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FLOATING DRUG DELIVERY SYSTEM (FDDS): TYPES, ADVANTAGES, DISADVANTAGES & APPROACHES

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ABSTRACT

In this review studying about the oral drug delivery system, where floating systems are low thickness frameworks that have adequate lightness to drift over the gastric substance and stay light in the stomach without influencing the gastric purging rate for a drawn-out timeframe. Floating drug delivery systems are planned to prolong the study of the dosage form in the g.i.t and help in enhancing the absorption. These types of systems are best suitable for drug having an improved solubility in acidic environment and also having specific site of absorption in upper part of the small intestine. Present review is to keep understanding or overcome the difficulties for the development of oral drug delivery system. FDDS are of particular interest of drugs that are locally active and have narrow absorption window in stomach or upper small intestine unstable in the intestinal and exhibit low solubility at high pH values FDDS in specific region of the GIT offers numerous advantages, especially the drugs having narrow absorption window in GIT, primary absorption in the stomach, Stability problems in the gut are caused by the stomach's poor solubility in alkaline pH. the reason that oral route achieved such popularity may be in part attributed to its ease of administration.

KEYWORDS: Floating drug delivery systems (FDDS), Oral drug delivery systems (ODDS)

INTRODUCTION

Oral delivery of the drug is by far the most preferable route of drug delivery due to the case of administration, patient compliance and flexibility in the formulations. For immediate release to site-specific delivery, oral dosage form has surely progressed. It is evident from the recent scientific and patented literature that an increased interest in oral dosage forms that are retained in the stomach for prolong and predictable period of time occur today in academic and industrialized research groups. Various attempts have been made to develop GIT delivery systems. Over the past three decades, the pursuit and exploration of devices designed to be retained in the upper part of the Gastro Intestinal Tract (GIT) has advanced consistently in terms of technology and selection, encompassing a variety of systems and devices such as floating systems, rate systems, increasing systems, swelling systems, bio adhesive systems and low-density systems. This technology benefits both patients and drugs that have a contracted window of absorption in the stomach and upper GI tract. 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 bio availability, reduces drug excess, and improves solubility for drugs that are less soluble in a high pH environment. Its applications also for local drug delivery to the stomach and proximal small intestine. Gastro retention comforts to provide superior availability of new products with new therapeutic possibilities and substantial benefits for patients.[1,2] Therefore, control of placement of a Drug Delivery Systems (DDS) in a specific region of the GIT offers advantages for a variety of important drugs characterized by a tapered absorption window in the GIT or drugs with a unstable.[3] These considerations have led to development of a single oral controlled release dosage form with gastro retentive properties. One of the most possible approaches for achieving a prolonged and predictable drug delivery in the GIT is to control the Gastric Residence Time (GRT), i.e. Gastro Retentive Dosage Form (GRDF). Floating systems or hydro dynamically balanced systems, are low-density systems that have sufficiently 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 and a better control of the fluctuations in plasma drug concentrations. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and allow micro spheres.

To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than1. It should stay in the stomach, maintain Its structural integrity, and release drug constantly from the dosage form.[5] Hence in the present wok is to and develop the sustained release floating tablets of Metformin Hydrochloride using Guar Gum and Microcrystalline cellulose as a polymer in order to enhance the absorption followed by improving bioavailability.

Metformin Hydrochloride is an anti-hyperglycemic agent, which improves the glucose tolerance in Type 2 diabetes. The indicated oral dosage is 500 mg 3 times in day or 650 mg twice daily, usually at a dose of 2g (maximum of 3g) per day.[8] The absolute bioavailability is 50-60%, biological half-life is 1.5-3 hrs. the main site of absorption is proximal small intestine.[9, 10] For these reasons the GFDDS was planned for Metformin Hydrochloride, as such system when administered would remain buoyant on the gastric fluids for a prolonged period of time and the drug would be obtainable in the dissolved form at the main site of its absorption.

1.1. Definition

Floating system 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.

1.2. Physiological Consideration of Gastrointestinal Tract

The stomach is divided into three anatomical districts lobe funds, body and pylorus. The former two act as reservoir for ingested material whereas the latter is the major site for motions (gastric emptying). The gastric emptying process is variable from limited minutes to little hours, depending on physiological state of the subject and the design of the formulation. This variability in turn could lead to altered bioavailability. The relatively brief gastric emptying time (GET) in humans, which normally averages 2-3 hours through the major absorption zones (stomach or upper part of the intestine) can result in inadequate drug release from the drug delivery system leading to reduced efficacy of the administered dose. Thus, orally administered controlled release forms suffer from mainly two adversities the short gastric retention time and unpredictable GET.

