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Gastro Retentive Drug Delivery Systems: A Review

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Gastric emptying is a complex and extremely variable process. This causes the unpredictability of the bioavailability of drug delivery systems. Gastro retentive drug delivery systems (GRDDS)s have received significant attention in the past decades primarily due to the fact that they can overcome the limitation of conventional oral controlled release drug delivery systems related to fast gastric emptying time. An optimum GRDDS can be defined as a system which remains in the stomach for a sufficient time interval and releases active ingredients in a controlled manner. This, significantly extends the duration of drug release, prolongs dosing interval and increases bioavailability of drugs and therefore improves compliance of the patients and effectiveness of pharmacotherapy. This article gives an overview of the main concepts used to design pharmaceutical dosage forms with prolonged gastric residence times as well as the parameters-affecting gastric emptying, advantages, shortcomings, formulation considerations and, factors that affect gastro retentive systems. The main emphasis is on the entire classification and different types of GRDDSs. Finally evaluation methods of these systems have been summarized.

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Introduction

Low cost, ease of administration and manufa- cturing process as well as flexibility in the formulation and higher level of patient compliance, make the oral route the most preferred and promising route of administration of therapeutic agents. Various drug delivery systems (DDS) have been developed for maximizing bioavailability, reducing drug waste, expanding therapeutic index and reducing the side-effects of the drug [1-6]. Production of oral controlled release (CR) formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long period of time. Despite major breakthroughs of the last decades in production of oral controlled drug delivery systems, there has been limited success in the case of drugs with poor absorption in the GIT [7-12]. Furthermore scintigraphic studies involving measurements of gastric emptying rates in healthy human subjects have revealed that several physiological problems such as inability to restrain and locate the drug delivery systems within the desired region of the GIT and the unpredictable gastric emptying time (approximately 8–12 hrs) variable gastric motility causes the major quantity of drug to be unabsorbed And it also reduces the efficacy of the administered dose because of the incomplete drug release from the dosage form. The gastric emptying of dosage forms in humans is affected by several factors and therefore wide inter- and intra-subject variations are observed [9, 13-16].

Furthermore the main concern in the development of once daily oral sustained release dosage form is not only to prolong the delivery of drugs for 24 hrs but also to extend the presence of dosage forms in the stomach or in the upper small intestine. Therefore, it is more desirable to design a controlled release drug delivery system (CRDDS) with extended GIT residence time and drug release independent of patient related variables such as age, race, sex, food eating habits and disease states, as they could seriously affect the release of a drug from the CRDDS [17-20]. GRDDS is an approach to prolong gastric residence time, by targeting site-specific drug release in the upper gastrointestinal tract for local or systemic effects.

Requirements for gastro retention

GRDDS is an approach to prolong gastric residence time (GRT) especially in the case of strong intestinal movement such as in diarrhea, drugs absorbed through the stomach, targeting site-specific drug release in the upper gastrointestinal tract for local or systemic effects, as well as slow content release to act as a reservoir and thus ensuring its optimal bioavailability. It is obvious that in order to achieve gastric retention ,the dosage form must have certain requirements . Mainly the dosage form must be able to withstand the forces that are caused by peristaltic waves in the stomach and the continuous contractions to resist early gastric emptying of drugsand also when its purpose has been served, the device should have the ability to leave the stomach easily and freely. [21-25]. Anatomy of stomach is shown in Figure 1.

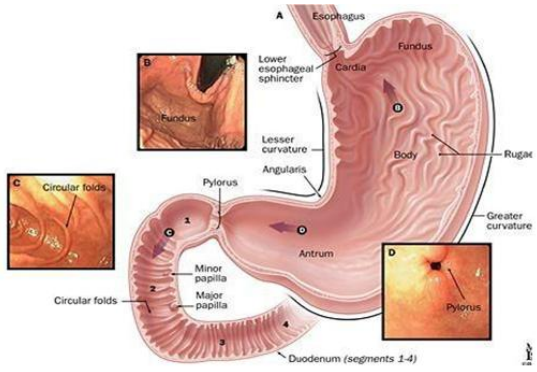

Fig. 1. Anatomy of Stomach

Advantages of GRDDS

Improving the local efficiency in the GIT sections over a prolonged period of time, limitation in the systemic exposure to the drugs, reduction in side effects of acidic drugs which cause irritation in the stomach wall and also reduction in the drug waste of the total administered dose and the administration frequency are main benefits of GRDDS. GRDDS minimized fluctuations in drug effects and concentration- dependent adverse effects which are associated with peak concentrations. These features are especially important for drugs with a narrow therapeutic index. Minimizing the fluctuations in drug concentration also makes it possible to obtain certain selectivity in the pharmacological effect of drugs that activate different types of receptors at

different concentrations [22, 24, 26-28]. These characteristics result in high patient compliance and therefore improve pharmacotherapy.

