Eudragit RLPO | Eudragit L100-55 |
|                  | Glycerol monooleate | Eudragit S 100 |

Spray drying method

Spray drying is the most widely used method for particle formation and drying. It is an ideal process where the required particle size distribution is narrow and required size of products can be obtained in a single step [44]. The mechanism of spray drying can be explained as follows. First, when the slurry is sprayed into the drying chamber, concentration gradient of the solute forms inside the small droplet with the highest concentration being at the droplet surface. This ultimately results in solid shell with increase of the quantity of solutes on the surface and so the internal pressure increases because the moisture cannot be released instantly. If the shell has porous structure, the pressure can be released slowly and the hollow structure forms, otherwise fractured shell will appear. Separation of the solid products from the gases is usually achieved by means of a cyclone separator and the products are stored for further use [45].

Aute et al.[46] developed gastroretentive floating microspheres of Nizatidine using both solvent evaporation and spray drying techniques. Entrapment efficiency was found to be 60-90% for solvent evaporated microspheres, and 60-80% for spray dried microspheres. In vitro drug release for all the formulations in 0.1 N HCl was diffusion controlled gradually up to 8 h and followed by first order kinetics.

Mane et al.[47] developed and evaluated Carvediol microspheres by spray drying technique using ethyl cellulose and PEG 6000. The developed microspheres were in size ranging from 13-22µ and shows drug release retardation up to 12 h. However, these microspheres are having poor flowability due to cohesive ness.

Swelling and expanding systems

The expansion of this type of DDS is generally due to the presence of specific hydrogel formers, which after swallowing, drastically increase in size upon contact with aqueous media. This increase in size prevents their exit from the stomach through the pyrerus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be referred to as the “plug type systems” since the dosage form is retained in the stomach for a long period of time.

Unfolding and modified shape systems

These are non-disintegrating geometric shapes moulded from silastic elastomer or extruded from polyethylene blends, which extend the gastric residence time depending on size, shape and flexural modulus of the drug delivery device. Devices with different geometrical shapes such as continuous solid stick, tetrahedron, ring, cloverleaf, planer disk, string and pellet/sphere were investigated. These systems consist of at least one erodible polymer (e. g., Eudragit® E, hydroxypropyl cellulose (HPC)), one nonerodible polymer (e. g., polyamides, polylefins, polyurethanes), and a drug dispersed within the polymer matrix. Cloverleaf, disk, string and pellet shapes were moulded from silastic elastomer, while tetrahedron and rigid-ring shapes were fabricated from blends of low-density polyethylene and ethylene:vinyl acetate copolymer [7].

Bioadhesive or mucosalhesve systems

Bioadhesive or mucosalhesive drug delivery systems are used to localize a delivery device within the lumen to enhance the drug absorption in a site specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface of the stomach. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, Carbopol®, lectins, chitosan, CMC etc. [49].

This type of dosage form offers following advantages:
1. Prolongs residence time in upper GIT
2. Enhances absorption and hence bioavailability of drug
3. Improved patient compliance

Following properties are exhibited by good mucosalhesive polymers:
1. Strong hydrogen-bonding groups [-OH,-COOH]
2. Strong anionic charges
3. Sufficient flexibility to penetrate the mucus network
4. Surface tension characteristics suitable for wetting mucus/mucosal tissue surface
5. Polymer must have high molecular weight to promote adhesion between polymer and mucus.

The mucosalhesive polymers can be classified as-

a) Hydrophilic polymers: Matrices developed with these polymers swell when put into aqueous media with subsequent dissolution of the matrix. The polyelectrolytes extend greater mucosalhesive property when compared with neutral polymers. Examples are PVP, Methyl cellulose, Sodium carboxymethyl cellulose, Hydroxypropyl cellulose

b) Hydrogels: This type of polymer swells when in contact with water and adhere to the mucus membrane. These are sub-classified as-

