REVIEW ARTICLE

A Review Report on Important Approches of Floating Drug Delivery System

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Abstract

Floating drug delivery systems (FDDS) are controlled release drug delivery systems, which get retained in the stomach for longer periods, thus helping in absorption of drug for the intended duration of time. Gastricretentive drug delivery devices can be useful for the spatial and temporal delivery of many drugs. In general, drugs with narrow therapeutic window and prone to degradation in intestine and colon along with drugs having low retention time in gastrointestinal tract (GIT) are selected for FDDS which helps drugs to stay long time in stomach thus increasing gastric residence time and reduces dosing frequency. The present review article shows the various methods of FDDS for increasing retention time of drugs in GIT.

Key words: Dosing frequency, floating drug delivery systems, gastric residence time

INTRODUCTION

Controlled release (CR) may be defined as a technique or approach by which active chemicals are made available to a specified target at a rate and duration designed to accomplished an intended effect. More specifically an oral controlled drug delivery system is in principle a device or dosage form that controls drug release into the absorption site in the gastrointestinal tract (GIT). An oral control release should allow a reduction in dosing frequency as compared to that presented as a conventional dosage form. CR technology may provide increased clinical value as well as extended product life. The advantage of an ideal CR dosage form over an immediate release product includes improved patient compliance due to a reduced dosing frequency, a decreased incidence or intensity of the side effects, a greater selectivity of pharmacological activity and a more constant or prolonged therapeutic effect as well as an increase of cost effectiveness.[1,2]

Floating system having a specific density lower than that of gastric fluid can remain buoyant in the stomach content thereby prolonging the gastric residence time. The advantages of using this drug delivery system include reduced variability of drug release, local drug delivery and action, and enhanced bioavailability for those drugs with a restricted absorption window in the gastrointestinal tract.[2]

Introduction to gastricretention and gastoretentive drug delivery system

The literature reveals that pharmaceutical dosage forms exhibiting good *in vitro* floating behavior show prolonged gastric residence *in vivo*. The physical properties of the drug delivery system (e.g., density and size) as well as the presence of food in the stomach have been identified as the two most important parameters determining the *in vivo* performance of the dosage form. In the absence of food in stomach, the stomach is cleared of undigested material every 1½-2 h by domestic waves. To give good floating behavior in the stomach, the density of the device should be less than that of the gastric contents (≅1.004 g/cm^3). Nonetheless, it has to be pointed that great *in vitro* floating behavior property alone is not adequate verification for effective gastric maintenance *in vivo*. The effects of the simultaneous presence of food and of the complex motility of the stomach are difficult to estimate. Clearly, exclusively *in vivo* studies

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will give definite proof that prolonged gastric residence is obtained.[3-6]

Extended-release dosage forms with prolonged residence times in the stomach are highly desirable for drugs (i) that are locally active in the stomach, (ii) that have an absorption window in the stomach or in the upper small intestine, (iii) that are unstable in the intestinal or colonic environment, and/or (iv) have low solubility at high pH values. These delivery systems can be used as sustained release devices by prolonging the gastric residence time as well as by increasing total gastrointestinal transit time. Hence, improvement in patient compliance by reducing frequency of administration. Recent approaches to increase the gastric residence time of drug delivery systems include (i) bioadhesive devices, (ii) systems that rapidly increase in size on swallowing, and (iii) low-density devices that float on the gastric contents.[7-11]

Floating tablets containing a mixture of drug and hydrocolloids that remain in the stomach for an extended period have been described.[12,13]

Gastroretentive dosage form (GRDF)

These are fundamentally CR drug delivery systems, which gets sustained in the gastrointestinal tract mainly in the stomach for longer periods, thus serving help in absorption of drug for the intended duration of time. Gastricretentive drug delivery devices can be useful for the spatial and temporal delivery of many drugs. The gastric emptying time which lasts from a few minutes to 12 h mainly depends on the design of the dosage form and physiological condition of the patient. The average gastric emptying time in human is 2-3 h through major absorption zone (stomach and upper part of the intestine), which leads to incomplete drug release from the DDS leading to diminished efficacy of the administered dose. Hence, drugs which have stability problem, GRDF plays an important role. These considerations have led to the development of oral CR dosage forms possessing gastricretention capabilities.[14]