Need for gastro retention

Drugs acting locally in the stomach, drugs with short half-life's primarily or rapidly absorbed in the stomach and drugs that are eliminated quickly from the systemic circulation and are unstable in the intestinal or colonic environment that have narrow absorption window in GIT disturb normal colonic microbes, and drugs that exhibit low solubility at high pH values are good candidates for GRDDS [4, 24, 26, 29-31]. After oral administration, such a drug delivery system would be retained in the stomach and would release the drug in a controlled manner, in such a way that the drug could be provided continuously to its absorption sites in the GIT and assure the maintenance of effective drug concentration in the systemic circulation for a long time.

Drugs which are unsuitable for GRDDS

There are certain situations where gastric retention is not a desirable option and will not benefit from incorporation into gastric retention systems, including drugs that are unstable in acidic environments, drugs that have very limited acid solubility, drugs which undergo significant first pass metabolism, drugs that are intended for selective release in the colon and non-steroidal anti-inflammatory drugs which cause gastric injuries. Other limitations of GRDDSs are those kinds of drugs that need sufficiently high levels of fluids in the stomach and presence of food to delay their gastric emptying period. [32-37].

Factors controlling gastric retention of dosage forms

The most important parameters affecting gastric emptying and hence the gastric retention time of oral dosage forms include: age, gender, body mass index, physical activity, disease states molecular weight. lipophilicity of the drug and density, size and shape of the device. Simultaneous administration of drugs also affects GRT, including drugs acting as anticholinergic agents, opiates and pro-kinetic agents, and because the aforementioned factors vary,therefore the prolongation process cannot be predicted precisely [24, 26, 38-41].

Ingredients used for the preparations of GRDDS

Various ingredients are used in GRDDS. The following polymers have been frequently used for preparation of floating drugs: HPMC K4 M, HPMC K15, HPMC K4, HPMC 4000, HPMC 100, calcium alginate, sodium alginate, Eudragit S100 Eudragit RL, Eudragit S, Eudragit RS, propylene foam, ethyl cellulose, poly methyl methacrylate, methocel K4M, polyethylene oxide, cyclodextrin, CMC, HPC, metolose, PVP, PVA, HPCH, HPC-M, acrylic polymer E4 M, polyethylene glycol, polycarbonate, and carbopol. Suitable hydrocolloids that are used in GRDDS include: synthetics, anionic or nonionic like hydrophilic gums, acacia, pectin, agar, alginates, gelatin, casein, bentonite, veegum, as well as modified cellulose derivatives, such as MC, HPC, HEC and NaCMC [22-24, 27, 42-49].

Other used ingredients in GRDDS are:

Effervescent agents like sodium bicarbonate, citric acid, tartaric acid, di-sodium glycine carbonate (Di-SGC) and citroglycine (CG).

Release rate accelerants like lactose and mannitol.

Release rate retardants such as dicalcium phosphate, talc and magnesium stearate.

Low density materials like polypropylene foam powder (Accurel MP 1000®).

Surfactants which are used as stabilizers or emulsifiers, play the role of hardening the microspheres as well, e.g. tween 80, span 80 and SLS.

Cross linking agents which are used as microspheres such as formaldehyde, glutaraldehyde or diacid chlorides such as terephthaloyl chloride and hardening agents which help to harden the microspheres formed in the processing medium. e.g. n-hexane and petroleum ether.

Inert fatty materials like beeswax, fatty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01.

Buoyancy- increasing agents such as ethyl cellulose, which has bulk density less than one, can be used to increase the buoyancy of the formulation.

Solvent systems such as:. water, ethanol, dichloromethane, acetonitrile, acetone, isopropyl alcohol and dimethylformamide [22, 27, 41, 46, 50-58].

