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Review Article

FLOATING DRUG DELIVERY SYSTEM- ANEW APPROACH IN GASTRIC RETENTION- A REVIEW

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ABSTRACT

The gastro retentive drug delivery system is a novel approach for the drugs having narrow absorption window in the gastrointestinal tract and has poor absorption. Gastro retentive drug delivery system mainly prolongs the gastric emptying time, thereby targeting site-specific drug release. Several approaches had been developed such as floating drug delivery system, low density system, raft system, mucoadhesive system, high density system, super porous hydro gel and magnetic system for effecient drug delivery. The physiological problems like short gastric residence time and unpredictable gastric emptying time were overcome with the use of floating dosage forms which provide opportunity for both local and systemic effect. Floating drug delivery system enable prolonged and continuous input of the drug to the upper part of the gastro retentional tract and improve the bioavailability of medication that is characterized by a narrow absorption window.

Keywords: Gastro retentive drug delivery system,Site specific drug release,Floating drug delivery system**,**

INTRODUCTION

In recent years there has been a growing interest in the development, design and evaluation of sustained or controlled release systems. The goal in designing sustained or controlled release systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at site of action, reducing the dose required, or providing uniform drug delivery. Many controlled release systems have been developed for maintaining a therapeutically effective concentration of drug in systemic circulation for longer period of time as well as to reduce side effects.

Sustained releases are dosage forms that provide medication over an extended period of time. Controlled release denotes that the system is able to provide some actual therapeutic contro.[1]

Controlled release (modified-release) dosage forms are growing in popularity. These more sophisticated systems can be used as a means of altering the pharmacokinetic behavior of drugs in order to provide twice or once a day dosage. This is achieved by obtaining a zero-order release from the dosage form. Zero-order release includes drug release from the dosage form that is independent of the amount of drug in the

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delivery system[1]. Other applications are enteric coating for the protection of drugs from degradation within the gastrointestinal tract or the protection of the stomach from the irritating effects of the drug, and the delivery of drugs to so called absorption windows or specific targets within the gastrointestinal tract, particularly the colon.[2]

Oral controlled drug release dosage forms should not be developed unless the recommended dosage interval for the controlled release dosage form is longer than that for immediate release dosage form or unless significant clinical advantages for the controlled release dosage form can be justified like the decreased side effects resulting from a lower C_{max} with the controlled release form as compared to the immediate release or conventional dosage form. In some cases, controlled release products may be therapeutically advantageous primarily for certain sub-population of patients.

Factors affecting the designing of drug delivery systems

Biological half life: Therapeutic compounds with short half life[3] are excellent candidates for sustained release preparations, since this can reduce dosing frequency. Drugs with half life shorter than 2 hours are poor candidate for sustained release preparations. Compound with long half life more than 8 hours are also not used in sustaining forms, since their effect is already sustained.

Absorption: The characteristics of absorption of a drug can greatly affect it's suitably as a sustained release product. Compounds that demonstrate true lower absorption rate constants will probably be poor candidates for sustaining systems.

If a drug is absorbed by active transport, sustained preparations may be disadvantageous to absorption.

One method to provide sustaining mechanisms of delivery for compounds such as these has been to try to maintain them with in the stomach. One such attempt is to formulate low density pellets, capsules or tablets. These float on top of gastric juice, delaying their transport out of stomach. Another attempt is that of bioadhesive materials. The principle is to administer a device with adhesive polymer having an affinity for the gastric surface, most probably with the mucin coat.

Metabolism: Drugs that are extensively metabolized before absorption either in the lumen or tissue of the intestine could cause decreased bioavailability from slow releasing dosage forms.

Rationale for Oral Controlled Drug Delivery Systems:

The oral route is one of the most promising ways of drug delivery. In order to deliver the drug through oral it has to depend upon several factors such as gastric emptying process, gastrointestinal transit time of dosage form and site of absorption of drugs.

The physiological limitations of the oral dosage form such as variable gastrointestinal transit, due to variable gastric emptying time[4]leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form within the stomach.