GRDF will also significantly improve the pharmacotherapy of the stomach itself through local drug release leads to high drug concentrations at the gastric mucosa, which is retained over a long period. Finally, GRDF will be used as carriers for drugs with so-called absorption windows: These substances are taken up only from very specific sites of the gastrointestinal mucosa, often in a proximal region of the small intestine. Need of gastroretention arises because of reason of improve the bioavailability of drugs such as cyclosporine, ciprofloxacin, ranitidine, metoprolol tartrate, and cefuroxime axetil which are mainly absorbed from the upper part of GIT or get degraded in alkaline PH.[15,16]

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Basic GIT

Anatomy[16-18]

Anatomically, the stomach is divided into three regions: Fundus, body, and antrum (pylorus). The distal part made of fundus and body acts as a reservoir for nondigested material, whereas the antrum is acted as a pump for gastric emptying by propelling actions and the major site for mixing motions. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however different in the main two states. During the fasting state, an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2-3 h. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following four phases.

1. Phase I (basal phase) occurs from 40 min to 1 h with rare contractions.
2. Phase II (preburst phase) occurs for 40 min to 1 h with sporadic action potential and contractions. As the phase progresses, the intensity and frequency also increase gradually.
3. Phase III (burst phase) occurs for 4-6 min. It includes intense and regular contractions for a short period. It is due to this wave that all the nondigested material is cleared out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4. Phase IV occurs for 0-5 min and occurs between Phases III and I of two consecutive cycles [Figure 1].

After the consumption of a mixed meal, the pattern of contractions changes from fasted to that of nonfasted or 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 <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. Scintigraphic studies determining gastric emptying rates revealed that orally administered CR dosage forms are subjected to basically two complications that of short

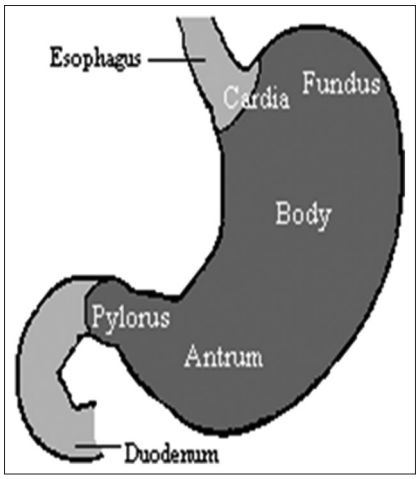

Figure 1: Stomach and its parts[16]

gastric residence time and unpredictable gastric emptying rate.

Physiology[19,20]

Various factors such as the absorption ability, presystemic clearance, gastric motility; gastrointestinal transit time, and gastrointestinal emptying time will have an influence on the bioavailability of drug from the dosage form.

Absorption ability

The absorption capability of various segments of GIT differs from each other. The highest extent of the absorption takes place in small intestine and lesser extent in colon and stomach. Unless drugs are absorbed equally in both the colon and in small intestine, the duration for most of the drugs is 3-8 h. This will be the major limiting factor for sustained release and CR drug delivery systems.

Presystemic clearance

Even if the drugs that can be absorbed equally well throughout the GIT, bioavailability is significantly reduced by the site-specific changes in presystemic clearance. Degradation of the drug is also carried out by hydrolysis in the stomach, enzymatic digestion, and metabolism in the brush border of the gut wall and by the microorganisms.

Such degradation may lead to high variation in plasma drug concentration and poor absorption of drug into the systemic circulation.