Types of gastro-retentive dosage forms

Several attempts have been made to design and develop GRDDS including:
High density systems that are retained in the bottom of the stomach, low density (floating) systems that cause buoyancy in gastric fluid, mucoadhesive systems that cause bioadhesion to stomach mucosa, superporous hydrogel systems, magnetic systems, raft forming systems, swelling systems, microballons or hollow microspheres and hydrodynamically balanced systems.

Non floating systems

Bioadhesive or mucoadhesive systems

Bioadhesive drug delivery systems are used as delivery devices to enhance drug absorption and thereby to improve bioavailability. Mucus is a viscoelastic and jelly-like slime that is mainly comprised of glycoproteins. The primary role of mucus is to protect the surface mucosal cells from acid and peptides. The epithelial adhesive properties of mucin are well known and have been applied to develop the GRDDS by using the bio/mucoadhesive polymers. A bio/mucoadhesive substance is a natural or synthetic polymer is able to adhere to the mucus lining and epithelial surface of the GIT. Different theories have been suggested to explain the mechanisms of the prolongation of gastric retention:
1. The electronic theory mentions attractive electrostatic forces including ionic bonds and covalent bonds between the glycoprotein mucin network and the bioadhesive material.
2. The adsorption theory intends that bio-adhesion is due to secondary forces such as Vander Waals forces and hydrogen bonding.
3. The wetting theory which is based on the ability of bioadhesive polymers to spread and contact with the mucus layers.
4. The diffusion theory proposes physical strand of mucin filaments and polymer chains, or an interpenetration of mucin components into the porous structure of the polymer network.
Factors that affect mucoadhesion are categorized into two groups: polymer related factors including molecular weight, concentration, spatial conformation, functional group, chain flexibility of polymer and physiological factors such as pH, contact time, mucin turnover rate and disease situations [59-62].

Advantages of mucoadhesive drug delivery system are as follow:
1. Close contact and long stay at the delivery site due to adhesion, result in higher drug bioavailability and less administration frequency culminates in better patient compliance and convenience.
2. Providing an excellent route of the systemic drug delivery for drugs with high first-pass metabolism.
3. Improvement in drug absorption and prolongation in drug release time throughout the GIT by localization of drug at the disease site with uniform and wide distribution of drug.
4. Increasing margin of safety of high potency drugs due to better control of plasma levels, reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.
Polymer and its degradation products should be non-toxic, non-irritant and free from impurities. Polymer should also have good viscoelastic properties, spreadability, wettability, solubility and biodegradability properties. Polymers should also possess sufficient mechanical strength, optimum molecular weight, acceptable shelf life and bioadhesive properties in both dry and liquid states [22, 61, 63-67].

High density systems

Gastric contents have a density close to water (1.004 g /cm3). Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the folds of the stomach body near the pyloric region, the lowest position in upright posture. When the patient is upright, small high-density pellets sink to the bottom of the stomach where they become entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach. A density higher than 2.5 g/cm^3 is necessary for considerable prolongation of GIT. The only major problem with such systems is that it is technically difficult to produce such formulations with high amount of drug (>50%) and to achieve a density of about 2.5 g/cm^3. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide iron powder, etc. These materials increase the density by up to 1.5–2.4g/cm^{-3} [29, 68-72].

Raft forming system

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in this type of GRDDS is the formation of viscous gel in contact with gastric fluids, forming a continuous layer called RAFT on the top of gastric fluids because of low bulk density that is caused by the formation of CO_2. Usually, this system's ingredients include a gel forming agent (e.g. alginic acid) and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense and float on the gastric fluids. Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. The created raft floats on the gastric fluids and prevents the reflux of the gastric contents into the esophagus by forming a barrier between the stomach and esophagus and is usually used for gastro esophageal reflux treatment [73-77]. Figure 2 shows the schematic view of raft forming systems.

