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An Approach to Oral Controlled Drug Delivery: Floating Drug Delivery System

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Abstract: The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available in the market are oral drug delivery systems. Technological attempts have been made in the research and development of rate-controlled oral drug delivery systems to overcome physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). It is known that differences in gastric physiology, such as, gastric pH, and motility exhibit both intra-as well as inter-subject variability demonstrating significant impact on gastric retention time and drug delivery behavior. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bioadhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices. In this review, current & recent developments of Stomach Specific FDDS are discussed. The present review addresses briefly about the floating drug delivery systems.
Key words: Floating drug delivery system; Gastric residence time; Buoyancy; Oral route

Introduction

Floating systems or Hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and 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[1,2]. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. To successfully modulate the gastrointestinal transit time of a drug delivery system through floating drug delivery system (FDDS) For maximal gastrointestinal absorption of drugs and site-specific delivery, one needs to have a good fundamental understanding of the anatomic and physiological characteristics of the human GIT[3,4]. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion modified shape systems or by the simultaneous administration of pharmacological agent that delay gastric emptying[5].

Factors Affecting Gastric Residence Time of FDDS

1. **Density of tablets**
   Density is the main factor affecting the gastric residence time of dosage form. A buoyant dosage form having a density less than that of the gastric fluids floats, since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period. A density of less than 1.0g/ml i.e. less than that of gastric contents has been reported. However, the floating force kinetics of such dosage form has shown that the bulk density of a dosage form is not the most appropriate parameter for describing its buoyancy capabilities[1,2].
2. **Size of tablets**
   Retention of floating dosage forms in stomach depends on the size of tablets. Small tablets are emptied from the stomach during the digestive phase, but large ones are expelled during the house keeping waves.

Floating and nonfloating capsules of 3 different sizes having a diameter of 4.8 mm (small units), 7.5 mm (medium units), and 9.9 mm (large units), were formulated and analyzed for their different properties. It was found that floating dosage units remained buoyant regardless of their sizes on the gastric contents throughout their residence in the gastrointestinal tract, while the nonfloating dosage units sank and remained in the lower part of the stomach. Floating units away from the gastro-duodenal junction were protected from the peristaltic waves during digestive phase while the non-floating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase[4].

3. **Shape of tablets**
   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 24 hr.
4. **Viscosity grade of polymer**
   Drug release and floating properties of FDDS are greatly affected by viscosity of polymers and their interaction. Low viscosity polymers (e.g., HPMC K100 LV) were found to be more beneficial than high viscosity polymers (e.g., HPMC K4M) in improving floating properties. In addition, a decrease in the release rate was observed with an increase in polymer viscosity[5,6].
5. **Posture**
   a. **Upright position**
      An upright position protects floating forms against postprandial emptying because the floating form remains above the gastric contents irrespective of its size. Floating dosage forms show prolonged and more reproducible GRTs while the conventional dosage form sink to the lower part of the distal stomach from where they are expelled through the pylorus by natural peristaltic movements.
   b. **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[3,5].
6. **Gender**
   Women have slower gastric emptying time than do men. Mean ambulatory GRT in meals (3.4±0.4 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface[1,6].
7. **Age**
   Low gastric emptying time is observed in elderly than do in younger subjects. Intra-subject and inter-subject variations also are observed in gastric and intestinal transit time. Elderly people, especially those over 70 years have a significantly longer GRT[3,6].
8. **Feeding regimen**
   Gastric residence time increases in the presence of food, leading to increased drug dissolution of the dosage form at the most favorable site of absorption. A GRT of 4-10 h has been reported after a meal of fats and proteins[7].
9. **Concomitant intake of drugs**
   Drugs such as prokinetic agents (e.g., metoclopramide and cisapride), anti Cholinergics (e.g., atropine or propantheline), opiates (e.g., codeine) may affect the performance of FDDS. The coadministration of GI-motility decreasing drugs can increase gastric emptying time[5,6].

Advantages of Gastroretentive Drug Delivery Systems

1. **Enhanced bioavailability**
   The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption[4,5].
2. **Enhanced first-pass biotransformation**
   In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input[5].
3. **Sustained drug delivery/reduced frequency of dosing**

For drugs with relatively short biological half life, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy[3, 4].

4. **Reduced fluctuations of drug concentration**
   Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects 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[6].
5. **Targeted therapy for local ailments in the upper GIT**
   The prolonged and sustained administration of the drug from GRDF to the stomach may be advantageous for local therapy in the stomach and small intestine. By this mode of administration, therapeutic drug concentrations may be attained locally while systemic concentrations, following drug absorption and distribution, are minimal[1,2].
6. **Improved selectivity in receptor activation**
   Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations[3,7].
7. **Reduced counter-activity of the body**
   In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency[1].
8. **Site specific drug delivery**
   A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency[8].
9. **Extended time over critical (effective) concentration**
   For certain drugs that have non-concentration dependent pharmacodynamic, such as beta-lactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration. The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes[9].
10. **Minimized adverse activity at the colon**
    Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance[3,4,10].

Limitations of floating Drug Delivery Systems

1. Drugs which have stability and solubility problems in GIT are not suitable candidates for these types of systems.
2. A high level of fluid in the stomach is required for drug delivery to float and work efficiently.
3. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
4. Drugs such as nifedipine, which under goes first pass metabolism may not be desirable for the preparation of these types of systems.
5. Drugs which are irritant to Gastric mucosa are also not desirable[1,10,11].

