GASTRO-RETENTIVE FLOATING DRUG DELIVERY SYSTEMS

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ABSTRACT

A drug delivery device for administering a drug at a controlled rate for a prolonged period of time to produce a local or systemic physiological or pharmacological effect is comprised of a wall surrounding a reservoir containing a drug. The reservoir is formed of a solid drug carrier permeable to the passage of the drug. The wall is formed in at least a part of a microporous material the pores of which contain a drug release rate controlling medium also permeable to the passage of the drug, but the rate of passage of the drug through the medium is lower than the rate passage of the drug through the solid drug carrier so that drug release by the medium in the microporous wall is the drug release rate controlling step for releasing drug from the drug delivery device.

KEY WORDS: FDDS, Mucoadhesive drug delivery, Effervescent Floating Dosage

1. INTRODUCTION

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.[36]

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa.[1]

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion [2], flotation [3], sedimentation [4], expansion modified shape systems [5] or by the simultaneous administration of pharmacological agent [6,7] that delay gastric emptying. This review focuses on the principal mechanism of floatation to achieve gastric retention. forms is not just to prolong the delivery of drugs for more than 12 hours, but to prolong the presence of the dosage

forms in the stomach or upper gastrointestinal (GI) tract until all the drug is released for the desire period of time.[8] Rapid GI transit could result in incomplete drug release from the drug delivery device in the absorption zone leading to diminished efficacy of the administered dose.[9]

Several approaches are currently used to retain the dosage form in the stomach. These include bio adhesive systems,[10] swelling and expanding systems [11-12], floating drug delivery systems(FDDS),[13-14] and other delayed gastric emptying devices.[15] FDDS, also called hydrodynamically balanced system, is an effective technology to prolong the gastric residence time in order to improve the bioavailability of the drug. [16] This technology is suitable for drugs with an absorption window in the stomach or in the upper part of the small intestine,[17] drugs acting locally in the stomach,[18] and for drugs that are poorly soluble or unstable in the intestinal fluid.[19] FDDS have a bulk density lower than the gastric fluid and thus 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. Based on the mechanism of buoyancy, two distinctly different technologies, i.e. noneffervescent and effervescent systems, have been utilized in the development of FDDS. The effervescent system utilizes matrices prepared with swellable polymers and effervescent components, e.g. sodium bicarbonate and citric acid or stearic acid. The matrices are fabricated such that in the stomach carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy. In noneffervescent FDDS, the drug is mixed with a gel forming hydrocolloid, which swells on contact with the gastric fluid after oral administration and maintains relative integrity of shape and a bulk density of less than unity within an outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms.[20]

2. BASIC GASTROINTESTINAL TRACT PHYSIOLOGY

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.[38]

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the two states. During the fasting state an interdigestive series of electrical events take place, which cycle goes through stomach and intestine every 2 to 3 hours.[39] This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following four phases as described by Wilson and Washington.[40]

Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.

Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the

small intestine. It is also known as the housekeeper wave.

Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of two consecutive cycles. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state, onset of MMC is delayed resulting in slowdown of gastric emptying rate.[41]

Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically two complications that of short gastric residence time and unpredictable gastric emptying rate.

3. APPROACHES TO DESIGN FLOATING DOSAGE FORMS OR MICROPOROUS DRUG DELIVERY.

The following approaches have been used for the design of floating dosage forms of single- and multiple-unit systems. [21]

a. Single-Unit Dosage Forms

In Low-density approach [22] the globular shells apparently having lower density than that of gastric fluid can be used as a carrier for drug for its controlled release. A buoyant dosage form can also be obtained by using a fluid-filled system that floats in the stomach. In coated shells. [23]

