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A REVIEW ON CONTROLLED RELEASE FLOATING DRUG DELIVERY SYSTEMS IN PHARMACEUTICAL FORMULATIONS

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ABSTRACT

Over the years there has been available a variety of drug modification and dosage forms, with which we have attempted to control the time course and specificity of drugs in the body maximize drug utilization, it is necessary to deliver the drug to its target tissue in the correct amount at the proper time to elicit the desired response. The most convenient method of controlled delivery of drug is undoubtedly oral, but oral controlled release of the drug for an extended period of time that exhibits more absorption in stomach and upper small intestine, has not been successful with conventional approaches. Consequently, most research efforts have been focused on platforms to extend gastric residence time (GRT) of these drugs. The novel design of Oral Controlled Drug Delivery System (OCDDS) should be primarily aimed at achieving a more predictable and increased bioavailability of drugs. However, the development process is precluded by several physiological difficulties, such as inability to restrain and localize controlled drug delivery systems (CDDS) within the desired regions of the gastrointestinal (GI) tract and highly variable nature of the gastric emptying process. Thus, conventional OCDDS has not been suitable for a variety of important drugs which has any of above mentioned characteristics, which is mainly due to the relatively short transit time of the dosage form in the stomach and upper part of small intestine. The overall results are accompanied by lesser bioavailability. Furthermore, the relatively brief gastric emptying time in humans, which normally range from 2 - 3 hours through the major absorption zone (stomach or upper part of intestine), can result in incomplete drug release from the dosage form leading to diminished efficacy of the administered dose. Thus, control of placement of drug delivery system in a specific region of the GI tract offers numerous advantages. From the formulation and technological point of view, the Floating Drug Delivery System (FDDS) is considerably an easy and logical approach in the development of gastro retentive dosage forms. Hence in the present study, the formulation of Gastro Retentive Dosage Forms (GRDFs) is done by FDDS.

KEYWORDS: Floating Drug Delivery System (FDDS), Controlled Drug Delivery Systems (CDDS), Gastro Retentive Dosage Forms (GRDFs) and Gastrointestinal (GI) tract.

INTRODUCTION

Great strides have been made in the management of disease through the intervention of drugs over the past 50 years, clearly, unless a drug can be delivered to its target area at a rate and concentration that both minimize side effects and maximizes the therapeutic effects, the drug will not be maximally beneficial to the patient and the extreme, an otherwise useful drug may be discarded. Over the years there has been available a variety of drug modification and dosage forms, with which we have attempted to control the time course and specificity of drugs in the body maximize drug utilization, it is necessary to deliver the drug to its target tissue in the correct amount at the proper time to elicit the desired response. Moreover, drug delivery must be continued at a rate such that the condition in question is cured or controlled in a minimum time with the fewest side effects.[1]

The most convenient method of controlled delivery of drug is undoubtedly oral, but oral controlled release of the drug for an extended period of time that exhibits more absorption in stomach and upper small intestine, has not been successful with conventional approaches. Consequently, most research efforts have been focused on platforms to extend gastric residence time (GRT) of these drugs. The underlying principle of gastric retentive system is to prolong the release of the drug in the stomach.[2]

Oral Controlled Drug Delivery System (OCDDS): The novel design of OCDDS should be primarily aimed at achieving a more predictable and increased

bioavailability of drugs. However, the development process is precluded by several physiological difficulties, such as inability to restrain and localize controlled drug delivery systems (CDDS) within the desired regions of the gastrointestinal (GI) tract and highly variable nature of the gastric emptying process.[3,4]

Oral controlled release dosage forms have been developed for the past 3 - decades due to their various advantages[5], which includes:

- Therapeutic advantages
- Reduction in adverse side effects
- Improvement in tolerability
- Patient comfort and compliance
- Reduction in healthcare cost

Despite the several advantages associated with oral controlled drug delivery systems, there are so many disadvantages[6], which include:

- The basic assumption that the drug should be absorbed throughout GI tract
- Limited gastric residence time which ranges from few minutes to 12 hours which lead to unpredictable bioavailability and time to achieve maximum plasma level
- Inter-subject variability
- Not applicable to drug which has any of the following characteristics[7,8]

- Narrow absorption window in GI tract, eg; Riboflavin, Levodopa.
- Primarily absorbed from stomach and upper part of GI tract, eg; Calcium supplements, Chlordiazepoxide, Cinnarizine.
- Act locally in stomach, eg; Antacids, Misoprostol.
- Drugs that degrade in colon, eg; Ranitidine Hydrochloride, Metronidazole.
- Drugs that disturb normal colonic bacteria, eg; Amoxicillin trihydrate.

