A comprehensive review on floating oral drug delivery system

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Received on: 15-01-2010; Revised on: 15-03-2010; Accepted on:15-04-2010

ABSTRACT

Floating Oral Drug Delivery System (FODDS) is an extension of Gastroretentive Drug Delivery System. FODDS enable prolonged and continuous input of the drug to the upper part of the gastrolesentinal tract and improve the bioavailability of medication that is characterized by a narrow absorption window. In recent years scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities like short gastric residence times and unpredictable gastric emptying times.

Keywords: Gastroretentive, FODDS, HBS.

INTRODUCTION

Floating Oral Drug Delivery System (FODDS) are retained in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids. The density of the system can be reduced by incorporating a number of low density fillers into the systems such as hydroxyl cellulose, lactates or microcrystalline cellulose. The drug usually keeps floating in the gastric fluid and slowly dissolves at a predetermined rate to release the drug from the dosage form and maintain constant drug levels in the blood. The concept of floating tablets is mainly based on the matrix type drug delivery system such that the drug remains embedded in the matrix which after coming in contact with the gastric fluid swells up and the slow erosion of the drug without disintegration of the tablet takes place. Sometimes for generating a floating system we even need to add some effervescent or gas generating agent which will also ultimately reduce the density of the system and serve the goal of achieving a floating system for onward drug delivery.

APPROACHES TO FLOATING ORAL DRUG DELIVERY SYSTEM (FODDS)

A number of approaches have been used to increase floating time of a dosage form in stomach which is as follows:11

a) Hydrodynamically balanced systems: HBS
b) Gas-generating systems
c) Raft-forming systems
d) Low-density systems

Floating systems

These have a bulk density lower than the gastric content. They remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug. Eventually, the residual system is emptied from the stomach. Gastric emptying is much more rapid in the fasting state and floating systems rely heavily on the presence of food to retard emptying and provide sufficient liquid for effective buoyancy.12-4 The three approaches used in designing intragastric floating systems will now be described.

Hydrodynamically balanced systems (HBS)

These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. Hydroxypropylmethylcellulose, Hydroxypropyl methylcellulose (HPMC) is the most commonly used excipient, although hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), sodium carboxymethylcellulose (NaCMC), agar, carrageenans or alginate are also used. Polysaccharides and matrix forming polymer such as polycarbophil, polycarlylates and polystyrenes, incorporated either in tablets or in capsules. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to this dosage forms (Figure 1).5

Gas-generating systems

Floatability can also be achieved by generation of gas bubbles. CO2 can be generated in situ by incorporation of carbonates or bicarbonates, which react with acid—either the natural gastric acid or co-formulated as citric or tartaric acid. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. An alternative is to incorporate a matrix with entrapped liquid, which forms a gas at body temperature (Figure 2).
RAFT-FORMING SYSTEMS

Here, a gel-forming solution (e.g., sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO₂ bubbles on contact with gastric fluid. Formulations also typically contain antacids such as aluminum hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastroesophageal reflux treatment as with Liquid Gaviscon (GlaxoSmithkline) (Figure 3).[6]

FIGURE 2: GAS-GENERATING SYSTEMS

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/cm³) with immediate buoyancy have therefore been developed. They are made of low-density materials, entrapping oil or air. Most are multiple unit systems, and are also called “microballoons” because of the low-density core. Generally, techniques used to prepare hollow microspheres involve simple solvent evaporation or solvent diffusion evaporation 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 solvent used (Figure 4).[7-11]

FIGURE 3: BARRIER FORMED BY A RAFT-FORMING SYSTEM

ADVANTAGES OF FLOATING ORAL DRUG DELIVERY SYSTEM

1. The principle of HBS of FODDS can be used for any particular medicament or class of medicament.
2. The FODDS formulations are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine e.g. Chlorpheniramine maleate.
3. The FODDS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.
4. The efficacy of the medicaments administered utilizing the sustained release principle of FODDS has been found to be independent of the site of absorption of the particular medicaments.
5. When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected under such circumstances it may be advantageous to keep the

DRUGS USED IN THE FORMULATION OF FLOATING DOSAGE FORMS

1. Floating microsphere: Aspirin, Griseofulvin, p-Nitroaniline, Ibuprofen, Terfinadine and Tranilast
2. Floating granules: Diclofenac sodium, Indomethacin and Prednisolone.
4. Floating tablets and Pills: Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxycillin Trihydrate, Atenolol, Diltiazem, Fluorouracil, Isosorbide mononitrate, para Aminobenzoic acid, Piretamide, Thyrophyline and Verapamil hydrochloride, etc
5. Floating In-Situ Gel: aluminum hydroxide or calcium carbonate