Gastric motility

Gastric emptying occurs during fasting as well as fed states. During the fasting state, an inter-digestive series of electrical events take place, which cycles through stomach and intestine every 2-3 h.[19,21]

Gastrointestinal transit time

Food content remains in each segment of the GIT for different periods of time. The resident time for both liquid and solid foods in each segment of the GIT is as reported by park [Table 1].[22]

Table 1: Transit time of food in each segment of the GIT

Segment	Liquid	Solid
Stomach	10-30 min	1-3 h
Duodenum	<60 s	<60 s
Jejunum and ileum	3±1.5 h	4±1.5 h
Colon	-	20-50 h

GIT: Gastrointestinal tract

Since most of the drugs are absorbed from the upper part of intestine, the total effective time for the drug absorption is 3-8 h. Hence, one has to take most of the drugs 3-6 times a day.

Factors affecting the gastric emptying time[23-25]

State of the stomach

Gastric emptying time depends on the fed state of the stomach, which increases the gastric emptying time as compared to unfed state.

Circadian rhythms

Which are increased in daytime and less during night, also affects the gastricretention time (GRT).

Size of the dosage form

High carbohydrate and fat content of the meal (high energy meal), longer the duration of emptying.

Density of the oral dosage form

The density of the gastric fluid is reported to be 1.2 g/cm^3. The density of the dosage form should be less than this for the buoyancy so that it is retained in the stomach for a longer period.

Diseased state

State of the stomach also affects the environment for the dosage form as in case of ulcers, flatulence and spasms.

Drug therapy

Plays an impotent role in gastric emptying, e.g., prokinetic drugs such as cisapride and mosapride increase the gastric emptying time.

Age

Increase in age decreases the gastric motility thereby increasing the gastric emptying time.

Posture

It was seen that the supine posture on the right side showed better results than on the left side.

Criteria for selection of drug candidate for GRD[26]

The gastricretentive drug delivery systems are suitable for following types of drug therapy.

Absorption from upper GIT

Drugs have a particular site for maximum absorption, e.g. ciprofloxacin, whose maximum absorption is in the

stomach only. The absorption of metformin hydrochloride is confirmed to small intestine only and the conventional sustained release dosage forms may be poorly bioavailable since absorption appears to diminish when the dosage form pass into large intestine.

Drugs having low P^{Ka}

Which remains unionized in stomach for better absorption.

Drugs having reduced solubility at higher P^{H}

For example, captopril and chlordiazepoxide and the bioavailability of drugs that get degraded in alkaline P^{H} can be increased by formulating GRDF. For example, doxifluridine that degrades in small intestine.

Local action

As it is seen in the treatment of *Helicobacter pylori* by amoxicillin and misoprostol for ulcers.

To reduce gastric irritation

Which may be caused by sudden increase of drug concentration in the stomach, e.g., nonsteroidal anti-inflammatory drugs s like ibuprofen.

Improve effectiveness of particular drugs

For example, antibiotics in the colon tend to disturb the microflora causing overgrowth of microorganisms like clostridium difficile causing colitis.

Gastoretentive drug delivery system[27]

As compared to other drug delivery system, oral drug delivery is the most convenient, easiest method of drug administration so it is the preferred method of administering therapeutic agents for their systemic effects. Oral medication is generally considered as the first avenue investigated in the development of pharmaceutical formulations because of patient acceptance, convenience in administration and cost-effective manufacturing processes. Oral route offers an attractive approach of drug targeting at the specific site within GI tract for certain types of drug.

Approaches to gastricretention

A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts. These include:

Floating systems[11]

Floating drug delivery systems (FDDS) have a bulk density low than gastric fluids and thus remain floating in the stomach for a prolonged period, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the optimal release of the drug, the remaining system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating systems can be mainly divided into two distinct categories, effervescent systems and non-effervescent systems.

Bio/muco-adhesive systems[28-30]

Bio/muco-adhesive systems are those which bind to the gastric epithelial surface or mucin and serve as a potential means of extending the GRT of drug delivery system (DDS) in the stomach.

The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDS based on bio/muco-adhesive polymers. The ability to provide adhesion of a drug (or a delivery system) to the GI wall provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect.

Binding of polymers to the mucin/epithelial surface of GI tract can be divided into three main categories:

- Hydration-mediated adhesion.
- Bonding-mediated adhesion.
- Receptor-mediated adhesion.