Fluid- filled floating chamber type of dosage forms includes incorporation of a gas-filled floatation chamber into a microporous component that houses a drug reservoir. [24]

b. Multiple-Unit Dosage Forms

The purpose of designing multiple-unit dosage form is to develop a reliable formulation that has all the advantages of a single-unit form and also is devoid of any of the above mentioned disadvantages of single-unit formulations. In pursuit of this endeavor many multiple-unit floatable dosage forms have been designed. Microspheres have high loading capacity and many polymers have been used such as albumin, gelatin, starch, polymethacrylate, polyacrylamine, and polyalkylcyanoacrylate. Spherical polymeric microsponges, also referred to as “microballoons,” have been prepared. Microspheres have a characteristic internal hollow structure and show an excellent in vitro floatability.[25]

4. CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEMS (FDDS) [26]

Floating drug delivery systems are classified depending on the use of 2 formulation variables: effervescent and non-effervescent systems.

a. Effervescent Floating Dosage Forms

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

A new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sublayers to avoid direct contact between the 2 agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37ºC, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO_2 was generated by the neutralization reaction between the 2 effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/mL. It was found that the system had good floating ability independent of pH and viscosity and the drug (para-amino benzoic acid) released in a sustained manner (Figure 1, A and B).

b. Non-Effervescent Floating Dosage Forms

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. 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.

5. EVALUATION OF FLOATING DRUG DELIVERY SYSTEMS [48]

Various parameters that need to be evaluated in gastroretensive formulations include floating duration, dissolution profiles, specific gravity, content uniformity, hardness, and friability in case of solid dosage forms. In the case of multiparticulate drug delivery systems, differential scanning calorimetry (DSC), particle size analysis, flow properties, surface morphology, mechanical properties and X-ray diffraction studies are also performed.

6. FACTORS CONTROLLING GASTRIC RETENTION OF DOSAGE FORMS

The stomach anatomy and physiology contain parameters to be considered in the development of gastroretentive dosage forms. To pass through the pyloric valve in to the small intestine the particle size should be in the range of 1 to 2 mm.[32] The most important parameters controlling the gastric retention time (GRT) of oral dosage forms include : density, size and shape of the dosage form, food intake and its nature, caloric content and frequency of intake, posture, gender, age, sex, sleep, body mass index, physical activity and diseased states of the individual (e.g. chronic disease, diabetes etc.) and administration of drugs with impact on gastrointestinal transit time for example drugs acting as anticholinergic agents (e.g. atropine, propantheline), Opiates (e.g. codeine) and prokinetic agents (e.g. metclopramide, cisapride.).[33] The molecular weight and lipophilicity of the drug depending on its ionization state are also important parameters.[34]

7. POTENTIAL DRUG CANDIDATES FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS

a. Drugs those are locally active in the stomach e.g. misroprostol, antacids etc.
b. Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. L-DOPA, para aminobenzoic acid, furosemide, riboflavin etc.
c. Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
d. Drugs that disturb normal colonic microbes e.g. antibiotics against Helicobacter pylori.
e. Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil HCl.

8. DRUGS THOSE ARE UNSUITABLE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS

a. Drugs that have very limited acid solubility e.g. phenytoin etc.
b. Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
c. Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc.

9. ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM [27, 28]

a. The gastroretensive systems are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, antacids.
b. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
c. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
d. The gastroretensive systems are advantageous for drugs meant for local action in the stomach. e.g. antacids.
e. When there is a 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 drug in floating condition in stomach to get a relatively better response.
f. Site specific drug delivery. [37]

10. DISADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM

a. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
b. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat, water.
c. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first

pass metabolism, are only desirable candidate.

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

11. FACTORS AFFECTING GASTRIC RETENTION[35]

The rate of gastric emptying depends mainly on viscosity, volume, and caloric content of meals. Nutritive density of meals helps determine gastric emptying time. It does not make any difference whether the meal has high protein, fat, or carbohydrate content as long as the caloric content is the same. However, increase in acidity and caloric value slows down gastric emptying time. Biological factors such as age, body mass index (BMI), gender, posture, and diseased states (diabetes, Chron's disease) influence gastric emptying. In the case of elderly persons, gastric emptying is slowed down. Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down.