Thus, conventional OCDDS has not been suitable for a variety of important drugs which has any of above mentioned characteristics, which is mainly due to the relatively short transit time of the dosage form in the stomach and upper part of small intestine. The overall results are accompanied by lesser bioavailability. Furthermore, the relatively brief gastric emptying time in humans, which normally range from 2 - 3 hours through the major absorption zone (stomach or upper part of intestine), can result in incomplete drug release from the dosage form leading to diminished efficacy of the administered dose. Thus, control of placement of drug delivery system in a specific region of the GI tract offers numerous advantages as described above.[8] It was also suggested that compounding a narrow absorption window drug in a unique pharmaceutical dosage form with prolonged gastric residence time would enable an extended absorption phase of the drug. It is reasonable to expect that unless a delivery system remains in the absorption site till its entire drug released.[9]

Gastro Retentive Dosage Form: It is evident from the recent scientific and patent literatures that an interest exists today in academic and industrial research group in developing novel dosage forms are retained in stomach for a prolonged and predictable period of time. [10, 11] One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT), i.e. Gastro Retentive Dosage Forms (GRDFs), will provide us with new and important therapeutic options. These efforts results in GRDFs that were designed based on the following approaches:

1. Low-density dosage forms that remains buoyant above gastric fluid (Floating Drug Delivery System).[4,12]

- High - density dosage form that is retained at the bottom of the stomach.[13]
- Muccoadhesive drug delivery systems.[14]
- Slowed motility of the GI tract by concomitant administration of drugs or pharmaceutical excipients.[15]
- Expansion by swelling or unfolding to a large size which limits emptying of the dosage forms through the pyloric sphincture.[16]
- Use of ion-exchange resins, which adhere to mucosa.
- Modified shape systems.

2. Gastro retentive dosage forms overcome the limitations of conventional oral controlled drug delivery system by[17]

- Prolonging the gastric residence time by retaining the dosage form in stomach and upper part of GI tract.
- Protecting the drug to degrade in colon and the degradation of normal GI flora by restricting the dosage form in stomach and upper part of GI tract.
- Giving sufficient time for the drug to be absorbed through GI tract.

From the formulation and technological point of view, the Floating Drug Delivery System (FDDS) is considerably an easy and logical approach in the development of gastro retentive dosage forms. Hence in the present study, the formulation of GRDFs is done by FDDS. Unfortunately, few, if any, of the CRDDS are deliberately designed to outlive the GI transit time so that obtaining a period of drug release beyond 12 hours in the general population is an exception rather than the rule. It is imperative that the next level of the sophistication in the design of oral sustained controlled delivery systems aim at prolonging the GI transit time of a given system.

Floating Drug Delivery System (FDDS): To comprehend the consideration taken in the design of the GRDFs and to evaluate their performance the relevant anatomy and physiology of the GI tract must be fully understood.

Stomach: An Overview

The stomach is a j - shaped organ located in the upper left hand portion of the abdomen just below the diaphragm. It occupies a portion of the epigastric and left hydrochondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Due to its small surface area very little absorption takes place from the stomach. It acts as a barrier to the delivery of drugs to the small intestine.[18,19]

