Review Article

A REVIEW ON GASTRORETENTIVE DRUG DELIVERY SYSTEM: AN EMERGING APPROACH TO IMPROVE THE GASTRIC RESIDENCE TIME OF SOLID DOSAGE FORMS

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ABSTRACT

Gastroretentive drug delivery systems have now become the most developing and interesting field in the present time. They proposed different types of technologies that are useful in increasing the gastric residence time of the dosage form, thus provide a controlled release of the drug candidate. Because of this, the enhanced absorption and bioavailability is achieved in the gastrointestinal region. Different approaches or technologies used in the gastroretentive drug delivery system are floating dosage system, swellable dosage system, bio/Mucoadhesive dosage system, high density dosage system etc. These different technologies provide improved and/or better therapeutic performance of the drug. Gastroretentive drug delivery system produce prolonged gastric residence time and controlled release of drug candidate which helps in reducing the dosing frequency, improve patient compliance and convenience and maintain less fluctuating plasma level. Basic anatomy and physiology of gastrointestinal tract is described with the explanation of gastric emptying, motility patterns, frequency of forces of contraction during each phase and average time period of each phase. The main purpose of this review is to aware the people about the recent literature, current advancement and many advantages in the field of gastroretentive drug delivery system. Many research programmes are going on in order to develop a gastroretentive dosage form of optimized therapeutics for the improvement of bioavailability and reduction in side effects.

Keywords: Gastroretentive drug delivery system, Floating, swellable, bio/Mucoadhesive, high density, gastrointestinal tract.

INTRODUCTION

Oral controlled release dosage forms have been used over many decades due to their therapeutic advantages like ease of administration, patient compliance and flexibility in formulation. However, in this approach several physiological difficulties have been encountered like targeting of the controlled drug delivery system at the desired place in gastro intestinal tract because of varying gastric emptying. A major review in oral controlled drug delivery is that not all drug candidates are absorbed uniformly throughout the gastro intestinal tract. Some drugs are absorbed in a particular segment of gastro intestinal tract only or absorbed to a different amount in various segments of gastro intestinal tract. Such drug candidates are said to have an absorption window. But, in case of narrow absorption window drugs, only the drug released in the region preceding and in close surrounding to the absorption window is available for absorption.

This causes the incomplete release of drug and hence reduced the efficacy of administered dose[1]. To avoid this limitation the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, the drug would remain in the stomach and release the drug in a controlled manner; hence the drug could be supplied continuously to its relative absorption sites in the gastrointestinal tract[2].Gastroretentive drug delivery systems may remain in the gastric region for few hours and hence significantly prolong the gastric residence time of drugs[3].

Some gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach, low density (floating) systems that causes buoyancy in gastric fluid, mucoadhesive systems that causes bioadhesion to stomach mucosa, unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach, super porous hydrogel systems, magnetic systems[4,5,6] etc. (Figure 1).

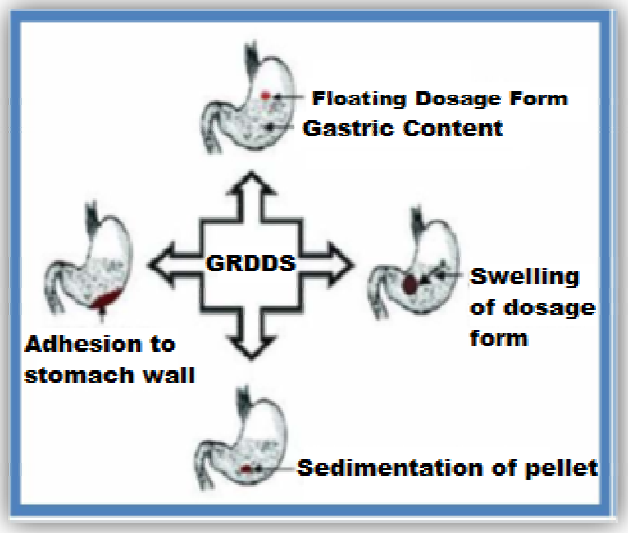

Figure 1: Different approaches of gastric retention.

The oral controlled drug delivery system should be aimed to achieving more predictable and increased bioavailability of drugs. Prolonged gastric retention results in improved bioavailability, reduced drug waste. It is useful for those drugs which are poorly soluble and unstable in intestinal fluids. Gastroretentive dosage forms greatly improved the pharmacotherapy of the gastro intestinal tract through local drug release, leading to high drug concentrations at the gastric mucosa (eradicating Helicobacter pylori from the submucosal tissue of the stomach), making it possible to treat gastric and duodenal ulcers, oesophagitis etc.