This may cause incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug

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passes down to the absorption site, the remaining quantity gets unabsorbed. The gastric emptying of dosage forms in humans is favored by several factors because of which wide inter- and intra-subject variations are observed. Since most of the drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability unpredictable. Hence a beneficial drug delivery system would be one which have the ability to prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site [3].

A significant obstacle, which may rise, is the narrow absorption window for drug absorption in the GIT, stability problem or the poor solubility of drug in the GIT fluids. GIT has versatile pH areas starting with strong acidic in stomach, less acid to slightly alkaline in intestine and alkaline in colon. The residence of dosage form in stomach determines the power of gastric movements during both the digestive and inter-digestive phase and it is usually up to 2 hours.

The small intestine transit is unaffected by food and is constant at 3 hours. The arrival of dosage form in colon is determined by the time of gastric emptying and not by the small intestinal transit time.

Though the dosage form remains in colon up to 35 ± 2 hours due to low fluid content, viscosity and presence of bacteria and enzymes, it provides unsatisfactory environment for drug delivery system.[2, 5]

Thus the main problem in the development of controlled release oral dosage form is not just to prolong the delivery of drugs for more than 12 hours but to prolong the residence time of dosage forms in the stomach or somewhere in the upper small intestine until all the drug is retained for the desired period of time.

CONTROLLED RELEASE THROUGH GASTRIC RETENTION:

During the previous decade, many studies have been performed concerning the sustained release dosage forms of drug, which have aimed at the prolongation of gastric emptying time (GET).The GET has been reported to be from 2 to 6 hours in humans in the fed state.[6] It is proved from the scientific and other patent literature that an increased interest in novel dosage forms that are retained in the stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. Gastric retention of drug delivery systems prolongs overall gastro intestinal transit time, thereby resulting in improved bioavailability. One of the most effective approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT). Dosage[7] forms with a prolonged GRT, i.e.gastroretentive dosage forms (GRDFs), will provide a new and effective therapeutic options.[3]

GRDFs extend the time over which the drugs may be released. Thus, they prolong dosing intervals and also increase the patient compliance beyond the level of existing controlled release dosage forms. This is found effective in delivery of sparingly soluble and insoluble drugs.[8] It is found that, as the solubility of a drug decreases, the time available for drug dissolution becomes less and thus the transit time becomes a

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significant factor affecting drug absorption.

Drugs that can be formulated into gastro retentive dosage forms include[9]:

- ❖ Drugs acting locally in the stomach.
- ❖ Drugs that are primarily absorbed in the stomach.
- ❖ Drugs that is poorly soluble at alkaline pH.
- ❖ Drugs with a narrow window of absorption.
- ❖ Drugs rapidly absorbed from the GI tract and
- ❖ Drugs that degrade in the colon

In the design and development of Hydro dynamically Balanced Systems (HBS), anatomical and physiological factors of the stomach plays an important role.

Factors Affecting Efficacy of GRDF'S[14]

Gastric residence time of an oral dosage form depends on several factors.

Particle size: To pass through the pyloric valve into the small intestine, the particle size should be in the range of 1 to 2 mm.[11]

Density: The density of a dosage form also affects the gastric emptying rate. A buoyant dosage form having a density of less than that of the gastric fluids floats. Since it is away from the pyloric sphincter, it can be retained in the stomach for a prolonged period.

Size: Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT when compared with those with a diameter of 9.9 mm

Shape of dosage form : Those with tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch are reported to have better GRT = 90% to100% retention at 24 hours compared with other shapes.

Fed or unfed state: Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the MMC that occurs every 1.5 to 2 hours. The MMC drags the 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.

Nature of meal: Feeding of indigestible polymers or fatty acids salts can change the motility pattern of the stomach, thus decreasing the gastric emptying rate and prolonging drug release.

Temperature of the meal: High or low temperature of the ingested fluid reduce the gastric emptying time.

Caloric content of meal: GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats content.