Swelling and expanding systems[31-34]

These are the dosage forms, which after swallowing; swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a longer. These systems may be named as "plug type system" since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state. Such polymeric matrices remain in the gastric cavity for few hours, even in the fed state of gastric cavity.

A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability and maintains its physical integrity for prolonged period.

High density systems[35]

These systems with a density of about 3 g/cm^3 are retained in the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm^3 acts as a threshold value after which systems can be maintained in the lower part of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert materials such as barium sulfate, zinc oxide, titanium dioxide, and iron powder.

Incorporation of passage delaying food agents[36]

Food excipients like fatty acids, e.g., salts of myristic acid change and modify the pattern of the stomach to a fed state,

thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in the gastric emptying after meals rich in fats is mainly caused by saturated fatty acids with chain length of C_{10}-C_{14}.

Ion exchange resins[37]

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Bicarbonate and a negatively charged drug are loaded in ion exchange resins. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. When it enter in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place, as a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads toward the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

Osmotic regulated systems[38]

It is comprised an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. On the quickly disintegration of the capsule in the stomach, it releases the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device composed of two main components, drug reservoir compartment and osmotically active compartment.

Types of fdds

Depending on the buoyancy mechanism, two distinctly different technologies have been utilized in the development of FDDS, which are:

- Effervescent system
- Noneffervescent system.

Effervescent system[39-40]

Effervescent systems include use of gas generating agents, carbonates (sodium bicarbonate), and other organic acids (citric acid and tartaric acid) to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it to float on the gastric fluid. These effervescent systems further classified into two types.

GAS GENERATING SYSTEMS

Intragastric single layer floating tablet or hydrodynamically balanced system

These are formulated by mixing the CO_2 generating agents and the drug with in the matrix tablet [Figure 2]. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. From the floating system, drug is slowly released at a desired rate and after the complete release the remaining system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

Intragastric bilayered floating tablets

These are compressed tablets and contain two layers for: (i) Immediate release layer and (ii) Sustained release layer [Figure 3].

Multiple unit type floating pills

These systems consist of sustained release pills as "seeds" surrounded by double layers. The effervescent agents present in inner layer 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 pill like balloon and float as the density decreases [Figures 4 and 5].

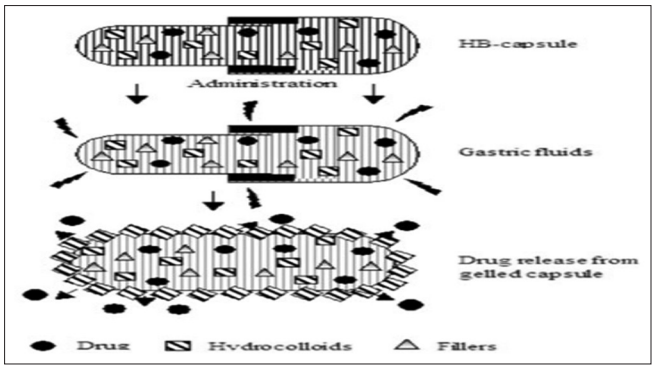

Figure 2: Hydrodynamically balanced system[39]

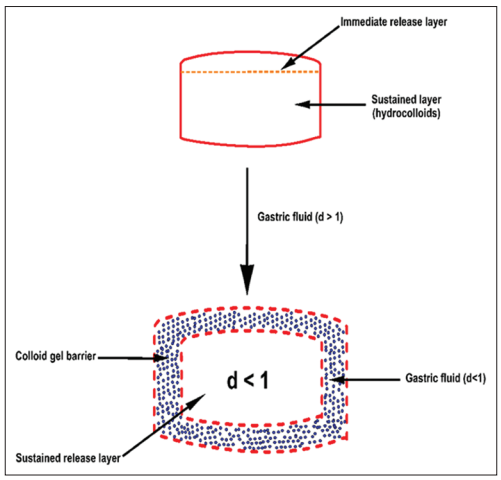

Figure 3: Intragastric bilayer floating tablet[22]

VOLATILE LIQUID/VACUUM CONTAINING SYSTEMS

Intragastric 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 microporus compartment [Figure 6].