Gastroretention provides the better availability of new products with suitable therapeutic activity and benefits for patients. This mode of administration would help in achieving the known pharmacokinetic and pharmacodynamic advantages of control release dosage forms of these drugs. This article deals with various gastroretentive approaches and future plans that have become leading methodologies now a days in the field of site-specific orally administered controlled release drug delivery systems and advantages.

POTENTIALLY ACTIVE DRUG CANDIDATES SUITABLE FOR GASTRORETENTION

The suitable candidates for gastroretentive drug delivery system are molecules that possess poor absorption but are characterized by better absorption:

• Drugs that have narrow absorption window in gastrointestinal tract.

e.g.- riboflavin and levodopa.

• Drugs that are primarily absorbed from stomach and upper part of gastrointestinal tract.

e.g. - calcium supplements, chlordiazepoxide and cinnarazine

• Locally active drugs in the stomach.

e.g. - antacids and misoprostol

• Drugs which degraded or unstable in the colon.

e.g.- ranitidine HCl and metronidazole

• Drugs that disturb normal colonic bacteria or microbes.

e.g. - amoxicillin trihydrate

GENERAL ASPECTS OF GASTROINTESTINAL TRACT

1. Anatomy of the gastrointestinal tract:

The gastrointestinal tract categorizes into three main parts:

a. Stomach

b. Small intestine- Duodenum, Jejunum and Ileum

c. Large intestine

The gastrointestinal tract is a long muscular tube, starting from the mouth and end at the anus, which capture the nutrients inside the body and eliminate waste by different physiological processes such as secretion, digestion, absorption and excretion. Figure 2 includes the basic construction of gastrointestinal tract from stomach to large intestine.

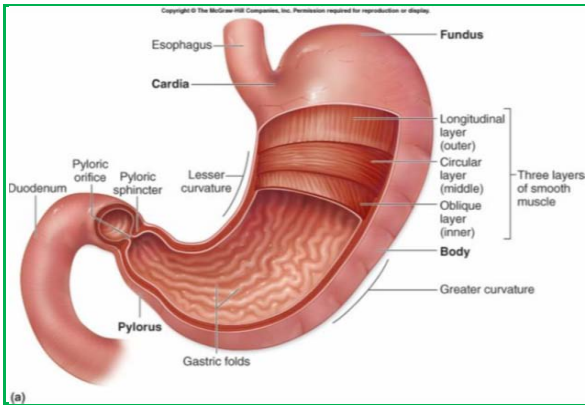

Figure 2: Anatomy of the gastrointestinal tract.

The stomach is a J-shaped organ which can be divided into four parts: cardia, fundus, body and antrum. The main function of the stomach is to store and mix food with gastric secretions.

It consists of serosa, longitudinal muscle, intermuscular plane, circular muscle, submucosa, lamina propria and epithelium. The stomach has a third muscle layer called as the "oblique muscle layer", situated in the proximal stomach, branching over the fundus and higher regions of the gastric body. The different smooth muscle layers performing the motor functions of the gastrointestinal tract, i.e. gastric emptying and intestinal transit[7].

2. Physiology gastrointestinal tract

The stomach anatomy is mainly consists of 3 regions; fundus, body, and antrum pylorus. The proximal part is made up of fundus and body. It serves as a reservoir for the materials which remain undigested, whereas the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions. Gastric emptying occurs during both fasting as well as fed states. The pattern of motility is distinguished in 2 states. During the fasting state an interdigestive series of electrical events takes place, which cycles through stomach and intestine every 2 to 3 hours[8].This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington[9]. (Figure 3)

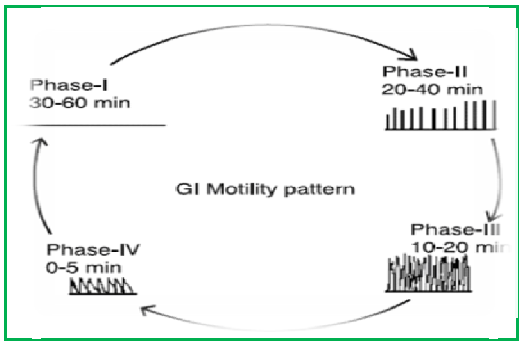

Figure 3: A simplified schematic diagram of the interdigestive balanced motility pattern.