Frequency of feed: The GRT can be increased by over 400 minutes when successive meals are given compared with a single meal.

Gender: Mean ambulatory GRT in males (3.4 ± 0.6 hours) is less compared with their age and race matched female counter parts (4.6 ± 1.2 hours) regardless of the weight, height and body surface.

Age: Elderly people and those above 70, have a significantly longer GRT.

Posture: Gastric retention is affected by posture of the patient.

Concomitant drug administration: Drugs that are gastric emptying include poorly soluble antacids (aluminium hydroxide), anticholinergics (atropine, propantheline), narcotic analgesics (morphine) and tricyclic anti depressants (imipramine, amitriptyline).

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Metoclopramide, domperidone and cisapride (antiemetics) stimulate gastric emptying.

Biological factors: Diseases like gastroenteritis, gastric ulcer, pyloric stenosis, diabetes and hypothyroidism retard gastric emptying. Partial or total gastrectomy, duodenal ulcer and hypothyroidism promote gastric emptying rate .

Approaches to Increase Gastric Retention:

Various new approaches have been worked out to improve the retention of oral dosage form in the stomach.

A.Swelling and expanding systems: In this the dosage form can be retained in the stomach for a longer time by increasing the size so that it cannot be passed through the pylorus into the intestine[17]. The dosage form should attain this large size once it is in the stomach and should also be strong enough to be able to withstand the powerful waves in the stomach.

The swelling systems utilize swellable hydrocolloids as a means to achieve buoyancy[18] .These hydrocolloids swell unrestrained via imbibitions of gastric fluid to an extent that it prevents the exit from the stomach. These systems are called as "plug-type systems" since they have a tendency to remain lodged near the pyloric sphincter.

Expanding systems work on the principle that by the use of super porous hydrogels that expand dramatically when immersed in water, swell rapidly in the stomach, causing medication to move more slowly from stomach to intestine.

B.Bio/Mucoadhesive Systems:

The term bio/mucoadhesion[21] implies attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion.

Bioadhesive drug delivery systems (BDDS) are used to localize a delivery device in the lumen to enhance the drug absorption in a site specific manner[22]. This approach helps to increase gastric residence time of the dosage forms binding them to gastric mucosa or epithelial cell surfaces. Thus it shows that the anionic polymers have better binding capacity than neutral or cationic polymers.

The mechanism of bioadhesion is thought to be the formation of electrocution and hydrogen bonding at the mucus-polymer boundary[23]. The adhesion is favored by rapid hydration. These bio-adhesive systems do not seem to be a very feasible solution as this bond formation is prevented by the acidic environment and thick mucus present in the stomach.

Some of the excipients that are used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin, etc. Some investigators have tried out a synergistic approach between floating and bioadhesion systems.

C. Modified shaped systems: These dosage forms are larger than the pyloric opening and so they are retained in the stomach. There are some drawbacks associated with this approach which include permanent retention of rigid, large sized single unit forms can cause bowel obstruction, intestinal adhesion and gastroplasty.

D. Co-administration of gastric emptying delaying drugs: This involves co- administration of a drug to

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delay gastric emptying together with a therapeutic drug. This has not received the favor of clinicians and regulatory agencies because of the questionable benefit-to-risk ratio associated with these devices[24].

E.Altered density dosage forms: The density of the dosage forms influence GI transit time to a large extent compared to their diameter. GRT can be improved by altering the density i.e., low density floating systems and high density non-floating systems.

a) Low-density or floating drug delivery system: This approach is based on the principle that the dosage form or substance, which has a density less than the gastric fluid (≈1.004g/cm^3) floats on the gastric contents. They also float due to the gaseous phase formed inside the system after they come in contact with the gastric environment.[18] Floating systems release the drugs locally in the stomach and these are useful for poorly soluble or unstable drugs in intestinal pH. Various attempts have been made to develop floating systems, which will float in the gastric contents for a long time. These dosage forms are prepared by incorporating a high level of one or more gel forming hydrocolloids eg: hydroxy ethyl cellulose, hydroxy propyl cellulose, hydroxy propyl methyl cellulose and Sodium carboxy methyl cellulose into the formulation and then compressing these granules into a tablet or encapsulating into capsules.