Classification of FDDS Based On Mechanism Of Buoyancy

1. **Single unit**
   Single unit dosage forms are easiest to develop but suffers from the risk of losing their effects too early due to their all-or-none emptying from the stomach and, thus they may cause high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the gastro intestinal tract[11].
   Non effervescent systems
   One or more gel forming, highly swellable, cellulosic hydrocolloids (e.g. hydroxyl ethyl cellulose, hydroxyl propyl cellulose, hydroxypropyl methyl cellulose [HPMC] and sodium carboxy methyl cellulose), polysaccharides, or matrix forming polymers(e.g., polycarbophil, polyacrylates, and polystyrene) are incorporated in high level (20-75% w/w) to tablets or capsules. For the preparation of these types of systems, the drug and the gelforming hydrocolloid are mixed thoroughly. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within

the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass[12,13].

Effervescent systems or gas generating systems

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1.

2. **Multiple unit**

Single unit formulations are associated with problems such as sticking together or being obstructed in gastrointestinal tract, which may have a potential danger of producing irritation. Multiple unit systems avoid the 'all-or-none' gastric emptying nature of single unit systems. It reduces the intersubject variability in absorption and the probability for dose dumping is lower.

Non effervescent systems

A little or no much report was found in the literature on noneffervescent multiple unit systems, as compared to the effervescent systems. However, few workers have reported the possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion process is reported. A mixture of drug, chitosan and acetic acid is extruded through a needle, and the extrudate is cut and dried. Chitosan hydrates float in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio.

Effervescent systems

A multiple unit system comprises of calcium alginate core and calcium alginate/PVA membrane, both separated by an air compartment was prepared. In presence of water, the PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment. Increase in molecular weight and concentration of PVA, resulted in enhancement of the floating properties of the system. Freeze-drying technique is also reported for the preparation of floating calcium alginate beads. Sodium alginate solution is added drop wise into the aqueous solution of calcium chloride, causing the instant gelation of the droplet surface, due to the formation of calcium alginate. The obtained beads are freeze-dried resulting in a porous structure, which aid in floating. The authors studied the behavior of radiolabeled floating beads and compared with nonfloating beads in human volunteers using gamma scintigraphy. Prolonged gastric residence time of more than 5.5 h was observed for floating beads. The nonfloating beads had a shorter residence time with a mean onset emptying time of 1 hr.

Floating microspheres

A controlled release system designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of floating microspheres. Techniques involved in their preparation include simple solvent evaporation, and solvent diffusion and evaporation. The drug release and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers, such as polycarbonate, Eudragit S and cellulose acetate, are used in the preparation of hollow microspheres, and the drug release can be modified by optimizing the amount of polymer and the polymerplasticizer ratio[14,15].

3. **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. Reckitt and Colman Products Ltd. have come out with such formulation in the treatment of H.pylori infections of GIT[16].

Evaluation:

1. **For Single Unit Dosage Forms:**
   - **A. Floating lag time**: The buoyancy lag time is determine in the U.S.P. dissolution test apparatus II in a acid environment. The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of the dissolution medium is buoyancy lag time or floating lag time.
   - **B. In vitro drug release and duration of floating**: This is determined by using USP II apparatus (paddle) stirring at a speed of 50 or 100 rpm at 37 ± 0.2 °c in simulated gastric fluid (pH 1.2 without pepsin). Aliquots of the samples are collected and analysed for the drug content. The time (hrs) for which the tablets remain buoyant on the surface of the dissolution medium is the duration of floating and is visually observed.

C. Tablet swelling indices

Tablet was weighed (W1) and placed in a glass beaker, containing 200 mL of 0.1 N HCl, maintained in a water bath at 37 ± 0.5° C. At regular time intervals, the tablet were removed and the excess surface liquid was carefully removed by a filter paper. The swollen tablet was then reweighed (W2). The swelling index (SI) was calculated using the formula:

SI = W2 – W1 / W1

D. In vivo evaluation for gastro-retention: This is carried out by means of X-ray or Gamma scintigraphic monitoring of the dosage form transition in the GIT. The tablets are also evaluated for hardness, weight variation, etc[17,18].

2. For Multiple Unit Dosage Forms

Apart from the In vitro release, duration of floating and in vivo gastro-retention tests, the multiple unit dosage forms are also evaluated for:

A. Morphological and dimensional analysis with the aid of scanning electron microscopy (SEM). The size can also be measured using an optical microscope.

B. % yield of microspheres: This is calculated from weight of microspheres obtained ×100 total weight of drug and polymer

C. Entrapment efficiency: The drug is extracted by a suitable method, analyzed and is calculated from: Practical amount of drug present ×100/Theoretical drug content

D. In vitro floating ability (Buoyancy %): A known quantity of microspheres are spread over the surface of a USP (Type II) dissolution apparatus filled with 900 ml of 0.1 N HCl containing 0.002% v/v Tween 80 and agitated at 100 rpm for 12 hours. After 12 hours, the floating and settled layers are separated, dried in a dessicator and weighed. The buoyancy is calculated from the following formula.

Buoyancy (%) = Wf / (Wf + Ws)×100

Where Wf and Ws are the weights of floating and settled microspheres respectively.

E. Drug-excipient (DE) interactions: This is done using FTIR. Appearance of a new peak, and/or disappearance of original drug or excipient peak indicate the DE interaction. Apart from the above mentioned evaluation parameters, granules are also evaluated for the effect of ageing with the help of Differential Scanning Calorimeter or Hot stage polarizing microscopy[19,20].

Conclusion

Gastro-retentive floating drug delivery systems have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. The increasing sophistication of delivery technology will ensure the development of increase number of gastroretentive drug delivery to optimize the delivery of molecules that exhibit absorption window, low bioavailability and extensive first pass metabolism. Growing understanding of impact of GIT physiology on drug delivery and increasing sophistication of drug delivery technology will ensure development of an increasing number of GRDDs to optimize drug delivery of molecules exhibiting regional variability in drug absorption. The research in this area is ongoing and it will not be long before an improved system is developed.

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