ABSTRACT

The purpose of this review on Floating Drug Delivery Systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. The recent developments of FDDS including the physiological and formulation variables which affect the gastric retention and approaches to design single-unit and multiple unit floating systems, their classification and formulation aspects are covered in detail. This review also summarizes various sophisticated and modern in-vitro techniques to evaluate the performance, advantages and applications of floating systems. These systems are useful to avoid all the problems that are encountered during the development of a pharmaceutical dosage forms. Thus floating drug delivery systems seems to be the promising delivery systems for control release of drugs.

Key words: Floating Drug Delivery Systems, in-vitro drug release, hydro dynamically balanced systems, Gastric retention

INTRODUCTION

Oral delivery of drug is by far the most preferred route of drug delivery due to ease of administration, patient compliance and flexibility in formulation [1]. Conventional oral dosage forms provide a specific drug concentration in systemic circulation without offering any control over drug delivery. These systems achieve as well as maintain drug concentration within therapeutically effective range needed for treatment only when taken several times a day. This results in significant fluctuation in drug levels. The design of oral controlled drug delivery system is primarily aimed at, to:

1. To achieve more predictable and increased bioavailability.
2. To achieve desired concentration in target tissue.
3. Optimization of the therapeutic effect of a drug by controlling its release in body with lower and less frequent dose.

Dosage forms that can be retained in stomach are called gastroretentive drug delivery systems (GRDDS). GRDDS can improve controlled delivery of drugs that have an proximal absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site, thus ensuring its optimal bioavailability. Drugs having narrow absorption window are mostly associated with improved absorption at jejunum and ileum due to their enhanced absorption properties e.g. large surface area, or because of enhanced solubility in stomach as opposed to the more distal parts of the GIT.

Types of drugs that benefit from using gastric retentive devices
1) Drugs acting locally in stomach e.g. Antacids
2) Drugs that are primarily absorbed in stomach e.g. Albuterol
3) Drugs that are poorly soluble at an alkaline pH
4) Drugs with a narrow window of absorption i.e. drugs that are absorbed mainly from the proximal small intestine e.g. Riboflavin and Levodopa
5) Drugs absorbed rapidly from GI tract e.g. Amoxycillin
6) Drugs that degrade in colon e.g. Metoprolol.

Anatomy and physiology of stomach

The stomach is situated in the left upper part of the abdominal cavity under the diaphragm, between the lower end of the esophagus and the small intestine and is the most dilated part of the GIT. Its opening to the duodenum is controlled by pyloric sphincter. The stomach can be divided into four anatomical regions namely fundus, body, antrum and pylorus. Its size varies according to the amount of distention up to 1500 ml following a meal; after food has emptied, a 'collapsed' state is obtained with a resting volume of only 25-50ml. The major functions of the stomach are to act as a temporary reservoir for ingested food and to deliver it to the duodenum at a controlled rate and to reduce ingested solids to chyme by the action of acid and enzymatic digestion. Owing to its small surface area compared to the total small intestine very little drug absorption occurs in stomach. Storage is the main function of the fundus and body, whereas mixing and grinding takes place in the antrum. The fundus helps to adjust the increased volume during eating by relaxing its fundus muscle fibers and also exerts a steady state pressure on gastric content, pressing them towards distal stomach. To pass through pyloric valve into the small intestine the particle size should be in the range of 1 to 2mm [2]. The stomach has a capacity of approximately 1.5 L, although under fasting conditions it usually contains no more than 50 ml of fluid, which are mostly gastric secretions. These include:

i) Acid secreted by the parietal cells, which maintain pH of stomach between 1.0 and 3.5 in fasted state.
ii) The hormone gastrin, which is a potent stimulator of gastric acid production.
iii) Pepsin, which is secreted by peptic cells.

Mucus that is secreted by surface mucosal cells and lines the gastric mucosa. In the stomach, the mucus protects the gastric mucosa from auto digestion by pepsin-acid combination [14]. Gastric volume is important for dissolution of dosage form in vivo. The resting volume of stomach is 25-50ml. Gastric pH affects absorption of drugs from controlled release dosage forms.