For the formulation of this device it must comply with the following criteria:

- ❖ It should have a proper structure to form a cohesive gel barrier.
- ❖ It must maintain lower specific gravity than that of the gastric contents.
- ❖ It should dissolve slowly enough to serve as a drug reservoir.

On contact with gastric fluid the hydrocolloid in this intragastric floating device start to become hydrated and forms a colloid gel barrier around its surface with thickness growing with time. This gel barrier controls the rate penetration of solvent into the device. It maintains a bulk density of less than 1 and thus remains buoyant in the gastric fluid inside the stomach for up to 6 hour.

1) Intragastric Floating Drug Delivery System (IGFDDS): An IGFFDS can be made to float in the stomach by incorporating a floatation chamber, which may be a vacuum, filled with air or a harmless gas. This can be achieved by;

i) Inflatable Gastrointestinal Delivery System: The residence time of the drug delivery device in the stomach can also be sustained by incorporation of an inflatable chamber, which contains liquid (e.g., ether) that gasifies at body temp which results the chamber to inflate in the stomach.

ii) Intragastric Osmotically Controlled Drug Delivery System: It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device.

b) High Density or Non-floating Drug Delivery Systems: Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae near the pyloric region[19], which is the part of the stomach with the lowest position in an upright posture. Dense pellets (approximately 3g/cm^3) trapped in rugae also tend to

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withstand the peristaltic movements of the stomach wall. Thus with pellets, the GI transit time can be extended from an average of 5.8–25 hours which depends more on density than the diameter of the pellets. This is achieved by formulating of dosage forms with the density that must exceed density of normal stomach content (≈1.004g/cm).Depending on the mechanism of buoyancy, two different methods like non-effervescent and effervescent systems have been used in the development of floating drug delivery systems (FDDS)

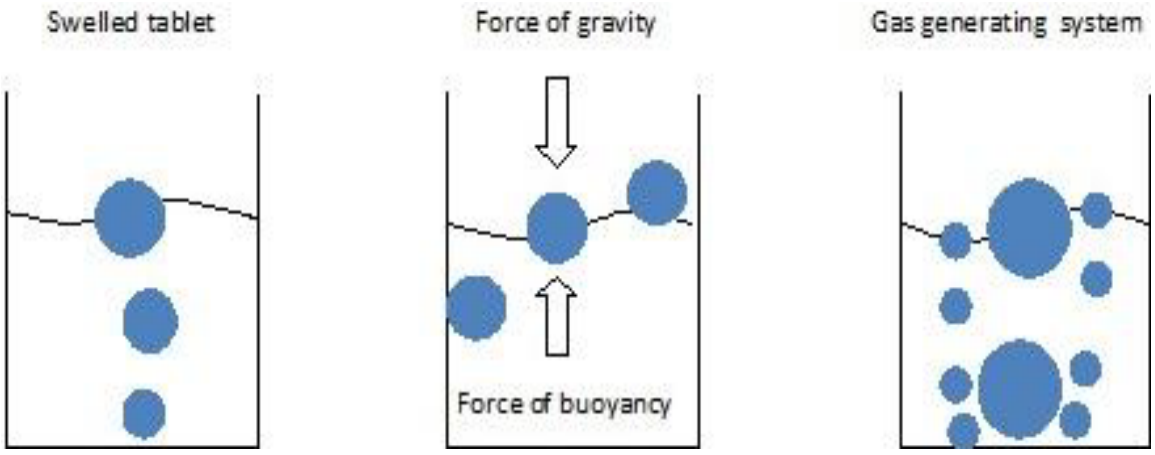

Fig:1 Different mechanisms of floating systems**.**

FLOATING DRUG DELIVERY SYSTEM

Based on the mechanisim of floating,the floating drug delivery system are of 2 type:

Non- effervescent and effervescent drug delivery system.