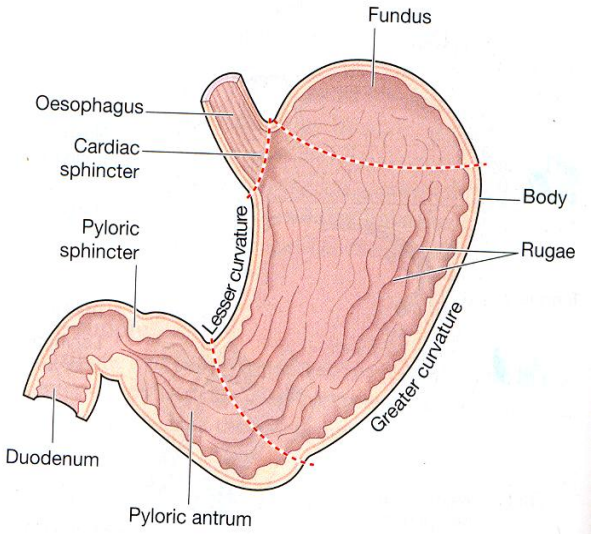

Figure 1: Anatomy of stomach.

Structure of Stomach: The stomach has 4 main regions[18,19]

1. Cardia
2. Fundus
3. Body and 4. Pylorus

The main function of the fundus and body is storage, whereas that of cardiac is mixing or grinding. The fundus adjusts the increased volume during eating by relaxation of the fundus muscle fibers. The fundus also exerts a steady pressure on the gastric contents pressing them towards the distal region. To pass through the pyloric sphincter into the small intestine, particle size should be of order of 1 - 2 mm.

Histology of Stomach[18,19]

The stomach wall is composed of the 4 - basic layers. Simple columnar epithelial cells line the entire mucosal surface of the stomach. Epithelial cells extend down into the lamina propria, where they form columns of secretary cells called gastric glands. The gastric glands contain 3 - types of exocrine gland cells (Figure 1) that secrete their products into the stomach lumen.

1. Mucous neck cells
2. Chief cells
3. Parietal cells

The chief cells secrete pepsinogen and gastric lipase. Parietal cells produce hydrochloric acid (Hcl) and intrinsic factor. Both mucosal surface cells and mucous neck cells secrete mucus and bicarbonate. They protect the stomach from adverse effects of Hcl as mucosa has a lubricating effect. It allows chyme to move freely through the digestive system.

Function of Stomach[18,19]

The stomach carries out 3 - major functions. It stores food, digests food and delivers food to the small intestine at a rate that the small intestine can handle and it mixes saliva food and gastric juice to form chyme.

1. It acts as a reservoir for holding food before it is to be released into the small intestine.
2. It secretes gastric juice, which contains hydrochloric acid, pepsin, intrinsic factor and gastric lipase.
3. It secretes gastric into the blood.

Regulation of Gastric Secretion and Motility[18,19]

Both neural and hormonal mechanism controls the secretion of gastric juice and the contraction of smooth muscle in the stomach wall. Events in gastric secretion occur in 3 - overlapping phases such as cephalic phase, gastric phase and intestinal phase.

Gastric Emptying: The process of gastric emptying occurs both during fasting and fed states, however, the pattern of motility differ markedly in the 2 - states. In the fasted state, it is characterized by and interdigestive myoelectric cycle or migrating myoelectric complex (MMC).[20,21] It is compose of 4 – phases;

Phase I - lasts for 45 - 60 minute, is quiescent, with rare low amplitude contractions.

Phase II - with a length of 30 - 40 minutes has intermediate amplitude contractions and involves in the bile secretion.

Phase III - is also termed as 'housekeeper waves' and extends for 5 - 15 minutes. It is initiated in the stomach in most cases or in the duodenum, has very high amplitude contractions, with a frequency of 4 - 5/min and maximal pyloric opening, characterizing this phase, which enables efficient evacuation of the stomach contents.

Phase IV - has a length of less than 5 minutes and connects between the maximal amplitude contractions to the basal phase. In the fed state, the gastric emptying rate is slowed since the onset of MMC is delayed. In other words, feeding results in a lag time prior to the onset of gastric emptying.

Factors Controlling Gastric Retention Time of Dosage Form: The gastric retention time (GRT) of dosage forms is controlled by several factors, such as density of the dosage form, size of the dosage form, food intake, nature of the food, posture of the host, age, sex, sleep and disease state of the individual (Eg; gastrointestinal diseases and diabetes) and administration of drugs such as prokinetic agents.