Synthetic polymers-Cellulose derivatives, Carbopol®
Natural polymers-Tragacanth, pectin, gelatin, sodium alginate, acacia

c) Newer second generation polymers:

i) Lectins: Lectins are naturally occurring proteins that are useful in biological recognition involving cells and proteins. Lectins are a class of structurally diverse proteins and glycoprotein that bind reversibly to specific carbohydrate residues.
ii) Thiolated polymers: These are thiomers which are derived from hydrophilic polymers such as polycrylates, chitosan or deacetylated gelan gum. The presence of thiol group increases residence time by promoting covalent bonds with the cysteine residues in mucus.

iii) Sentry Polyox WSR: These are high molecular weight polyethylene oxide having good mucoadhesion e.g. Sentry Polyox WSR 303 etc.

Mucoadhesive gastroretentive microspheres

Mucoadhesive gastroretentive microspheres are controlled drug delivery systems which provide mucoadhesion along-with gastroretention.

Mucoadhesive microspheres can be manufactured using any of the following techniques:

a) Solvent evaporation
b) Hot melt microencapsulation
c) Hydrogel microspheres
d) Spray drying

Out of above, solvent evaporation and spray drying techniques are already discussed in detail under microballoons section.

Hot melt microencapsulation

This method was first utilized by Mathiowitz and Langer [48] to prepare microspheres of poly (bis-(p-carboxyphenoxy) propane anhydride) (PCPP) copolymerized with sebacic acid (SA). Ratio of PCPP to SA was kept at 21:79. The polymer is first melted and then mixed with solid particles of the drug with particle size less than 50 μm. The mixture is suspended in a non-miscible solvent (like silicone oil), continuously stirred, and heated to 5 °C above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting microspheres are washed by decantation with petroleum ether. The primary objective for developing this method is to develop a microencapsulation process suitable for the water labile polymers, e.g. polyamphdrides.

Hydrogel microspheres[49]

Microspheres made of gel type polymers, such as alginate, are produced by dissolving the polymer in an aqueous solution, suspending the drug in the mixture and extruding through a precision device, producing micro droplets which fall into a hardening bath that is slowly stirred. The hardening bath usually contains calcium chloride solution, whereby the divalent calcium ions crosslink the polymer forming gelled microspheres. The method involves an all-aqueous system and avoids residual solvents in microspheres.

Evaluation of mucoadhesion

The best approach to evaluate mucoadhesive microspheres is to evaluate the effectiveness of the mucoadhesive polymer to prolong the residence time of drug at the site of absorption, thereby increasing absorption and bioavailability of the drug. The quantification of the mucoadhesive forces between polymeric microspheres and the mucosal tissue is a useful indicator for evaluating the mucoadhesive strength of microspheres. In vitro techniques have been used to test the polymeric microspheres against a variety of synthetic and biological tissue samples, such as synthetic and natural mucus, frozen and freshly excised tissue, etc.

Table 4 illustrates various in vitro tests for evaluation of mucoadhesion of dosage forms.

| Tests                                      | Method                                                                 |
|--------------------------------------------|------------------------------------------------------------------------|
| Tensile stress measurement using Wilhelmy plate technique | The Wilhelmy plate technique is generally used for the measurement of dynamic contact angles and involves the use of a microtensiometer or a microbalance. By using the CAHN software system, three essential mucoadhesive parameters can be analyzed: fracture strength, deformation to failure and work of adhesion. |
| Novel electromagnetic force transducer (EMFT) | The electromagnetic force transducer (EMFT) is a remote sensing instrument that uses a calibrated electromagnet to detach a magnetic loaded polymer nanoparticle/microsphere from a tissue sample. It has the unique ability to record remotely and simultaneously the tensile force information as well as high magnification video images of mucoadhesive interactions at near physiological conditions. The EMFT measures tissue adhesive forces by monitoring the magnetic force required to exactly oppose the mucoadhesive force. The primary advantage of the EMFT is that no physical attachment is required between the force transducer and the particle. |
| Shear stress measurement                    | The shear stress measures the force that causes a mucoadhesive to slide with respect to the mucus layer in a direction parallel to their plane of contact. Adhesion tests based on the shear stress measurement involve two glass slides coated with a polymer and a film of mucus. Mucus forms a thin film between the two polymer coated slides, and the test measures the force required to separate the two surfaces. |
| Miscellaneous methods                       | Adhesion number, in vitro wash-off test for microspheres, falling liquid film method, everted sac technique, novel rheological approach, flow-through approach etc. |