1. Gastric pH- In stomach there are several types of cells that secrete up to 2-3l of gastric juice daily. Types of cells present in gastric cavity include [12]...
Gastric emptying

The time a dosage form takes to traverse the stomach is usually termed gastric emptying time. Gastric emptying is highly variable and is dependent on the dosage form and the fed/fasted state of the stomach. Normal gastric residence time usually ranges between 5 minutes and 2 hours, although much longer times (over 12 hours) have been recorded, particularly for large single units. The GI tract is in a state of continuous motility consisting of two modes (a) Interdigestive motility pattern (b) Digestive motility pattern. The former is dominant in the fasted state with a primary function of cleaning up the residual content of upper GI tract. The fasted state is associated with various cyclic events, commonly referred to as the migrating motor complex (MMC), which regulates GI motility patterns. This series of electrical events originates in the foregut and continues to the terminal ileum in the fasted state, repeating every 2-3 hrs. Concentration of the hormone motilin in blood controls the duration of the phases: The administration of food rapidly interrupts the MMC cycle and the digestive phase is allowed to take place. The motor activity in the fed state is induced 5-10 minutes after ingestion of a meal and persists as long as food remains in the stomach. The larger the amount of food ingested, the longer the period of fed activity, with usual time spans of 2-6 hours and more typically 3-4 hours. When CRDDS are administered in fasted state, the MMC may be in any of its phases, which can significantly influence total gastroretentive time (GRT) and transit time in the gastrointestinal tract (GIT). This assumes even more significance for drugs that have an absorption window because it will affect the time that the dosage form spends in the region preceding and around the window. The less time spent in that region the lower the degree of absorption. Therefore the design of GRDDS should take into consideration resistance of the dosage form to gastric emptying. 

Factors controlling gastric retention time of dosage forms

The GRT of dosage forms is controlled by several factors.

1. Size of the dosage form:
   In general it is known that indigestible solids larger than 1-2 mm are retained in stomach throughout the post-prandial period, after which they are emptied by cyclically recurring burst of interdigestive gastric contractions [18]. However many recent studies have shown that non-disintegrating tablets as large as 7mm can be emptied from human stomach during the post-prandial period, while 13 mm tablets are retained until arrival of subsequent sweeping "housekeeper wave". This emphasizes the need for size enlargement of dosage forms in stomach in order to prolong GRT.

2. Density of Dosage Form:
   The density of gastric fluid is reported to be 1.004g/cm³. The density of the dosage form should be less than this for buoyancy, so that it is retained in stomach for longer period of time.

3. Shape of the dosage form:
   The shape of dosage form is one of the factors that affect its gastric residence time. Six shapes (ring tetrahedron, cloverleaf, string, pellet, and disk) were screened in vivo for their gastric retention potential. The tetrahedron (each leg 2cm long) rings (3.6 cm in diameter) exhibited nearly 100% retention at 2, 3, 4, 24 hr. On the other hand discs (2.5cm diameter) exhibited 67% retention and pellets (4mm) 0% retention at 24 hours.

4. Viscosity grade of polymer [19]:
   Drug release and floating properties of FDDS are greatly affected by viscosity of polymers and their interaction. Low viscosity polymers (HPMC K100 LV) were found to be more beneficial than high viscosity polymers (HPMC K4M) in improving floating properties. In addition, a decrease in the release rate was observed with an increase in polymer viscosity.

Diosyncratic factors

1. Gender: Generally females have a slower gastric emptying rate (4.6±1.2 hours) than males (3.4±0.6 hours) regardless of weight, height and body surface [20].

2. Age: Elderly people especially those over 70; have a significantly longer GRT due to changes in physiology with increasing age and hormonal responses responsible for gastric emptying.

Body Posture [21]

1. Upright position:
   An upright position protects floating forms against postprandial emptying because the floating form remains above the gastric contents irrespective of its fasted/fasted state. Floating dosage forms show prolonged and more reproducible GRTs while the conventional dosage form sink to the lower part of the distal stomach where they are expelled through the pylorus by antural peristaltic movements.

2. Supine position:
   This position offers no reliable protection against early and erratic emptying. In supine subjects large dosage forms (both conventional and floating) experience prolonged retention. The gastric retention of floating forms appear to remain buoyant anywhere between the lesser and greater curvature of the stomach. On moving distally, these units may be swept away by the peristaltic movements that propel the gastric contents towards the pylorus, leading to significant reduction in GRT compared with upright subjects [16].

Other factors

1. Type of meal:
   Feeding of indigestible polymers or fatty acid salts can change the motility pattern of stomach to a fed state, thus decreasing gastric emptying rate and prolonging drug release [22].