1. Phase I (basal phase).

2. Phase II (preburst phase).

3. Phase III (burst phase).

4. Phase IV.

FACTORS INFLUENCING GASTRIC RETENTION OF DOSAGE FORM

1. Density of dosage forms

Gastroretention is a function of dosage form buoyancy which depends upon the density of dosage forms. Only those dosage forms can float in the gastric fluids which acquire lower density than the gastric contents, while high density systems sink to bottom of the stomach. A density of < 1.0 gm/cm3 is required to exhibit floating property[11].

2. Size and shape of dosage form

The size of the dosage form is another important factor that influences gastric retention. Shape and size of the dosage forms are important in designing indigestible single unit solid dosage forms. In fed conditions, the smaller units get emptied from the stomach during the digestive phase and the larger units during the housekeeping waves. The larger the dosage form the greater will be the gastroretention, due to the larger size of the dosage form would not allow this to quickly pass through the pyloric antrum into the intestine[12]. Ring-shaped and tetrahedron shaped devices are reported to have a better gastroretention as compared with other shape.

3. Food intake and nature of food

The gastroretention time of the dosage form in gastrointestinal tract may also be influenced by the presence or absence of the food. The presence of food in the gastrointestinal tract usually improves the gastric retention time of the dosage form and thus, the absorption of the drug increases by allowing its stay at the absorption site for a longer period.

Again, increase in acidity and caloric value shows down gastric emptying time, which can improve the gastric retention of dosage forms[13]. In the experiment of Whitehead et. al[14]. a gamma scintigraphic study of a bilayer floating capsule of misoprostol, the mean gastric residence time was 199 ± 69 minutes; after a light breakfast, a remarkable enhancement of average GRT to 618 ± 208 minutes was observed.

4. Effect of gender, posture and age

A study by Mojaverian et. al.[15] found that females showed comparatively shorter mean gastroretentive time than males and the gastric emptying in women was slower than in men. In the upright position, the floating systems floated at the top of the gastric contents in upright position and stay for a long time in gastric fluid, showing prolonged gastroretention time. But the non-floating units settled to the lower part of the stomach and undergo faster emptying. However, in supine position, the floating units are emptied faster than non-floating units of similar size.

DIFFERENT TECHNOLOGIES USED IN GASTRORETENTIVE DOSAGE FORMS

Many systems have been developed to increase the gastroretention time of dosage forms by employing a variety of concepts. These systems have been classified as:

A) Floating drug delivery systems

B) Expandable systems

C) Bio/Mucoadhesive systems

D) High-density systems

A. Floating drug delivery systems

Floating systems was firstly developed by Davis in 1968. Floating drug delivery system is an effective technology to prolong the gastric residence time in order to improve the bioavailability of the drug. Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting 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. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.

Floating drug delivery system can be divided into non-effervescent and effervescent (gas-generating) systems.

1) Non-effervescent

These floating drug delivery system are normally prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene, polymethacrylate, carbopol, hydroxyl propyl methyl cellulose, sodium alginate, chitosan etc.

These systems can be further divided into following four sub-types:

i) Hydrodynamically balanced systems (HBS)

They are also known as colloidal gel barrier system.Seth and Tossounian[16] first designated the hydrodynamically balanced systems. Hydrodynamically balanced systems have gained a lot of importance in recent days to improve absorption of drugs. Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. These systems contain drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers such as hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, polycarbophil, polyacrylate, polystyrene, agar, carrageenan or alginic acid. When the system is come in contact with gastric fluid, the hydrocolloids in the system

become hydrates and form a colloidal gel barrier around its surface. This imparts buoyancy in gastric juice for a long period due to its continuous erosion of the surface; this allows water penetration to the inner layers maintaining surface hydration and buoyancy to the dosage form (Figure 4).[17]

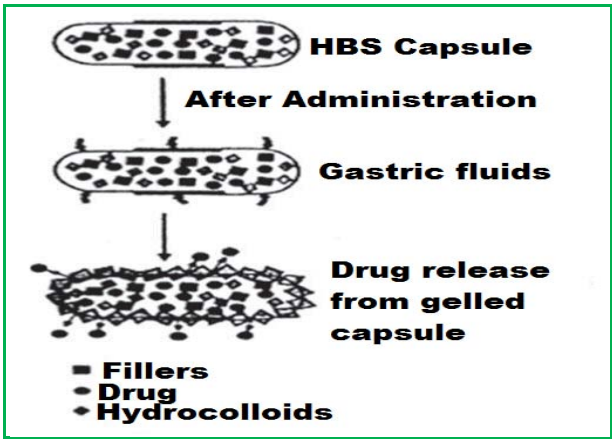

Figure 4: Mechanism of hydrodynamically systems as Floating Drug Delivery System.

ii) Micro porous compartment system

This technology is comprised of encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom surfaces. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the pores, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption. The micro porous compartment system is shown in (Figure 5).