Density of Dosage Form[22,23]

Dosage forms having density lower than that of the gastric fluids experience the floating behavior and hence the gastric retention. A density of <1.0 g/cm3 is required to exhibit the floating property. However, the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium. The density of the dosage form is found to influence the GRT. Generally, the denser systems settle to bottom of the stomach at a faster rate than the less dense systems, experiencing a faster gastric emptying. A highly significant difference was observed in the time for 50 % of pellets to empty from the stomach, and 2.8 g/cm3 pellets showed an extended residence time in both fed and fasted state.

On the other hand, some studies showed that the gastric emptying is independent of the density of the dosage form.[23] The subjects were scanned supine for 30 min and then allowed to ambulate for 30 min and this may be the reason that the specific gravity of the dosage forms did not show a significant effect on the GRT.

Size of the Dosage Form[22,24]

The size of the dosage form is another factor influencing gastric retention. The mean gastric residence times of the non-floating dosage forms are highly variable and greatly dependent on their sizes, which are small, medium and large units.[4] In fed conditions, the smaller units get emptied from the stomach during the digestive phase and the larger units during the housekeeping waves. In most cases, the larger the size of the dosage form, the greater will be the gastric retention time because the larger size would not allow the dosage form to quickly pass through the pyloric antrum into the intestine. Thus the size of the dosage form appears to be an important factor affecting the gastric retention. However, apart from size, the position of the floating forms far away from the pyloric sphincter prevents early and erratic emptying. The mean resting pyloric diameter in humans is 12.8 ± 7.0 mm. Hence, it is important that the gastric retention dosage forms should dissolve or erode after drug release to the size that allows the elimination of the delivery system without leading to gastric obstruction.

Nature of Food[22,24]

Food intake, the nature of the food, caloric content and frequency of feeding has profound effect on the gastric retention of the dosage form. The presence or absence of food in the stomach influences the GRT of the dosage form. Usually the presence of food increases the GRT of the dosage form and increases drug absorption by allowing it to stay at the absorption site for a longer time. However, some studies reported that food does not influence drug absorption from the dosage forms. The GRT of the both non-floating and floating single units is shorter in fasted individuals and is prolonged after a meal. However, meal size did not affect the GRT of the beads. At the end of digestion, when the floating forms reach the lower part of the stomach, the size of the dosage form may influence its gastric retention. As a result, the smaller units may experience shorter residence time and the medium and larger units a comparatively longer residence time. Meal emptying rates and the time interval between administrations of meal also influence the gastric emptying time of the dosage form. In comparison to lighter meal, the heavier meal slowed the rate of gastric emptying and prolonged the small intestinal transit time. Moreover, its high packing velocity plus its high packing factor means that intervoid space is relatively low.[25]

Effect of Gender, Posture and Age[26]

The females showed comparatively shorter mean ambulatory GRT than that of the males and the gastric emptying in women is slower than in men. The authors also studied the effect of posture on GRT, are found no significant difference in the mean GRT for individuals in upright, ambulatory and supine state. The floating and non-floating systems behaved differently. In the upright position, the floating systems floated to the top of the gastric contents and remained for longer time, showing prolonged GRT. But, the non-floating systems showed an opposite trend and sank rapidly into the gastric contents. In the upright position, the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of the peristaltic contractions, and the floating units remain away from the pylorus. However, in supine position, the floating units are emptied faster than the non-floating units of similar size. Apart from the upright position, the posture of the individual in the ambulatory state may have different effects on the gastric emptying of the dosage form. When the individual rests on the left side, the floating of the dosage form will be towards the pyloric antrum; when the individual rests on the right side, the floating of the dosage form will be in the opposite direction. Faster gastric emptying was observed in the individuals resting on their left side, because the raft floats towards the pyloric antrum, making it subject to faster emptying. Because of the changes in physiology with increasing age and the hormonal responses responsible for gastric emptying, the GRT of the dosage forms may vary with the age of the individual.