Inflatable gastrointestinal delivery systems

In these systems, an inflatable chamber is incorporated, which contains liquid that gasifies at body temperature to cause the chamber to inflate in the stomach. Inflatable gastrointestinal delivery systems are manufactured by loading the inflatable chamber with a drug reservoir, which may be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chambers automatically swallow and maintain the drug reservoir compartment in floating position. The drug continuously released from the reservoir into the gastric fluid [Figure 7].

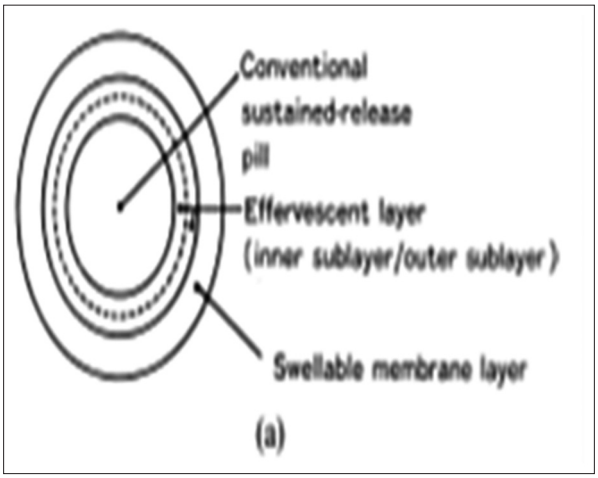

Figure 4: A multi-unit type oral floating dosage system[40]

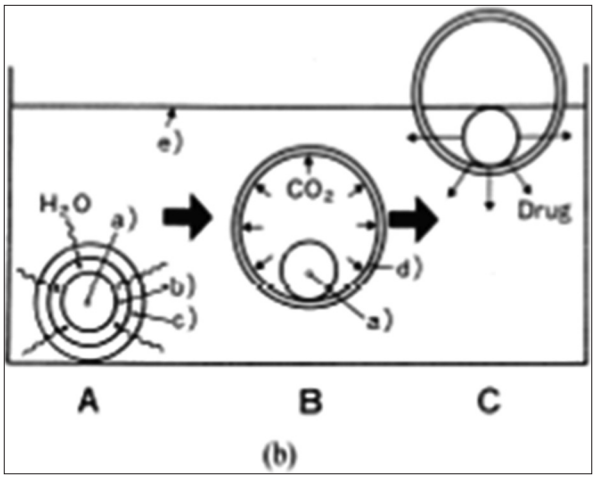

Figure 5: Stages of floating mechanisms[40]

Intragastric osmotically controlled drug delivery system

It is comprised an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The deformable hollow polymeric bag forms by inflatable support present inside that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment of these systems is enclosed by a pressure responsive collapsible bag and has a drug delivery orifice and which is impermeable to vapor and liquid. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and turns in forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release in solution form through the delivery orifice.

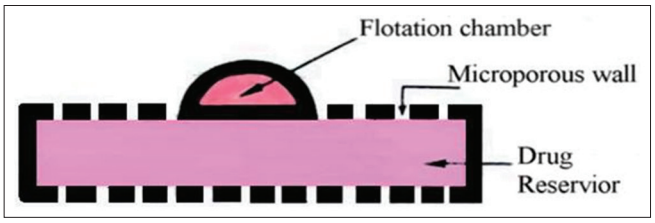

Figure 6: Intragastric floating gastrointestinal drug delivery device[39]

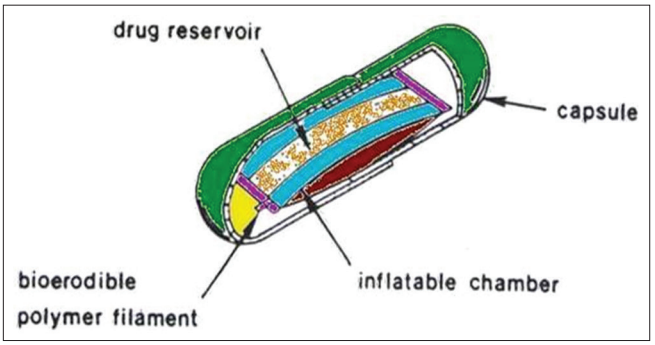

Figure 7: Inflatable gastrointestinal delivery system[22]

The floating support is also contains a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach [Figure 8].