2. Caloric content:
   GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.

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5. Gastric emptying:
   Gastric emptying of dosage form is different in fasted and fed condition. The gastric emptying is highly variable depending the nature of dosage form and food intake in particular has shown that gastric emptying for a matrix type dosage form is of the order of 3 h ± 1 hr irrespective of 3 h ± 1 hr constant in fed and fasted patients. However the intestinal transit time was remarkably constant for fasted/fed state of stomach.

Approaches to gastroretentive dosage forms [23]

Several techniques are reported in the literature to increase the gastric retention of drugs.

1. Highdensity systems
   These systems, which have a density of ~3g/cm3, are retained in the rugae of stomach and capable of withstanding its peristaltic movements [18, 20]. The only major drawback with these systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and achieve required density of 2.4-2.8g/cm3. Diluents such as barium sulphate, zinc oxide, titanium oxide, and iron powder must be used to manufacture such high density formulations. These systems are also called as "Plug type system", since they exhibit tendency to remain logged in the pyloric sphincters. These polymeric matrices remain in the gastric cavity for several hours even in fed state.
Swellable tablet in stomach

By selection of polymer with the proper molecular weight and swelling properties controlled and sustained drug release can be achieved. Upon coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is a result of the presence of physical chemical cross links in the hydrophilic polymer network. These cross link prevents the dissolution of polymer and thus maintain its physical integrity for prolonged period. On the other hand, a low degree of cross linking results in extensive swelling followed by the rapid dissolution of polymer.

3. Incorporating delaying excipients

Another delayed gastric emptying approach of interest include feeding of digestible polymers or fatty acid salts that charges themotility pattern, of the stomach to a fed stage thereby decreasing the gastric emptying rate and permitting considerable prolongation of the drug release. Protons or extruded from polyethylene blends, which extend the GRT depending on size, shape and flexural modules of drug delivery device.

4. Modified systems

Systems with non disintegrating geometric shape molded from silastic elastomers or extruded from polyethylene blends, which extend the GRT depend- ing on size, shape and flexural modules of drug delivery device.

5. Mucosalhesive and bioadhesive systems

Bioadhesive 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 in the stomach. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin, etc.

6. Floating systems

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. Floatation of a drug delivery system in the stomach can be achieved by incorporating floating chamber.

7. Raft forming systems

The basic mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. The raft floats because of the buoyancy created by the formation of CO2 and act as a barrier to prevent the reflux of gastric Contents like HCl and enzymes into the esophagus. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of to make the system less dense and float on the gastric fluids.

Evaluation of floating drug delivery systems

Various parameters that need to be evaluated in gastro retentive formulations which includes floating duration, dissolution profiles, specific gravity, content uniformity, hardness and friability in case of solid dosage forms. In case of GRT of drug delivery system consists of incorporating delaying excipients like trietanolamine myristate in a delivery system.

4. Determination of moisture content:

The water content per se is seldom of interest. Rather, it shows whether a product intended for trade and production has standard properties such as · Storability · Dry substance content · Concentration or purity · Commercial grade (compliance with quality agreements)

Thus moisture content of the prepared formulations was determined by Karl fisher titration, vacuum drying, Thermo gravimetric methods, Air oven method, Moisture Meters, Freeze drying as well as by physical methods [11].

5. Swelling studies:

Swelling studies were performed to calculate molecular parameters of swollen polymers. Swelling studies was determined by using Dissolution apparatus, optical microscopy and other sophisticated techniques which include H1NMR imaging, Confocal laser scanning microscopy (CLSM), Cryogenic scanning electron microscopy (Cryo-SEM), Light scattering imaging (LSI) etc. The swelling studies by using Dissolution apparatus was calculated as per the following formula. Weight of wet formulations (Swelling ratio = Weight of formulations [26]

6. Determination of the drug content

Percentage drug content provides how much of the drug that was present in the formulation. It should not exceed the limits acquired by the standard monographs. Drug content was determined by using HPLC, HPTLC methods, near infrared spectroscopy (NIRS), Microtitrimetric methods, and Inductively Coupled dissolution apparatus. Plasma Atomic Emission Spectrometer (ICP AES) and also by using spectroscopy techniques.