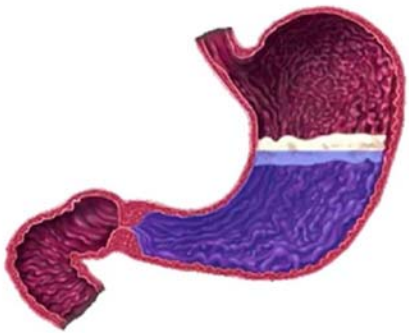

Fig. 2. Schematic picture for raft forming system [40]

Magnetic system

Magnetic systems are used for diagnosis and treatment of diseases. These systems are based on a simple idea that the dosage form contains small gastroretentive capsules containing a magnetic material, whose elimination from the stomach is prevented by the interaction with a sufficiently strong magnet applied to the body surface in the region of the stomach at specific positions that result in increasing drug absorption in stomach or intestines. Despite numerous reports about successful tests, the actual usefulness of these systems is of doubtful reliability because the desired results can be achieved only when the magnet position is selected with very high precision that can compromise patient compliance. The development of new conveniently applied magnetic field sources is necessary in order to improve this concept [78-82].

Expandable systems (Swelling/ Unfolding systems)

Swelling drug delivery systems are designed to prolong the gastric residence time after oral administration, at particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. These systems are made of biodegradable polymers and are capable of being mechanically increased in size relative to the initial dimensions. They are available in different geometric forms like tetrahedron, ring or planner membrane of bio erodible polymer compressed within a capsule which extends in the stomach. A dosage form in the stomach will resist the gastric transportation if it is bigger than the pyloric sphincter. After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus and therefore, the dosage form is prone to be retained in the stomach for a long period of time. Sustained and controlled drug release may be achieved by selecting a polymer or mixture of polymers with the proper molecular weight and swelling properties. Upon coming in contact with gastric fluid, the polymer imbibes water and swells. A drug can be either contained in a polymeric composition or be included as a separate component. Several methods were suggested to provide for the self-unfolding effect such as the use of hydrogels swelling in contact with the gastric juice, osmotic systems, comprising an osmotic medium in a semipermeable membrane and systems based on low-boiling liquids converting into a gas at the body temperature. The extensive swelling of these polymers is a result of the presence of physical–chemical crosslinks in the hydrophilic polymer network. These cross-links prevent the dissolution of the polymer and thus maintain the physical integrity of the dosage form. A balance between the extent and duration of swelling is maintained by the degree of crosslinking between the polymeric chains. A high degree of crosslinking retards the swelling ability of the system and maintains its physical integrity for a prolonged

period. On the other hand, a low degree of cross-linking results in extensive swelling followed by the rapid dissolution of the polymer. An optimum amount of cross-linking is required to maintain a balance between swelling and dissolution. These polymeric matrices remain in the gastric cavity for several hours even in the fed state. Gastro-retentivity is improved by high rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach. These systems should also erode in the presence of gastric juices so that after a predetermined time the device can no longer attain or retain the expanded configuration. On the other hand, the dosage form must be small enough to be swallowed, and must not cause gastric blockade either singly or by accumulation. Consequently, three structures are required, a small configuration for oral intake, an expanded gastroretentive form and a final small form enabling emptying following drug release. Reduced fluctuations of drug concentration, extended time over effective concentration, improved selectivity in receptor activation and minimized adverse activity at the colon are some of the advantages of expandable systems. Expandable systems have also some shortcomings including: inability to easily store many easily hydrolysable, biodegradable polymers, being difficult to industrialize, not being cost effective, causing brief obstruction, intestinal adhesion and gastropathy [24, 28, 64, 83-86]. Schematic picture of these systems is shown in Figure 3.

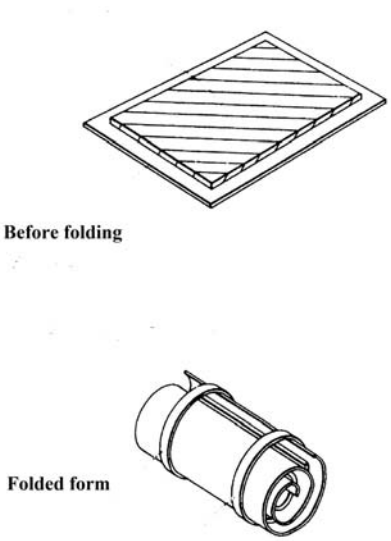

Fig. 3. Schematic picture for Expandable systems (Unfolding systems) [83]

Floating drug delivery systems

Floating drug delivery systems (FDDS) or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a much prolonged period without affecting the gastric emptying rate. While the system floats over the gastric contents, the drug is released slowly at the desired rate. After drug release , the residual system is emptied from the stomach. this culminates with an increased GRT and better control of the fluctuations in plasma drug concentration. However, a minimal gastric content is also needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force is also required to keep the dosage form to be constantly buoyant on the surface of the gastric fluid [4, 31, 87-89].