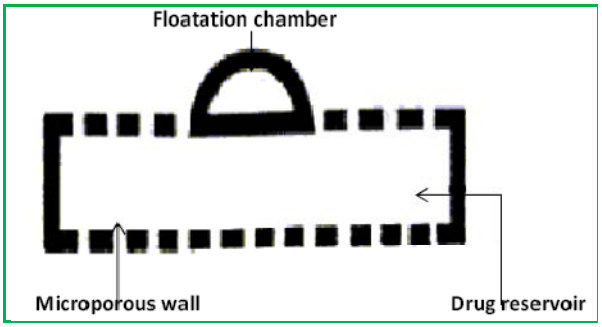

Figure 5: Micro porous intra-gastric floating drug delivery device

iii) Alginate beads

Talukdar and Fassihi[18] recently developed a multiple-unit floating system based on cross-linked beads. They were made by using Ca^{2+} and low methoxylated pectin (anionic polysaccharide) or Ca^{2+} low methoxylated pectin and sodium alginate. In this approach, generally sodium alginate solution is dropped into aqueous solution of calcium chloride and causes the precipitation of calcium alginate. These beads are then separated and dried by air convection and freeze drying, which leads to the formulation of a porous system, which can maintain a floating force for over 12 hrs. These beads improve gastric retention time more than 5.5 hrs.

iv.) Hollow microspheres / Microballoons

Hollow microspheres loaded with drug were prepared by an emulsion solvent diffusion method to create a hollow inner core[19] (Figure 6), which prolongs the gastroretention time of the dosage form. Mainly polymers used to develop these systems such as polycarbonate, cellulose acetate, calcium alginate, agar and low methoxylated pectin etc. The polymer was dissolved or dispersed in the organic solvent and the drug was either dissolved or dispersed in the polymer solution.

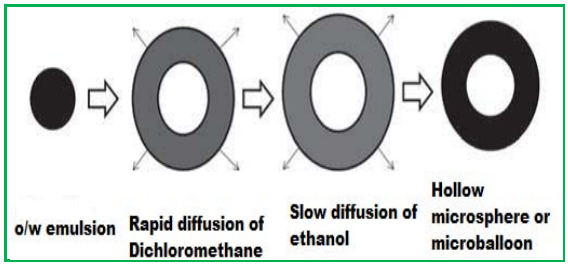

Figure 6: Formulation of Floating hollow microsphere or microballoons

The solution containing the drug was emulsified into an aqueous phase containing polymers to form an oil-in-water emulsion and after formation of stable emulsion, the organic solvent was evaporated either by increasing the temperature under pressure or by continuous stirring. The solvent removal results in polymer precipitation at oil/water interface of the droplets with formation of cavity, and thus, hollow microspheres were formulated. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer polymer ratio and the solvent used for formulation. The microballoons floated continuously over the surface of an acidic dissolution media containing surfactant for greater than 12 hours.

2) Effervescent (Gas-generating) systems

Effervescent systems utilize gas generating agents such as sodium bicarbonate, citric acid or tartaric acid to achieve floating. Other approaches and materials that have been reported are swellable polymers like methocel, hydroxypropyl methylcellulose, chitosan. The system is so prepared that upon arrival in the stomach; carbon dioxide is released, causing the formulation to float in the stomach. These effervescent systems further classified as gas generating systems and volatile liquid/vacuum systems.

a) Gas generating systems

i) Intragastric single-layered floating tablets

They are formulated by mixing the carbon-di-oxide generating components and drug within tablet matrix (Figure 7)[20]**.** These have lower bulk density than the gastric content and thus achieve buoyancy in the stomach

enhance the gastric emptying rate for a prolonged period of time. The drug is released from the matrix tablet in a sustained manner at a desired rate.