In vitro characterization of gastroretentive dosage forms

There are several parameters which are commonly applicable to all types of gastroretentive drug delivery systems e.g. drug content, related substances, residual solvents etc. as per compendial or regulatory requirements. But there are specific parameters which can be adapted for evaluation depending upon type of dosage form. Various parameters need to be evaluated for gastro retention are mentioned below:

Buoyancy lag time

It is determined in order to assess the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. This parameter can be measured as a part of the dissolution test.

Total floating time

Test for floatation is usually performed in SGF-Simulated Gastric fluid maintained at 37°C. The time for which the dosage form continuously floats on the dissolution media is termed as total floating time.

Resultant weight determination

Bulk density and floating time are the main parameters for describing buoyancy. But only single determination of density is not sufficient to describe the buoyancy because density changes with change in resultant weight as a function of time. So to measure real floating capabilities of a dosage form, novel method has been devised by Timmermans and Moes[50] Novel apparatus (resultant weight apparatus) and method has been designed to monitor in vitro the total force F acting vertically on an immersed object. This force F determines the resultant weight of the object in immersed conditions and may be used to quantify its floating or non-floating capabilities. The magnitude and direction of force F, and hence resultant weight, correspond to the vector sum of the buoyancy (F buoy) and gravity (F grav) forces acting on the object.

\[ F = F_{buoy} - F_{grav} \]
gamma emitting radionuclides, e. g. Technetium-99m (Tc-99m), are used to visualize the food or fluid for gastrointestinal transit. Visualisation is achieved by the incorporation of short half-life isotopes of the radionuclide into the fluid. [50]

The resultant weight apparatus operates by measuring the force equivalent to F required to maintain the object totally submerged in the fluid. [50]

Swelling index

After immersion of swelling dosage form into SGF at 37°C, dosage form is removed out at regular interval and dimensional changes are measured in terms of increase in tablet thickness/diameter with time [51].

Water uptake

It is an indirect measurement of swelling property of swellable matrix. The study is done by immersing the dosage form in SGF at 37°C and determining the dimensional changes like tablet diameter and/or thickness at regular intervals, the tablets were removed from beaker, and the excess surface liquid was removed carefully using the paper. The swollen tablets were then reweighed and WU is measured in the terms of percent weight gain, as given by equation:

\[
WU = \frac{Wt - Wo}{Wo} \times 100
\]

In which Wt and Wo are the weights of the dosage form at time t and initially, respectively.

Dissolution study

Dissolution is carried out for quality control purposes and also to establish in vitro in vivo correlation. Traditional compendia dissolution methods have been shown to be poor predictors of in vivo behavior of gastro retentive dosage forms [52]. USP apparatus 2 is associated with problems like adherence of dosage form on the shaft, test does not mimic the release of acid from stomach lining and gastric emptying through pylorus opening.

In case of USP apparatus 4, the dosage form remains stationary during the test in the cell and hence floating ability cannot be examined effectively. Gohel et al. [52] proposed modified version of Rossett-Rice Test apparatus (see 8) which is a popular in vitro test for evaluating the neutralization efficiency of antacids. A 100 ml glass beaker was modified at the base by adding an S-shaped glass tube so that the glass beaker can hold 70 ml of dissolution medium. The medium was stirred on a magnetic stirrer. A burette was mounted above the beaker to deliver the dissolution medium at a flow rate of 2 ml/min.

**In vivo characterization of gastro retentive dosage forms**

**X-Ray radiography**

The floating behavior of monolithic or multiple unit systems (Microballoons, minitablets etc.) can be characterized by administering the same dosage form loaded with Barium sulfate (BaSO₄) as radiopaque agent, to human volunteers, beagle/mongrel dogs, albino rabbits, rats etc. The study can be conducted in fed and fasting conditions. The location of dosage form can be monitored in the gastric region at predetermined time intervals using X-Ray apparatus. Both floating time and GRT of the system can be recorded and studied [53].