NON-EFFERVESCENT FDDS

The main excipients in this type of drug delivery system are gel forming or highly swellable[20] cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonates, polyacrylates, etc. In other approach, gel forming hydrocolloid swells when it comes in contact with gastric fluid after oral administration and also maintains a relative integrity of shape and the bulk density of less than unity within gastric environment[21]

a. Colloidal gel barrier systems

In this hydrodynamically balanced system[11] (HBS), contains drugs with gel forming swellable hydrocolloids. These systems incorporate a high level (20-75%w/w) of one or more gel forming, highly swellable, cellulose type hydro-colloids, polysaccharides and matrix forming polymers. On coming in contact with an aqueous medium, imbibes water and starts to hydrate, thereby forming a gel at the surface. The drug in the dosage form dissolves and diffuses out into the diffusing solvent forming a receding boundary within the gel structure.

b. Microporous compartment systems:

This system is based on the encapsulation of a drug reservoir inside a micro porous compartment with

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apertures along its top and bottom walls. The peripheral walls of the drug reservoir compartment are protected to prevent any direct contact of the gastric mucosal surface with the undissloved drug.

After engulfing the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents.Intragastric floating and SR granules of cellulose and calcium silicate as floating carriers, which had a characteristically porous structure with numerous pores and a large individual pore volume

c. Alginate beads:

Multiunit floating dosage forms have been developed from freeze dried calcium alginate. Spherical beads of approximate 2.5 mm in diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium chloride. After the interval gelation was complete, beads were separated from the solution and snap-frozen in liquid nitrogen before being freeze dried at -40ºC for 24 hours.

The results suggested that these beads maintained a positive floating force for over 12 hours. Floating systems comprising of a calcium alginate core separated by an air compartment from a membrane of calcium alginate or calcium alginate/polyvinyl alcohol (PVA) have also been developed.Jain NK et al have studied the formulation and performance evaluation of hydrodynamically balanced capsules of diazepam for oral controlled release and studied the buoyancy characteristics of capsules in the stomach. Capsules remained buoyant in simulated gastric fluid and the integrity of the matrix was maintained *in vitro* for more than 12hours. All the methods can be used to increase gastric residence time of the drugs. All of them have some drawbacks and most of them show reliable retention for only a few hours.

EFFERVESCENT FDDS

These buoyant drug delivery systems utilize matrices prepared with swellable polymers such as Methocel or polysaccharides, e.g., chitosan[25] and effervescent components, e.g., sodium bicarbonate and citric acid and tartaric acid[20]. These matrices are formulated in a way that upon arrival in the stomach, CO_2 is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid, which causes an upward movement of the dosage form and maintains its buoyancy. MD. Selim Reza[26] worked on theophylline loaded gastroretentive floating tablets based on hydrophilic polymers: preparation and *in vitro* evaluation in which the effervescent method was effective with methocel.

It was found that the addition of carbonates to the dosage form not only imparts buoyancy to these forms but they also provide the initial alkaline micro environment for polymers to gel.

Effervescent system was classified into

i. Volatile liquid containing systems: These have an inflatable chamber which contains a volatile liquid e.g. ether, cyclopentane, that evaporates at body temperature to cause the inflation of the chamber in the stomach. These systems are osmotically controlled floating systems containing a hollow deformable unit. There are two chambers in the system first contains the drug and the second chamber contains the volatile liquid.

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ii. Gas generating systems: These buoyant delivery systems utilize effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the jellified hydrocolloid layer of the system, thus decreasing its specific gravity and making it float over chime

RAFT FORMING SYSTEMS

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The basic mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. The raft floats because of the buoyancy created by the formation of CO2 and act as a barrier to prevent the reflux of gastric Contents like HCl and enzymes into the esophagus. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbo-nates responsible for the formation of to make the system less dense and float on the gastric fluids.