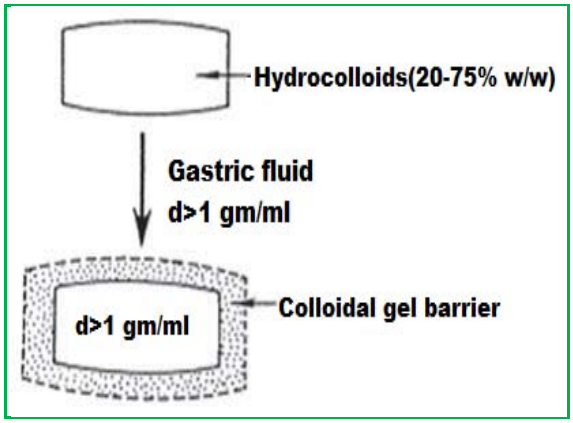

Figure 7: Intra gastric single-layered floating

ii) Intragastric bi-layered floating tablets

This type of tablets contains the gas generating mechanism in one hydrocolloid containing sustained release layer and immediate release layer (Figure 8)[21].

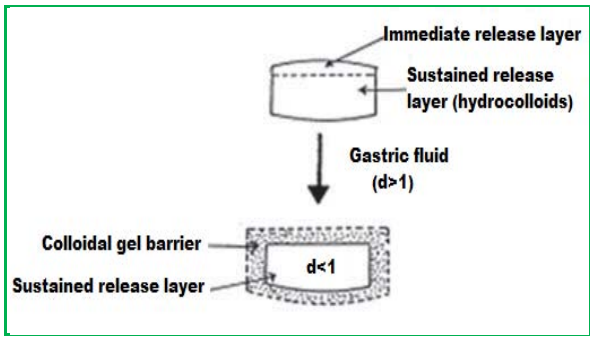

Figure 8: Intra gastric bi-layered floating tablet

iii) Multiple-unit type of floating pills:

These systems consist of sustained release pills as seeds surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of carbon-di-oxide within the system (Figure 9).

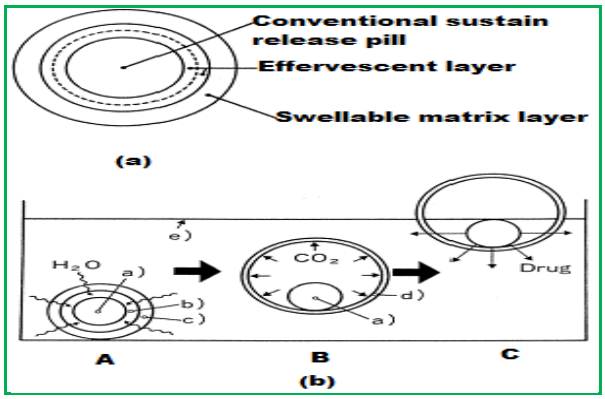

Figure 9: (a) multiple-unit oral floating dosage system. (b) Stages of floating mechanism.

b) Volatile Liquid / Vacuum Systems

i) Intragastric/gas filled Floating Gastrointestinal Drug Delivery System

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment, as shown in (Figure 5).

ii) Inflatable Gastrointestinal Delivery Systems

In this system an inflatable chamber is used, which contains liquid ether that converted into gas at body temperature to cause the chamber to float in the stomach. These systems are fabricated by loading the floating chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug together with the inflatable chamber. The inflatable chamber automatically floats and retains the drug reservoir into the gastric fluid. The system is shown in (Figure 10).

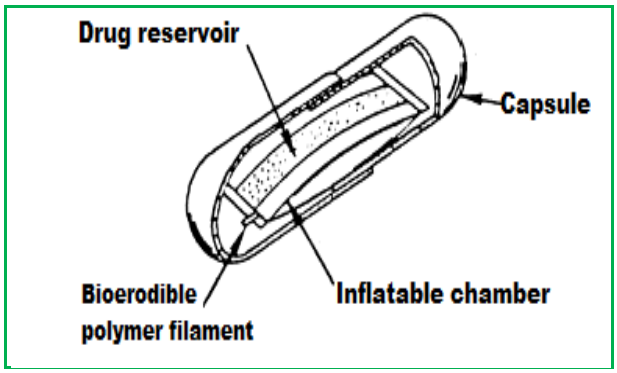

Figure 10: Gastro-inflatable drug delivery device

iii) Intra gastric osmotically controlled floating delivery systems:

The osmotic pressure controlled floating systems consist of two compartments: a drug reservoir compartment and an osmotically active compartment. In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device as shown in (Figure 11). The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag. This bag is impermeable to vapor and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the gastrointestinal fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment, which dissolves the osmotically salt. An osmotic pressure is then created which acts on the collapsible bag, because of which the drug release through the delivery orifice.