**Gamma (ɤ)-scintigraphy**

Gamma scintigraphy is an imaging technique that enables the direct visualisation and quantification of events occurring in vivo, in real time. Visualisation is achieved by the incorporation of short half-life gamma emitting radionuclides, e. g. Technetium-99m (Tc-99m) and Indium-111 (111In). The chosen radionuclide(s) is used to label the drug product or, for pharmacodynamic investigations, the component of interest (e.g. food or fluid for gastrointestinal transit). The radiation dose to the subject is minimal. A gamma camera is used to detect the gamma rays and record these as primary counts which are represented as an image. 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 [53]. Nowadays, combination of scintigraphy technique with pharmacokinetic studies (pharmacoscintigraphy) has become a vital tool to provide information regarding the transit and release behaviour of dosage forms with subsequent drug absorption pattern [54].

**Pharmacokinetic studies**

Pharmacokinetics study is performed from blood sampling estimating Cmax, Tmax and AUC from the observed mean drug plasma concentration against time profile. K0 and t½ are also computed. The extent of absorption from the prepared test formulation relative to the marketed or nonfloating 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 [53].

**Clinical Significance of GRDDS**

Waterman et al. [55] has discussed regarding comparative clinical success of various types of gastroretentive dosage forms in humans. Despite the tremendous efforts have been envisaged in the field of gastroretentive drug delivery systems, only limited number of
dosage forms have succeeded to stay in stomach for extended period of time. Out of the three major GR technologies viz. mucoadhesion, floatation and expansion, only the latter appears to provide true gastric retention. To achieve adequate size to prevent passage through the pylorus yet be able to be swallowed requires very significant expansion at least in two dimensions after ingestion of dosage form. In addition, the expanded form must have adequate strength to withstand the forces in the stomach.

### Potential advantages of gastroretentive drug delivery systems

Various advantages of gastroretentive drug delivery systems are outlined below:

1. Improves bioavailability of P-glycoprotein substrates like Pregabalin, Gabapentin etc.
2. Increases bioavailability of drugs which are soluble at acidic pH e.g. Dipyridamole etc.
3. Produce extended release of drugs from dosage forms

4. Can provide site specific drug delivery and therefore useful in the treatments of stomach and small intestine (e.g. for treatment of H. pylori infection)
5. Provide controlled release mode of drug administration and minimizes fluctuation in blood drug concentrations (i.e. between peak and trough). Therefore, concentration dependent side effects can be minimized.

### Commercial products incorporating various gastroretention technologies

Following table summarizes some of the successful gastroretention technologies and their commercial examples [57]

### Recently granted US patents in the field of GRDDS

Following table highlights some of the recently granted US patents in the area of gastro retentive drug delivery technologies [58].