1.3. Stomach: Basic Anatomy, Physiology and Problems

1.3.1. Anatomy

The stomach situated between the oesophagus (proximally) and the duodenum (distally). It contrasts broadly in size and shape depending on the person, the food content, and the posture of the body. Anatomically stomach is J-shaped normally and the pyloric part lies horizontally or ascends to meet the proximal part of the duodenum

Anatomycally, the stomach is divided into 3 parts

1. Fundus: The superior part of the stomach, this lies above the imaginary horizontal plane passing through the cardiac orifice.

2. Body: This lies between the fundus and the antrum, and it is the largest part of the stomach.

3. Antrum: This lies in the imaginary transpyloric plane and to the right of the angular notch (incisuraangularis). Antrum and pyloric canal joints with each other and it are on right side of the pyloric canal.

1.3.2. Physiology

The physiology and disease state of stomach has a direct on design of controlled drug delivery system because drug is absorbed from and enters into site of action. Different factors as like pH, nature of the stomach, volume of gastric secretions, and gastric mucosa play an important role in drug release and absorption.

1.3.3. pH

Environmental pH affects the performance of orally administered drugs in to GIT. When patient administrated large volume of water with any oral dosage form initially changes the pH of stomach. This change occurs because stomach does not have enough time produce sufficient quantity of acid before emptying of liquid the stomach.

1.3.4. Volume

The resting volume of stomach is about 25-52ml and gastric volume have significant role for dissolution of oral dosage forms in vivo study.

1.3.5. Gastric Secretion

Acid's pepsin, gastric, mucus and some other enzymes are the secretions of the stomach. Normal adults produce a basal secretion up to 60ml with approximately 4mmol of hydrogen ions every hour. Other potent stimulators of gastric acid are the hormone gastric, peptides amino acids and gastric distention.

1.4. Factors controlling Gastric Retention dosage forms

The development of gastro retentive dosage forms basically depends on the parameter of consider in stomach anatomy and physiology. To pass through the pyloric value in to the small intestine the particle size should be in the range of 1 to 2mm. The most important parameters controlling retention time (GRT) of oral dosage forms include: density, size and shape of the dosage form, age, sex, sleep, body mass index, physical activity and diseased states of the individual (e.g. chronic disease, diabetes etc.) and administration of drug with impact on gastrointestinal trabsit time. The important parameters of drugs are ionization of drug which is depending on molecular weight and lipophilicity of the drug.

1.4.1. Density of dosage forms

The density of dosage form affects the gastric emptying rate and determines the location of the system in the

stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density system sink to bottom of the stomach. A density of <1.0gm/cm' is required to exhibit floating property.

1.4.2. Shape and Size of the dosage form

Shape and size of the dosage system forms are important in designing indigestible single unit solid dosage forms.

In most cases, the larger size of the dosage forms the greater will be the gastric retention time (GRT) due to the larger size of the dosage form would not allow this to quickly pass through the pyloric anturm into the intestine. Dosage forms having a diameter of more than 7.5 mm show better gastric residence time compared with one having 9.9mm. Ring shaped and tetrahedron-shaped device have a better gastric residence time as compared with other shapes.

1.5. Basie GIT Physiology Gastric Emptying

The stomach is anatomically divided into three parts:

a) Fundus
b) Body
c) Antrum (pylorus)

The separation between stomach and duodenum is the pylorus. The 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. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct for the two states. During the fasting state an inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2-3 hrs. This is called the inter digestive my electric cycle or migrating my electric cycle (MMC), which is further divided into four phases.25

Following four phases as described below:[26]

PHASE-I: (basal phase) lasts from 30-60 min with rare contractions.

PHASE-II: (preburst phase) lasts for 20-40 min with the intermittent action potential and contractions as the phase progresses, the intensity and the frequency also increase gradually.

PHASE-III: (burst phase) lasts for 10-20 min it includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of stomach to small intestine.

PHASE-IV: Lasts for 0-5 min and occurs between phase 3 and 1 of two consecutive cycle.

1.5.1 Floating Drug Delivery Systems

Floating drug delivery systems are the systems which are retained in the stomach for a longer period of time and thereby, improve the bioavailability of drugs. If the drugs are poorly soluble in the intestine due to alkaline pH, gastric retention may increase solubility before they are emptied resulting in gastrointestinal absorption of drugs with narrow therapeutic absorption window, as well as, controlling release of drugs having site specific-absorption limitation. Drugs that could take advantage of gastric retention include the drugs whose solubility is less in the higher pH of the small intestine than the stomach (e.g. chlordiazepoxide and cinnarizine), the drugs prone for degradation in the intestinal pH (e.g. captopril), and the drugs for local action in the stomach (e.g. misoprostol). Antibiotics, catecholamine's, sedatives, analgesics, anti convulsants, muscle relaxants, anti-hypertensive and vitamins can also be administered in HBS dosage form.