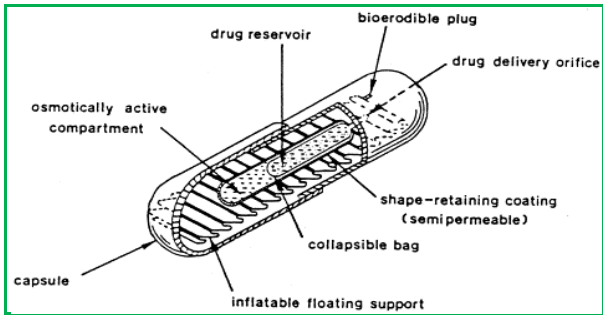

Figure 11: Intragastric osmotic controlled drug delivery system.

B) Expandable systems

These gastroretentive drug forms are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their gastroretention time (Figure 12). Their dimensions are minimized after the release of the drug solution. If the dosage form can attain the larger size than pylorus, the gastroretentivity of that dosage form will be possible for long time. Expandable gastroretentive dosage forms have been designed over the past three decades. They were originally created for possible veterinary use but later the design was modified for enhanced drug therapy in humans. Unfoldable systems are made of biodegradable polymers. Klausner et. al.[22, 23], described a gastroretentive delivery of levodopa, based on unfolding polymer membranes that combines extended dimensions with high rigidity. In humans, 67 % of the drug delivery systems containing levodopa were retained in the stomach during 5 hours[23].

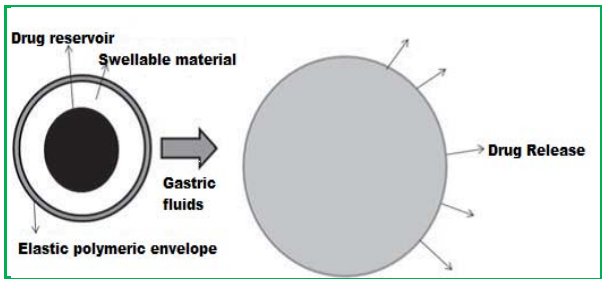

Figure 12: Drug release from swellable systems.

C.) Bio/Mucoadhesive systems

Bioadhesive drug delivery systems are used as a delivery device within the lumen in order to enhance absorption of the drug in a site specific manner. Bioadhesive polymers are used in this approach which can adhere to the epithelial surface in the stomach[24]. Gastric mucoadhesion does not tend to be strong enough to impart ability to dosage forms to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastroretentive force. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan and gliadin, etc.

D. High-density systems

These dosage forms have a density (3 g/ml) which is much greater than that of normal stomach contents (1 g/ml) and thus retained in rugae of the stomach and are capable of unchanged its peristaltic movements. The density of these systems should have to be at least 1.004 g/ml. This is accomplished by coating the drug with heavy inert materials such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc.[25]

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

1) Absorption enhancement

Gastroretentive drug delivery systems enhance the absorption of drugs that have poor bioavailability because of their poor absorption in upper part of gastrointestinal tract.

2) Sustained drug delivery

Hydrodynamically Balanced System type dosage forms increase the gastric residence time and thus release the drug over a prolonged period of time. These dosage forms have bulk density less than one. Madopar hydrodynamically Balanced System formulation has shown to release levodopa for up to 8 hour in vitro, whereas the standard formulation released levodopa is less than 30 min.

3) Site specific drug delivery

Gastroretentive dosage forms are useful for drugs that have specific absorption, e.g. riboflavin, furosemide etc. This site-specific drug delivery reduces undesirable effects of side effects. Hence they are useful in the treatment of disorders related to stomach and small intestine (e.g. eradication of Helicobacter pylori).

4) Enhanced first-pass biotransformation

The pre-systemic metabolism of the drug 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) Reduced fluctuation of drug concentrations

By the use of gastroretentive dosage form fluctuations in drug effects are minimized and concentration dependent side effects that are associated with peak concentrations can also be prevented.

CONCLUSION

The oral drug delivery system is the most popular and perhaps the most complex delivery system. Gastroretentive drug delivery system mainly includes floating, bioadhesive, swelling, high density and magnetic systems that have been developed as current approaches for enhancing the bioavailability and controlled delivery of drugs that show a narrow absorption window. These systems provide controlled release of the drug for a

prolonged period as well as present the drug in an absorbable form at the site of optimized absorption by prolonging the gastric emptying time of the dosage form. It is a real challenge for pharmaceutical scientists the field to formulate an optimized gastroretentive dosage form. In the future, it is expected that they will become the most efficient drug delivery systems that provide an improved efficient types of pharmacotherapies. A number of approaches are going to be discovered and developed for this purpose.

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