Floating dosage form with prolonged residence time in stomach is highly desirable for drugs that are locally active in stomach, have absorption window in stomach or in upper small intestine, are unstable in intestinal or colonic environment and have low solubility at high pH values.

Floatation of a drug delivery system in the stomach can be achieved by incorporating floating chamber filled with vacuum, air, or inert gas. Many buoyant systems have been developed based on granules, powders, capsules, tablets and hollow microspheres [31, 36, 45, 88, 90-94].

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which include effervescent systems and non- effervescent systems.

Hydrodynamically balanced system

Hydrodynamically balanced systems (HBS) are systems that contain one or more gel forming hydrophilic polymers; these systems when come in contact with the gastric fluids swell and form a colloidal gel barrier that results in low density. The polymer is mixed with drug and usually administered in a gelatin capsule. The capsule rapidly dissolves in the gastric fluid, and consequently hydration and swelling of the surface polymers produces a floating mass.

Figure 4 shows the mechanism of drug release from these systems.

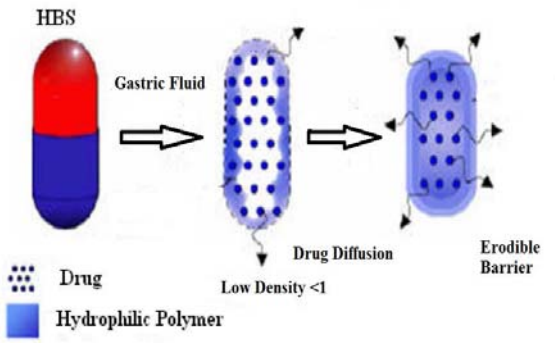

Fig. 4. Hydrodynamically balanced system (HBS)

The technology for the development of hydro-dynamically balanced system involves mixing of drug with the hydrocolloid such as hydroxypropyl methyl cellulose (HPMC) K4M, K15M, and K100M. The low density fatty acid materials are also used in the development of HBS. The advantages of using these materials are the ability to control the drug release effectively as well as providing the buoyancy to the dosage forms. Hydrodynamically balanced drug delivery systems have great potentials as controlled-release drug delivery systems. They allow increased penetration of the mucus layer and therefore may increase drug concentration at the site of action. These systems can remain in the stomach for several hours, resulting in improvement of the dissolution as well as bioavailability of the drugs that are poorly soluble in a high pH environment. These systems are also used for local delivery of drugs to the stomach and proximal small intestine [4, 40, 95-99]. Gastroretention property helps provide better availability of new products with new therapeutic possibilities and benefits for patients.

Microballoons / Hollow microspheres

Hollow microspheres are known as the microballoons. Hollow microspheres are considered as one of the most promising buoyant systems. These systems contain central hollow space and outer polymer shell loaded with drug. The outer polymer shell is made up of polymers like polycarbonate, cellulose acetate, Eudragits, calcium alginate, agar, etc. Buoyancy lag time and drug release from the system is dependent on the quantity of polymers used in the formulation and the polymer-plasticizer ratio. These are prepared by simple solvent evaporation or emulsion-solvent diffusion method. The drug release and better floating properties are mainly dependenton the type of polymer, plasticizer and the solvents employed for the preparation. Microballoons were floatable in vitro for 12 hrs, when immersed in aqueous media. Radio graphical studies proved that microballoons orally administered to human were dispersed in the upper part of stomach and were retained there for more than 3 hrs against peristaltic movements [48, 65, 95, 96, 100-103].

Superporous hydrogels

Water absorption by conventional hydrogel is a very slow process and several hours may be needed to reach an equilibrium state. Superporous hydrogels (SPH)are porous hydrophilic with a three dimensional cross linked, network like structure and have the ability of absorbing aqueous fluids up to a hundred times of their own weight. This is achieved by a co- formulation of a hydrophilic particulate material. Maximum swelling is generally reached in a fraction of a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores (average pores of 200 μm).In addition to swelling to a large size, they tend to have sufficient mechanical strength to resist pressure by gastric contractions. For years, the synthetic features and properties of these SPH materials have been modified and improved to meet the requirements for gastric retention applications [104-108].