1.6. Factors Floating Drug Delivery System

1.6.1. Physiological factors

Size of dosage form: Dosage forms having diameter greater than the diameter of pyloric sphincter escape from gastric emptying and remain within gastric region. Shape of dosage form: Round or Ring-shaped dosage form are considered better in Comparation in other shape.

Density System Location of the particular gastro retentive dosage form in gastric region depends on density of the system. Those with low density tend to float on the gastric fluid surface while high density systems sink to bottom of stomach. b)

1.6.2. Biological Factors

Age: Geriatric patients show a longer gastric retention time, while the neonates and children have low gastric retention time, in comparison to a normal adult.

Gender: Gastric retention time in male (3-4 hours) is less than the female (4-6 hours).

Fed or Unfed state: Gastric motility is higher in fasting conditions which depicts lesser gastric retention time.

Fed frequency- Here the frequency of taking food, longer will be will be the gastro retention time.

Nature of weal: High of a hand her indigestible polymers generally decrease the gastric retention time by the altering gastric motility.

Concomitant drug administration: Administration of certain drugs along with gastric motility enhancers (metoclopramide, císapride) or depressants (atropine), greatly affect gastric retention time and hence absorption of stomach specific absorbing drugs.

Disease state: Gastro retentive time is altered during the various gastric diseases like Crohn' s disease etc.

1.7 Advantage of Floating Drug Delivery System

1. The Floating systems are beneficial for drugs absorbed through the stomach. E.g. Ferrous salts, antacids.
2. Acidic substances like aspirin cause inflammation and irritability 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.
3. Administration of extended-release floating dosage forms as like tablet or capsules affect dissolution of the drug in the gastric fluid. Extended dosage form dissolve in the gastric fluid would be available for

absorption in the small intestine after pouring 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.

4. The Floating drug delivery systems are beneficial for drugs intended for local action in the stomach. E.g. Antacids.
5. 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.

Disadvantage of Floating Drug Delivery System

1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
2. These systems require a high level of fluid in the stomach for drug delivery to float and week officially-coat, water.
3. The drugs that are significantly absorbed through out gastrointestinal tract.

1.9. Stomach Specific floating drug delivery system (FDD)

Stomach Specific floating drug delivery system (FDD%) 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 dug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentration. The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as 'hydrodynamically balanced systems' (1118 degrees) since they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3-4 hours) on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents. Among the different hydrocolloids recommended for floating form formulations, cellulose ether polymers are most popular, especially Microcrystalline cellulose (MCC). Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy Parallel to formulation studies, investigations have been undertaken in animals and humans to evaluate the intragastric retention performances of Boating forms. These assessments were realized either indirectly through pharmacokinetic studies with a drug tracer, or directly by means of X-ray and gamma scintigraphic monitoring of the form transit in the GI tract.

1.10. Types of Floating drug delivery system

Floating drug delivery system met for gastric retention, float on the face of the gastric fluids, due to their low density and produce prolonged effect by showing the release, while being buoyant on gastric fluid surface. This type of delivery system is of great value for drugs which get absorbed from upper part of their absorption window resides in upper part of stomach. Though, immediate floating of the delivery system can only be achieved if the density of the delivery system is on lower side 18 Delivery system with higher density, initially settle down in stomach and them tend to float with decrease in the density of the system. But, with such system, there may be a possibility of gastric emptying of system, before the floating starts, Low density of system, which leads to floating, rendered either by incorporation of low-density excipients or by providing a mechanism which leads to air entrapment within the system Different types of floating systems have been developed, which may involve generation of gas (effervescent) or non-effervescent. These systems consists of hydrophilic gel forming polymers like HPMC, hydroxy ethyl cellulose, hydroxy propyl cellulose, agar, alginic acid etc. and are generally designed for single unit dosage 41 In this approach, hydrophilic polymer is mixed with drug along with other excipients and encapsulated in gelatin shell. Gelatin, being hygroscopic in nature dissolves rapidly in the gastric fluid and exposes the hydrophilic polymer and drug content to the fluids.23 Polymer fraction present on the surface then undergoes hydration and swelling, to produce a floating mass.

1.10.1. High Density System

It is a well-known fact, that the density of the gastric content is approximately similar to water. So, when the density of the dosage form is higher than water, it tends to deposit or sink at the bottom of the stomach, near pyloric region. These sinked dosage forms, there, withstand against peristaltic contractions and do not get emptied from the stomach. Retarded gastrointestinal transit, in case of such dosage form has been reported to extend gastric retention time up to 6 to 24 hours. Commonly used excipients in such dosage forms are barium sulphate, titanium oxide etc, which ranses the density of system up to 1.4 to 2.5 gram per cubic centimeter. Such type of system has shown promising results in the animals, but no system has been in the market for human consumption.