7. In-vitro release

In vitro release studies were performed to provide the amount of the drug that is released at a definite time period. The test for in vitro drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 370 C. Dissolution tests are performed using the USP dissolution apparatus. Samples are withdrawn periodically from the dissolution medium, replaced with the same volume of fresh medium each time, and then analyzed for their drug contents after an appropriate dilution. Recent methodology as described in USP XXIII states that the dosage unit is allowed to sink to the bottom of the vessel before rotation of blade is started[13].

8. Percentage entrainment efficiency

Percentage entrainment efficiency was reliable for quantifying the phase distribution of drug in the prepared formulations. Entrainment efficiency was determined by using three methods such as Microdialysis method, Ultra centrifugation, and pressure Ultra filtration. studies.

9. Powder x-ray diffraction

X-ray powder diffraction is the predominant tool for the study of polycrystalline materials and is eminently suited for the routine characterization of pharmaceutical solids. Samples were irradiated with a radiation and analyzed between 2 °C and 60 °C. The voltage and current used were 30KV and 30mA respectively[16].

10. Fourier transform infrared analysis

Fourier transform infrared spectroscopy (FT-IR) is a technique mostly used to identify organic, polymeric, and some inorganic materials as well as for functional group determination. Fourier Transform Infrared Analysis (FT-IR) measurements of pure drug, polymer and drug-loaded polymer formulations were obtained.

11. Differential scanning calorimetry (DSC)

It is used to characterize water of hydration of pharmaceuticals. Thermo grams of formulated preparations were obtained using DSC instrument equipped with an intracooler.Indian/Zinc standards were used to calibrate the DSC temperature and enthalpy scale. The sample preparations were hermatically sealed in an aluminum pan and heated at a constant rate of 10°C/min; over a temperature range of 25 °C - 65 °C. Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 30ml/min.

12. Pharmacokinetic studies

Pharmacokinetic studies include AUC (Area under Curve), Cmax, and time to reach maximum plasma concentration (Tmax) were estimated using a computer. Statistical analyses were performed using a Student t test with p, 0.05 as the minimal level of significance.
ADVANTAGES OF FLOATING DOSAGE FORM [25]

1. These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and furosemide.

2. The fluctuations in plasma drug concentration are minimized, and concentration-dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

3. The efficacy of the medications administered utilizing the sustained release principle of floating formulation has been found to be independent of the site of particular medications.

4. Complete absorption of the drug from the floating dosage form is achieved even at the alkaline pH of the intestine. The dissolution of the drug in gastric fluid occurs and then the dissolved drug is available for absorption in the small intestine after emptying of the stomach contents.

5. Poor absorption is expected when there is vigorous intestinal movement and a shorted transit time as might occur in certain type of diarrhea. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

6. Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption (Shah SH, 2009). A significant increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric coated LASIX long product (29.5%).

Limitations of floating drug delivery systems [26]

1. A high level of fluid in the stomach is required for drug delivery to float and work efficiently.

2. Drugs which have stability and solubility problems in GIT are not suitable candidates for these types of systems.

3. Drugs such as nifedipine, which undergoes first pass metabolism may not be desirable for the preparation of these types of systems. Drugs which are irritant to gastric mucosa are also not desirable.

4. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable phenomenon and prolonging gastric retention of the dosage form extends the time for drug absorption and attempts to make it more uniform as well as reproducible. Floating Multiparticulate Drug Delivery systems promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing towards commercializing this technique. It is hoped that in the near future biopharmaceutically better therapeutic systems in the form of floating drug delivery devices would be introduced in clinics in greater number.

Future scope of floating multiparticulate drug delivery systems

Floating multiparticulates can greatly improve the pharmacotherapy of the stomach through local drug release, used to eradicate Helicobacter pylori from the sub-mucosal tissue of the stomach most effectively and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis. This system allows administration of non-systemic, controlled release antacid formulation containing calcium carbonate and also locally acting anti-ulcer drugs (such as Lansoprazole) in stomach. Buoyant micro particles are considered as a beneficial strategy for the treatment of gastric and duodenal cancers. Floating multiparticulate systems may be used as a carrier for the drugs having narrow absorption windows, these substances, for example antiviral, antifungal, and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Aminoglycosides, and Tetracyclines) are absorbed only from very specific regions of GI tract. In addition, by continually supplying the drug to its most efficient site of absorption, the dosage form may allow for more effective oral use of peptide and protein drugs such as calcitonin, erythropoitin, vasopressin, insulin, low molecular weight heparin, and LHRR.

REFERENCES


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