The First generation SPH named as conventional SPHs. Ingredients that are used in the preparation of conventional SPHs contain monomers with high water absorbing affinity. The cross linking agent, foam stabilizer chemical initiator pair, distilled water and a buffer to adjust the pH also exist. Acrylic acid, acetic acid and hydrochloric acid are commonly used as monomers in SPH. After adding the initiator and blowing agent, monomers interact with sodium, ammonium, potassium carbonates and therefore polymerization and foaming take place which enhance the viscosity of reaction mixtures which lead to trapping of bubbles that are formed in foaming reactions. The major difficulty that is caused when using this conventional hydrogel is its mechanical strength. These conventional hydrogels are fragile and the whole structure can be easily broken under low pressures. Modifications to conventional SPH to improve the mechanical properties formed second generation SPH composite by adding super disintegrant. Composite materials do not show any

pharmacological effects but they enhance the mechanical strength of hydrogels.

Recent breakthrough in this field is the development of third generation SPH hybrids, which are prepared by incorporating water soluble or water dispersible polymer and can be cross-linked after the superporous hydrogel is formed. Hybrid agent is a polymer that is soluble and dispersible in water. Compared with first generation and second generation SPH, third generation SPH hybrids are not easily breakable when stretched because they possess highly elastic properties in the swollen state, which can be very useful for the development of gastrointestinal devices. Water soluble hydrocolloids, including sodium alginate, sodium carboxymethyl cellulose, pectin, polyvinyl alcohol and chitosan, have been used alone or in combination as the preferred hybrid agents [109-113].

Effervescent floating dosage forms/ Gas generating systems

These buoyant delivery systems utilize effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to release CO2 , which gets entrapped in the jellified hydrocolloid layer of the systems to decrease its specific gravity and causing it to float over gastric fluid. They are formulated in such a way that when they come in contact with the acidic gastric contents, C02 is generated and entrapped in swollen hydrocolloids which provides floating to the dosage forms.

Schematic diagram of such a systems is shown in figure 5.

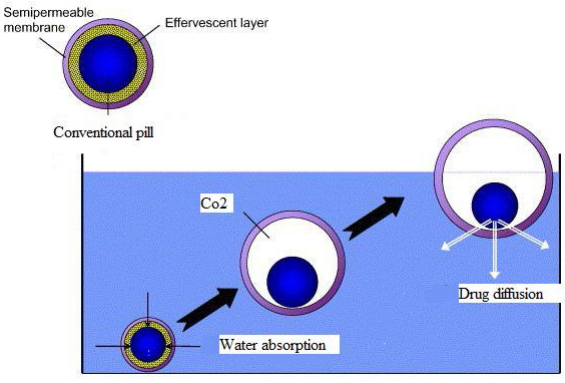

Fig. 5. Schematic diagram for effervescent floating drug delivery system

Multiple unit type of floating pills, which generate CO_2, have been also developed. This system is consisted of a sustained release pill as seed, surrounded by double layers. The inner layer is an effervescent layer containing sodium bicarbonate besides tartaric acid and the outer layer is a swellable membrane layer containing PVA, shellac etc. Figure 6 shows the schematic diagram of these systems.

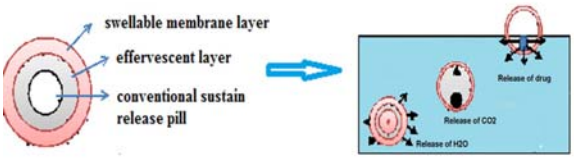

Fig. 6. Gas generating low density system

Another effervescent system consisting of a collapsible spring, which controls the release of drug from the polymer matrix, has also been developed. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating which is insoluble but permeable, allows permeation of water. Thus, CO_2 is released, causing the beads to float in the stomach. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. Other reported approaches and materials that have been reported are able to be highly swollen hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate and floating mini-capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with HPMC [4, 31, 36, 40, 114-117].