Noneffervescent systems[39,40]

The noneffervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in noneffervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming materials such as polycarbonates, polyacrylates, polymethacrylates, and polystyrenes and bioadhesive polymer such as chitosan and carbopol.

The various types of these systems are.

Single layer floating tablets

They are formulated by intimate mixing of gel-forming hydrocolloid with the drug, which swells in contact with gastric fluid and keeping maintain bulk density of <1. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

Alginate beads

By using freeze-dried calcium alginate multi-unit floating dosage forms were developed. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 h. These alginate floating beads gave a prolonged residence time of more than 5.5 h.

Hollow microspheres

Multiple-unit hollow microspheres by emulsion solvent diffusion technique were prepared with drug and acrylic polymer.

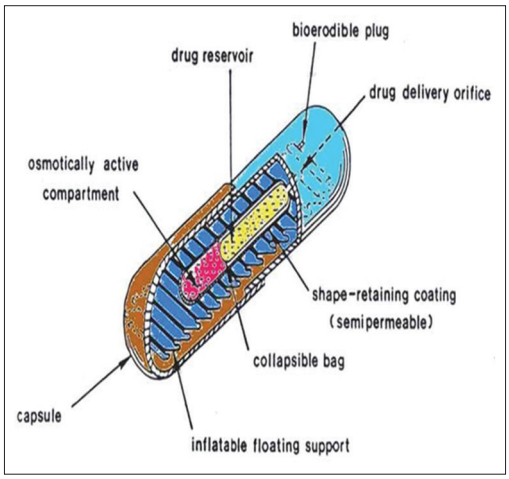

Figure 8: Intragastric osmotically controlled drug delivery system[40]

These were dissolved in an ethanol-dichloromethane mixture, and poured into an aqueous solution of polyvinyl alcohol with stirring to form emulsion droplets. The rate of drug release in micro balloons was controlled by changing the polymer to drug ratio. *In vitro* condition microballoons were floatable for 12 h when immersed in aqueous media. Radiographical studies proved that micro balloons orally administered to humans were dispersed in the upper part of stomach and retained there for 3 h against peristaltic movements.

Advantage of floating drug delivery system[11,20,41,37,42-44,45-51]

Improved bioavailability

The bioavailability of riboflavin CR-GRDF is significantly improved and 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 GIT, that act concomitantly to influence the magnitude of drug absorption.

Improved first-pass biotransformation

In a similar fashion to the enhanced efficacy of active transporters exhibiting capacity limited activity, the presystemic metabolism of the tested compound may be considerably enhanced when the drug is presented to the metabolic enzymes (cytochrome P450, in particular, CYP3A4) in a sustained manner, rather than by a bolus input.

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 related with enhanced patient compliance, and thereby improvement in therapy.

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. For example, antibiotic for *H. pylori* based ulcer, antacid.

Reduced fluctuations of drug concentration

Continuous input of the drug following CR-GRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are reduced and concentration-dependent adverse effects that are associated

with peak concentrations can be avoided. This feature is of special importance for drugs with a narrow therapeutic index.

Improved selectivity in receptor activation

Reduction in fluctuations in drug concentration also makes it possible to get certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at various different concentrations. 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.

Extended time over critical (effective) concentration

For certain drugs that have nonconcentration dependent pharmacodynamics, 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. It enables extension of the time over a critical concentration by the sustained mode of administration and thus enhances the pharmacological effects and improves the clinical outcomes.

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, unintended and undesirable activities of the drug in colon may be prevented. This pharmacodynamics 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.

Site specific drug delivery

A floating dosage form is a suitable approach for those 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 minimizes 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.

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