12. FACTORS AFFECTING FLOATING DRUG DELIVERY SYSTEM

a) Density: Density of the dosage form should be less than the gastric contents (1.004gm/ml).

b) Size and Shape: Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5 kilopond per square inch (KSI) are reported to have better GIT for 90 to 100 % retention at 24 hours compared with other shapes.[42]

c) Fed or Unfed State: Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.[43]

d) Nature of the meal: Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release.[44]

e) Caloric Content: GRT can be increasedbetween 4 to 10 hours with a meal that is high in proteins and fats.

f) Frequency of feed: The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.[45]

g) Gender: 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.

h) Age [46]: Elderly people, especially those over 70 years have a significantly longer GRT.[47]

i) Posture: GRT can very between supine and upright ambulatory states of the patients.[46]

j) Concomitant drug administration: Anticholinergic like atropine and propentheline opiates like codeine and

prokinetic agents like metoclopramide and cisapride.

13. LIMITATIONS OF FLOATING DRUG DELIVERY SYSTEM

a. Require quite high level of fluids in the stomach for the drug delivery system to float.
b. Drugs with significant first pass are not desirable candidate for floating drug delivery system. Eg nifedipine.
c. Drugs irritant to gastric mucosa may also pose problem, if developed as floating drug delivery system.

14. APPLICATION

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

a. Sustained Drug Delivery: Floating drug delivery system can remain in the stomach for a long period and hence can release the drug for prolonged period of time. The problem of short gastric residence time encountered with an oral controlled release formulation, can be overcome with these systems. These systems have a bulk density of less than 1, as a result of which they can float on the gastric contents.[29]

b. Site-Specific Drug Delivery : Floating drug delivery systems are particularity advantageous for drugs that are specifically absorbed from stomach or proximal part of small intestine eg, riboflavin and furosemide. A bilayer floating capsule was developed for local delivery of misoprostol, which is a synthetic analog of prostaglandin used as a protectant for gastric ulcers caused by administration of NSAID,s.[30]

c. Absorption Enhancement : 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.

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%). [31]

15. CONCLUSION

Gastro-retentive floating drug delivery systems have emerged as an efficient means of enhancing the bioavailability and controlled delivery designing controlled release systems for better absorption and enhanced bioavailability. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms.

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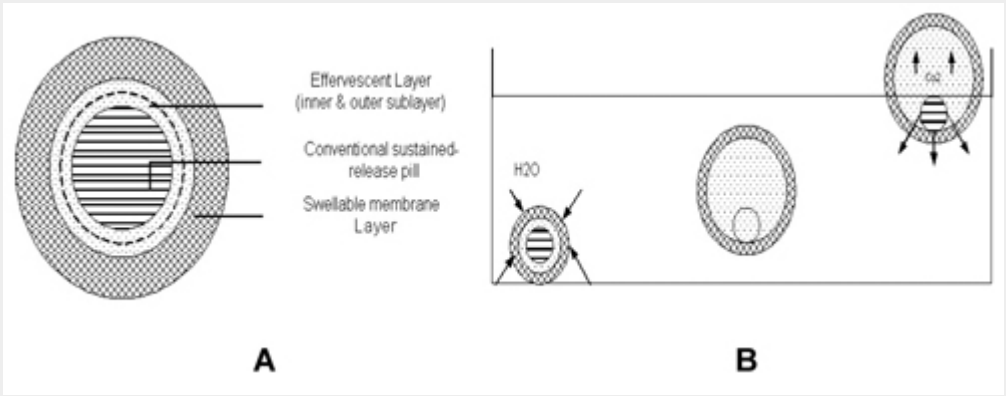

Figure 1. (A) Multiple-unit oral floating drug delivery system. (B) Working principle of effervescent floating drug delivery system.