Floating system with Ion-Exchange resins

This system is a floating system using ion exchange resin that is loaded with bicarbonate by mixing the beads with sodium bicarbonate solution. The loaded beads are then surrounded by a semipermeable membrane to avoid sudden loss of CO_2. When they came in contact with gastric fluid, chloride and bicarbonate ions exchanged and resulted in CO_2 generation thereby beads were floated on the top of gastric contents and produced a floating layer of resin beads. Studies showed that the gastric residence time was prolonged considerably (24 hrs) compared with uncoated beads (1 to 3 hours) [61, 118, 119].

Low density systems

Gas-generating systems inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. Low-density systems (<1 g/cm^3) with immediate buoyancy have therefore been developed. They are made of low-density materials, entrapping oil or air. Generally, techniques used to prepare hollow microspheres involve simple solvent evaporation or solvent diffusion methods. Polycarbonate, Eudragit S, cellulose acetate, calcium alginate, agar and low methoxylated pectin are commonly used as polymers. Buoyancy and drug release are dependent on quantity of polymer, the plasticizer–polymer ratio and the type of solvent that has been used [49, 56, 120, 121].

Evaluation of physicochemical characteri- stics of GRDDS

Various parameters need to be evaluated in the case of solid dosage forms such as content uniformity, hardness, friability, encapsulation efficiency as well as micromeritic properties such as angle of repose, tapped density, true density and compressibility index. The dimensional changes can be measured in terms of the increase in tablet diameter or thickness over time [21, 27, 47, 122, 123]. Furthermore in the case of multi- particulate drug delivery systems, differential scanning calorimetry (DSC), particle size analysis using scanning electron microscopy (SEM), flow properties, surface morphology and mechanical properties are also performed. The tests for floating ability, floating duration, buoyancy lag time and *In vitro* drug release studies are generally performed in simulated gastric fluids at 37ºC [4, 31, 36, 44, 99, 117, 124].

The *in vivo* floating behavior can be studied by X-ray photography of microparticles loaded with barium sulphate in the stomach. The insertion of radio-opaque materials into a solid dosage form enables it to be visualized by X-rays, therefore allowing the imagining of the GI transit of the dosage form [27, 117, 124, 125].

In scintigraphy similar to X-ray photography, emitting materials, mainly 99Tc, are integrated into dosage form and images are taken by scintigraphy method [126, 127].

Gastroscopy or oral endoscopy is used to examine visually the effect of prolongation in stomach and evaluation of GRDDS [83, 128].

In the magnetic marker monitoring, dosage form is magnetically marked with incorporating iron powder inside and images can be taken by very sensitive bio-magnetic measurement equipment [129-131].

In ^{13}C octanoic acid breath test, ^{13}C octanoic acid is incorporated into GRDDS. In stomach due to chemical reaction, octanoic acid liberates CO_2 gas which comes out in breath. The carbon atom which will convert in CO_2 is replaced with ^{13}C isotope. Therefore up to time which $^{13}CO_2$ gas observed in breath considered as GIT of dosage form. Since the dosage form moves to intestine, there is no reaction and as a result no CO_2 release [132-134].

Conclusion

Based on the literature, it may be concluded that drug absorption in the gastrointestinal tract is a highly variable process and prolonging gastric retention of the dosage form extends the time for drug absorption. Gastro retentive drug delivery systems are able to prolong the continuous input of the drug to the upper parts of the GIT and improve the bioavailability of many drugs. GRDDS have multiple advantages that include greater flexibility and adaptability of dosage forms which give clinicians and pharmacists powerful tools to optimize pharmacotherapy. The increasing growth of delivery technology will ensure the development of increasing number of GRDDSs in order to optimize the delivery of drugs that exhibit narrow absorption window, low bioavailability and extensive first pass metabolism. The control of gastro intestinal transit could be the focus of the future studies and may result in new therapeutic capacities with considerable benefits for patient and hence it is very probable that these systems can gain popularity. To design a successful GRDDS, it is necessary to take into consideration the physiological parameters in the GIT, physicochemical properties of the drug, formulation approaches and combination adjustment of drug and excipients. Due to the complexity of pharmacokinetic and pharmacodynamics parameters, in vivo studies are required to establish the optimal dosage form for a specific drug.

Conflict of interest

Authors certify that no actual or potential conflict of interest in relation to this article exists.

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