1.10.2. Gas generating systems (Effervescent systems)

Floating to a system can also be produced by the gas bubble generation. For this, carbon dioxide is generated within the system by incorporating bicarbonates and carbonates. which on reaction with gastric content (gastric acid) produce gas.[23] System utilizes the presence of swellable polymers like mythical, chitosan etc, along with effervescent components like bicarbonates with citric or tartaric acid for gas generation 18 General approach for preparation of such system involves preparation of core with drug, swellable polymer along

with effervescent system and coating with hydrophobic polymer like ethyl cellulose, which acts as semi-permeable membrane to regulate the inflow of the gastric content and keep the system intact within the polymer coating for complete gastro retention period.

1.10.3. Raft forming system

This type of system, a gel forming solution is prepared that swells on coming in contact with gastric contents and form viscous gel like layer which resemble same as a raft in river. This, raft like layer of gel, has a very low bulk density due to the generation of carbon dioxide within system, which makes the layer to float on the surface of gastric content. Raft forming system consists of a gel forming polymeric agent and carbon dioxide producing agents like bicarbonates and carbonates 43 Gel forming agents that are being widely utilized for the formation of the raft like consistency are from the alginate category e.g. alginic acid. Such formulations also include antacids such aluminum hydroxide, calcium carbonate etc. for reduction of the gastric acidity. As the solution after gel formation floats on the surface of the gastric fluids, such systems are used for the treatment of the gastro-esophageal reflux.[35]

1.10.4. Low density system

Major limitation in case of effervescent delivery system in the time lag before floating on the gastric contents. In this time period, it may be possible that the delivery system may get evaluated and drug. Before floating and drug release. So, in order to overcome this limitation, low density systems (lesser than 1000 mg per cubic centimeter) have been developed which show immediate floating and release of drug on the gastric content surface. System is basically consisting of low-density materials which entrap oil or air.

1.10.5. Expandable System

A dosage form, which is bigger in size than the diameter of the pyloric sphincter can withstand with the gastric transit and escape the evacuation from the gastric region. But while designing such system, it should be kept in mind that the dosage form should be of adequate size, so that it can be easily swallowed and should not cause gastric obstruction should also be considered, that after complete drug release from system, it can be evacuated easily from the gastric system. The concept of designing such expandable system is to prepare a carrier (e.g. capsule) and tincorporate in it, a compressed system which expands, as it comes in contact with the gastric contents. As, the size of the system increases and reaches to diameter or dimensions, greater than the size of the pyloric sphincter, it cannot leave the stomach while gastric emptying process.

1.10.6. Mucoadhesive and Bioadhesive Systems

Mucoadhesive systems adhere to gastric mucosa and remain in the gastric region for prolong time. Adherence occurs due to hydration and swelling of the adhesive polymer on contact with gastric contents. Materials that are commonly used for imparting the mucoadhesive or bioadhesive property to the whole system include carbopol, chitosan, tragacanth, PEG, HPMC etc. However, it is very difficult to maintain the system adhered within the gastric region, due to rapid turnover rate of the gastric mucus. Such systems also pose another problem that it is very difficult to control the specific adhesivity of system to gastric mucosa and it may also adhere to other surfaces, e.g., esophagus.

1.10.7. Magnetic System

Magnetic system involves the incorporation of the small magnet inside the core matrix of the system and application of another magnet on the abdomen region. externally. This system, however, provide satisfactory results, there is a problem of placing the magnet externally at the right position with great accuracy and precision.

1.10.8. Mechanism of Floating System

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosages form (gas generating systems and swelling or expanding systems), moccadhesive systems, high density systems, modified shape systems, gastric-emptying delaying devices and co administration of gastric-emptying delaying drugs. Among these, the floating dosage forms have been most commonly used. 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 in 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. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.

1.11. SINGLE UNIT FLOATING DOSAGE SYSTEMS

1.11.1. Effervescent Systems (Gas-generating Systems)

These buoyant systems utilized matrices prepared with swellable polymers like HPMC, polysaccharides like GUAR GUM, effervescent components like sodium bicarbonate acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for g generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with Microcrystalline cellulose. The coating, which is insoluble but permeable, allows permeation of water.

1.11.2. Non-effervescent Systems

This type of system, after swallowing, swells unrestrained via imbibition's of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the "plug-type systems" since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier.

CONCLUSION

Floating drug delivery system (FDDS) is a type of system to regulate the Drug absorption in the GIT and it is a highly variable procedure to prolonging gastric retention of the dosage form persists the time for drug absorption. The Floating drug delivery systems are benefits for drugs intended for local action in the stomach. FDDS obligation to be a likely approach for gastric retention. While there are number of disputes to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique. This type of delivery system is of great value for drugs which get absorbed from upper part of their absorption window reside in upper part of stomach.

Conflict of Interest: The authors declare that the review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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