#### Table 5: Commercial products employing various gastroretentive drug delivery technologies

| Technology                      | Drug                       | Commercial products | Company                   |
|---------------------------------|----------------------------|---------------------|----------------------------|
| Bioadhesive tablets             | Rifaximin                  | Xifaxan             | Lupin, India               |
| Effervescent Floating System    | Ofloxacin                  | Zanocin OD          | Ranbaxy, India             |
|                                 | Metform in Hydrochloride   | Rifimet OD          |                          |
|                                 | Ciprofl oxacin             | Cifran OD           |                           |
| Colloidal gel forming floating system | Ferrous Sulfate         | Conviron            | Ranbaxy, India             |
| Foaming based floating system   | Simethicone                | Inon Ace Tablets    | Sato Pharma, Japan         |
| Polymers based swelling technology: Acuform | Gabapentin             | Graisse one daily  | Depomed, Inc., USA         |
|                                 | Tapentadol                 | Nucenta ER          |                           |
| Effervescent and swelling based floating system | Prazosin Hydrochloride | Prazopress XL       | Sun Pharma                 |
| Minextab Floating System        | Metform in hydrochloride   | Metformin hyd chl   | Galenix, France            |
|                                 | Cefaclor                   | Cefaclor LP         |                            |
|                                 | Tramadol                   | Tramadol LP         |                            |
| Erodible Matrix based system    | Ciprofl oxacin hydrochloride | Cipro XR         | Bayer, USA                 |
| Expandable film filled in capsule | -                         | Accordion Pill     | Intec Pharma               |
| Coated multilayer floating and swelling system | Baclofen           | Baclofen GRS        | Sun Pharma                 |
| Gastroretentive with osmotic system | Carvediol                | Coreg CR            | Glaxosmithkline            |
| Floating CR Capsule            | Levodopa and benserazide  | Medopar             | Roche, UK                  |
|                                 | Diazepam                   | Valrelease           |                            |
| Effervescent floating liquid alginate preparation | Alginic acid and sodium bicarbonate | Liquid Gaviscon | Reckitt Benckiser Healthcare, UK |
| Bilayer floating capsule        | Misoprostol                | Cytotec             | Pharmacia Ltd., UK         |
| Floating Liquid alginate        | Aluminium magnesium antacid | Topalkan           | Pierre Fabre Medicament, France |

#### Table 6: List of recently granted US patents [58]

| S. No. | US patent No | Title of patent | Publication Date/Year | Applicant/Owner                        |
|--------|--------------|-----------------|-----------------------|----------------------------------------|
| 1      | US 9393205 B2 | Gastroretentive Tablets | 19-Jul-16            | Sun Pharmaceutical Industries Ltd., Ranbaxy |
| 2      | US 9387179 B2 | Pharmaceutical Cyclosporin Compositions | 12-Jul-16 | Sigmoid Pharma Ltd. |
| 3      | US 9381163 B2 | Floating Capsules Encapsulating Particles Loaded With One Or More Drugs | 5-Jul-16 | Nanyang Technological University |
| 4      | US 9314430 B2 | Floating Gastric Retentive Dosage Form | 19-Apr-16 | Jagotec Ag |
| 5      | US 9301934 B2 | Gastric Retentive Dosage Forms For Extended Release Of Acamprosate Into The Upper Gastrointestinal Tract | 5-Apr-16 | Depomed Inc |
| 6      | US 9265722 B2 | Botulinum Toxin Formulation For Oral Administration | 23-Feb-16 | Allergan Inc |
| 7      | US 9259387 B2 | Carbidopa/Levodopa Gastroretentive Drug Delivery | 16-Feb-16 | Intec Pharma Ltd |
| 8      | US 9211263 B2 | Compositions And Methods of Treating Metabolic Disorders | 15-Dec-15 | Elcelyx Therapeutics Inc |
| 9      | US 9205094 B2 | Compositions Comprising Bile Acid Sequestrants For Treating Esophageal Disorders | 8-Dec-15 | Ironwood Pharmaceuticals |
| 10     | US 9198861 B2 | Methods Of Producing Stabilized Solid Dosage Pharmaceutical Compositions | 1-Dec-15 | Mallinckrodt Inc |
Present review describes recent innovations and techniques regarding fabrication and evaluation of gastroretentive drug delivery systems. Despite the numerous efforts seen in the last two decades in the field of GRDDS, only few products have been successfully reached to market due to limited clinical success for different types of GR dosage forms. Variable gastric emptying time is also one of the crucial factors for variable in vivo data for GR dosage forms. Gastric emptying time may largely depend upon type of food, caloric content, gender, age etc. [59]. So in future, more robust GR formulations need to be designed keeping in mind various physiological barriers to get reproducible gastro-retention. Also some novel natural and modified natural polymers need to be explored in conjunction with synthetic polymers to formulate dosage forms with more swelling and expanding capabilities along with sufficient matrix forming capabilities. This eventually results into formulation of dosage forms with better in vivo drug release profile with enhanced bioavailability.

This can be achieved by employing essential QbD principles and utilizing various experimental design (DOE) techniques.

### CONFLICTS OF INTERESTS

Declared none

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