Effect of Sodium Bicarbonate on drug release:

The use of gas generating agents in floating formulations has been tried. The gas generating component interacts with an acid source influenced by contact with water or simply with gastric fluid to generate carbon dioxide that gets entrapped within the hydrated gel matrix of the swelling composition. The gas generating agents such as carbonates and bicarbonates may be present in amounts from about 5% to about 50%, preferably from about 10% to about 30%, by weight of the composition. These salts may be used alone or in combination with an acid source as a couple. The acid source may be citric acid,sodium bi carbonate and tartaricacid[27].

Increasing the concentration of sodium bicarbonate decreases the floating lag time because of the faster and higher CO_2 generation. At higher concentration of effervescent agents the coating of the tablets becomes less stable due to increase in the internal pressure and thereby rupturing the polymer coating. This causes the sudden increase in the drug release.

Shrad N.Shinde[28] reported that the increase in sodium bicarbonate produces change in Salbutamol Sulphate release rate, this is due to alteration in the microenvironment pH within the gel network, affecting the dissolution rate of drug.

For the floating system, the ideal dosage form should be coated. The ideal coating material should be highly impermeable for the dissolution medium in order to initiate CO_2 formation and should be highly permeable for generated CO_2 in the wet state to promote floating.

Chander Shekar B[29] investigated for the preparation and evaluation of gastro retentive floating tablets of ketoconazole to found the effect of effervescenting agent on the combination of polymers.

In present study, in acidic media the sodium bicarbonate reacts to generate carbon dioxide. This might have contributed to the faster drug release in acidic media.

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Effect of Hydroxy propyl methyl cellulose

Hydroxy propyl methylcellulose(HPMC)[30] is the first choice for formulation of hydrophilic matrix system, providing robust mechanism, choice of viscosity grades, nonionic nature, consistent reproducible release profiles, cost effectiveness and utilization of existing conventional equipment and methods .Water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion from dosage form is controlled by the hydration of HPMC, which forms the gel barrier through which the drug diffuses.

Direct compression was used to compress the tablets, as keeping in mind that HPMC is a hydrophillic polymer that swells to a significant extent upon contact with water.

Technological Developments in Floating Drug Delivery Systems (FDDS)

Floating drug delivery system or hydrodynamically balanced system (HBS) is a formulation of drug in gel forming hydrocolloid meant to remain buoyant on stomach contents. This not only prolongs GI residence time but also does so in an area of the GIT that would maximize drug reaching its absorption site.

In the formulation of the FDDS, polymers play an important role. They not only hold the formulation ingredients together but also give a floating property and sustained release. The most commonly used polymers are HPMC and sodium alginate. HPMC comes in various grades like Methocel K4M, Methocel K50M, Methocel K100M, Methocel E4, Methocel E50, Methocel E100 etc[30] which have their own characteristics based on their molecular weight. These excipients absorb a significant amount of water (more than 20% of their dry weight) while maintaining a distinct 3-dimensional structure. As a result, they conform to the definition of hydrogels. When a dosage form is immersed in a specific medium, hydration occurs, which leads to gel formation.

The process of erosion causes the de-aggregation and the creation of new gel layers, affecting both the volume and the weight of the dosage form. This in turn causes the controlled drug release.

It has been observed that only hydrophilic polymers are not sufficient for floating characteristics and better results are possible with use of some soluble or gas-evolving excipients[31], the release rate was indirectly proportional to viscosity and concentration of the polymer used[28].

Sodium alginate gel system has been evaluated for sustained release oral delivery system with a potential for prolonged gastric residence. The gelatin and the cross linking of alginate molecules are due to stacking of the glucuronate blocks in the alginate chains, with the formation of the “egg-box junction upon adding chelating divalent cations such as Ca^{++}.

A novel floating system based on the ion exchange resins has been investigated. The method relies on the ion exchange resins loaded with bicarbonate, which on contact with media containing hydrochloric acid, release carbon dioxide causing the resin to float. This has been achieved in using theophylline as a model drug[4].