FIGURE 4: THE STRUCTURE OF THE LOW-DENSITY, FLOATING MATRIX TABLETS

FACTORS AFFECTING THE FLOATING AND FLOATING TIME

1. Density: - Floating is a function of dosage form buoyancy that is dependent on the density.
2. Shape of dosage form: - Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better floating, 90% to 100% retention at 24 hours compared with other shapes.
3. Single or multiple unit formulation: - Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.
4. Fed or unfed state: - Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours.[12]
5. Nature of meal: - Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.[13]
6. Caloric content: - Floating can be increased by four to 10 hours with a meal that is high in proteins and fats.
7. Frequency of feed: - The floating can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
8. Age: - Elderly people, especially those over 70, have a significantly longer; floating.
10. Concomitant drug administration: - Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride; can affect floating time.
11. Biological factors: - Diabetes and Crohn’s disease, etc.
drug in floating condition in stomach to get a relatively better response.

6. FODDS provides advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.

7. Certain types of drugs can benefit from using FODDS. These include:
   a) Drugs acting locally in the stomach.
   b) Drugs those are primarily absorbed in the stomach.
   c) Drugs those are poorly soluble at an alkaline pH.
   d) Drugs with a narrow window of absorption.
   e) Drugs absorbed rapidly from the GI tract.
   f) Drugs those degrade in the colon.

DISADVANTAGES OF FODDS

1. There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted.

2. Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems.

3. Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system.

LIMITATIONS

1. The major disadvantage of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float. However this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach.

2. Floating system is not feasible for those drugs that have solubility or stability problem in gastric fluids.

3. The dosage form should be administered with a minimum of glass full of water (200-250 ml).

4. The drugs, which are absorbed throughout gastro-intestinal tract, which under go first-pass metabolism (nifedipine, propranolol etc.), are not desirable candidate.

5. Some drugs present in the floating system causes irritation to gastric mucosa.

MARKETED PRODUCTS

Table 1. Marketed Products of FODDS

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Delivery system</th>
<th>Drug (dose)</th>
<th>Company name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valerelease® HBS</td>
<td>Floating capsule</td>
<td>Diazepam (15mg)</td>
<td>Hoffmann-LaRoche, USA</td>
</tr>
<tr>
<td>Madopar® HBS (Prolup® HBS)</td>
<td>Floating, CR capsule</td>
<td>Benzerazide (25mg) &amp; L-Dopa (100mg)</td>
<td>Roche Products, USA</td>
</tr>
<tr>
<td>Liquid Gaviscon®</td>
<td>Effervescent Floating liquid alginate</td>
<td>Al hydroxide (95 mg), Mg Carbonate</td>
<td>GlaxoSmithKline, India</td>
</tr>
<tr>
<td>Topalkan® HBS</td>
<td>Floating liquid alginate preparation</td>
<td>(358 mg)</td>
<td>Pierre Fabre Drug, France</td>
</tr>
<tr>
<td>Almagate Flotcoat®</td>
<td>Floating dosage form</td>
<td>Al – Mg antacid</td>
<td>——</td>
</tr>
<tr>
<td>Conviron®</td>
<td>Colloidal gel forming FDDS</td>
<td>Ferrous sulphate</td>
<td>Ranbaxy, India</td>
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APPLICATIONS

1. Recent study indicated that the administration of diltiazem floating tablet twice a day might be more effective compared to normal tablets in controlling the blood pressure of hypertensive patient.

2. Madopar® HBS- containing L-dopa and benzerazide- here drug was released and absorbed over a period of 6-8 hour and maintain substantial plasma concentration for parkinson’s patients.


4. As it provides high concentration of drug within gastric mucosa, it is used to eradicate pylori (A causative organism for chronic gastritis and peptic ulcers).

5. 5-Fluorouracil has been successfully evaluated in patients with stomach neoplasm.

6. Developing HBS dosage form for tacrine provides a better delivery system and reduces its GI side effects in alzheimer’s patients.

7. Treatment of gastric and duodenal cancers.

8. Alza corporation has developed a gastroretentive platform for the OROS® system, which showed prolong residence time in a dog model as the product remain in the canine stomach at 12 hrs post dose and was frequently present at 24 hrs.

FUTURE POTENTIAL

FODDS is novel drug delivery system which is so far limited to the experimantal works, but system is having lot of potential. In present era patient compliance is a major issue in front of formulation and development pharmacist. In such situation FODDS will play an important role in following aspects. The reduced fluctuations in the plasma level of drug results from delayed gastric emptying. Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailability. FODDS considered as a beneficial strategy for the treatment of gastric and duodenal cancers. FODDS concept can also be utilized in the development of various anti-reflux formulations.

REFERENCES


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Source of support: Nil, Conflict of interest: None Declared