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A recent patent issued to Searl & Co[32] described a bilayer buoyant dosage form consisting of capsule, which includes a non-compressed bilayer formulation. One layer was a drug release layer containing Misoprostal and the other was a floating layer. Each layer includes a hydrocollid gelling agent such as HPMC, gums, polysaccharides and gelatin, which upon contact with gastric fluid formed a gelatinous mass sufficient for cohesive binding of the drug release layer and floating layer.

Dennis et al[33] described a buoyant controlled release powder formulation, which may be either filled in the capsules or compressed into tablets. The formulation consisted of a drug of basic character. pH dependent polymer, which was a water soluble salt of alginic acid, and a pH dependent hydrocolloid gelling agent and binder.

Advantages[34]

1. The HBS can be used to deliver any medicament or class of medicament.
2. The HBS formulations are not only restricted to medicaments that are principally absorbed from the stomach but also for medicaments that are absorbed from the intestine e.g. Chlorpheniramine maleate.
3. The HBS are advantageous for drugs that are absorbed through the stomach and for drugs meant for local action in the stomach.
4. The efficacy of the medicaments that are utilizing the sustained mechanism has been found to be independent of the site of absorption.
5. Prolonged release floating dosage forms of tablet may results in dissolution of the drug in gastric fluid, so that the dissolved drug gets fully absorbed after food is emptied from the stomach.
6. It may be advantageous to keep the drug in floating condition in stomach to get a relatively better response during vigorous peristalsis and diarrheal condition.
7. Gastric retention helps in the delivery of drugs which having narrow absorption windows in the small intestinal region.
8. Once-a-day dosage forms will have a suboptimal absorption due to dependence on the transit time of the dosage form, so a system designed for longer gastric retention will prolong the time of dosage form to increase the absorption.
9. Classified drugs are having benefit from using gastro retentive devices.

Disadvantages

1. There are certain conditions where gastric retention is not desirable.Eg: Aspirin and non-steroidal anti-inflammatory drugs.
2. The drugs that may cause irritation in the stomach lining or that are unstable in its acidic environment cannot be formulated in gastro retentive systems.
3. The drugs that are absorbed

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equally throughout the GI tract will not benefit from incorporation into a gastric retention system.

Limitations of FDDS[35]:

- The major limitation of floating system is the requirement of sufficient high level fluids in the stomach for the drug delivery to float. But this limitation can be overcome by coating the tablet with bioadhesive polymers that easily adhere to the mucosal lining of the stomach.
- The retension time in the stomach depends upon the digestive state. Hence, FDDS should be administered after the meal.
- The ability to float depends on the hydration state of the dosage form. In order to keep these tablets floating *in vivo*, intermittent administration of water (a tumbler full, every 2 hours) is beneficial.
- The retentions of in the stomach depend upon the subject being positioned upright.
- FDDS are not suitable for the drugs that have solubility and stability problems in the gastric fluid.
- Drugs like nifedipine, which undergoes significant first pass metabolism, is not a desirable candidates for FDDS since the slow gastric emptying may lead to the reduced systemic bio-availability

Applications of floating Drug Delivery Systems[36]:

1. Sustained Drug Delivery: HBS system can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. These systems have bulk density of <1, as a result of which they can float on the gastric contents.

Recently sustained release floating capsules of nicardipine were developed and evaluated *in vivo* and the formulation was compared with commercially available MICARD capsules using rabbits. Plasma drug concentration time profile showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD cap (8 hours)

2. Site specific drug delivery: These systems are particularly advantages for drugs that are specifically absorbed from stomach or the proximal part of the small intestine e.g. riboflavin furosemide and misoprostal.

3. Absorption Enhancement: Drugs that have poor bioavailability due to its site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

4. Maintenance of Constant Blood Level:

These systems provide an easy way of maintaining constant blood level with an ease of administration and better patient compliance.

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CONCLUSION

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. It seems that to formulate an efficient FDDS is sort of a challenge and the work will go on and on until an ideal approach with industrial applicability and feasibili-ty arrives.

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