Floating Drug Delivery System (FDDS): Development Approaches

These systems are also called as Hydrodynamically Balances Systems (HBS). It is an oral dosage form designed to prolong the residence time of the dosage form within the gastrointestinal track. To provide good floating behavior in the stomach, the density of the FDDS should be less than that of gastric content (< 1.0049 g/cm3). The various types of buoyant preparations include hollow microspheres, microparticles, granules, powders, capsules, tablets, cylinders and laminated films. Based on the mechanism

of buoyancy, 2 - distinctly different technologies have been utilized in development of FDDS, which are effervescent systems and non-effervescent systems.[22,27]

Effervescent System[27,28]

Effervescent system includes the use of gas generating agents, carbonates or any other organic acids (eg; citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, are usually incorporate in the dosage form, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature. The most commonly used excipients utilized in the development of effervescent FDDS are swellable polymer such as Hydroxy Propyl Methyl Cellulose (HPMC), Poly Saccharides, eg; Chitosan, Sodium Alginate. The matrices are so prepared that upon arrival in the stomach CO_2 is liberated by the acidity of the gastric contents and is trapped in the jellified hydrocolloid, which create an upward motion of the dosage form and maintains its buoyancy. The CO_2 gas generating agents may be intimately mixed within the tablet matrix containing hydrophilic swellable polymer like HPMC alone or in combination, in which case a single layer tablet.[28]

For Example; Sustained release floating granules containing Tetracycline hydrochloride was reported. The granules are a mixture of a drug granulates of two stages A and B, A containing 60 parts of Hydroxypropyl methylcellulose, 40 parts of polyacrylic acid and 20 parts of drug and B containing 70 parts of sodium bicarbonate and 30 parts of tartaric acid. Sixty parts of weight of granules of stage A and 30 parts by weight of stage B were mixed along with lubricant and filled into the capsule. In the dissolution profile, the capsule shell dissolved and liberates the granules, which showed a floating time of more than 8 hours and sustained drug release of 80 % in about 6.5 hours.

Floating or pulsatile drug delivery system based on effervescent core by using HPMC with an effervescent component along with drug. The effervescent component contained sodium bicarbonate and citric acid in the ratio of 1:0.7 in a concentration range of 30-50% w/w of the core. The PEG 4000 in the range of 4 % w/w and lactose or microcrystalline cellulose was added as filler. When the system comes in contact with aqueous medium, the generated CO2 interacted with in the polymeric matrix, which enabled the dosage form to float.

Baumgartner et al., performed optimization studies of floating matrix tablets containing a high dose of freely soluble drug. Pentoxifylline was used as a model drug in the study. Several formulations were prepared and characterized for crushing force, floating properties and drug release. Increase in crushing force for the same composition of tablets resulted in significant reduction in floating properties. The formulation containing HPMC K4 M, microcrystalline cellulose (Avicel ® PH 101) and a gas-generating agent showed very good floating properties and could even incorporate high amount of drug.[7,27]

A multiple-unit system prepared by Iannuccelli et al., comprised of calcium alginate core and calcium alginate/PVA membrane, both separated by an air compartment. In presence of water, the PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment. Increase in molecular weight and concentration of PVA, resulted in enhancement of the floating properties of the system. Freeze-drying was also reported for the preparation of floating calcium alginate beads. Sodium alginate solution was added drop-wise into the aqueous solution of calcium chloride, causing the instant gelation of the droplet surface as a result of the formation of calcium alginate. The obtained beads were freeze-dried, resulting in a porous structure that aids in floating.

The authors compared the behavior of radio labeled floating beads with non-floating beads in human volunteers using gamma scinitigraphy. Prolonged gastric residence time of more than 5.5 hours was observed for floating beads. The non-floating beads had a shorter residence time with a mean onset emptying time of 1 hour.[29]

Non-Effervescent System[27,28,29]

Non-effervescent FDDS is based on the mechanism of swelling of the polymer or bio adhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are jell forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate as well as bioadhesive polymers such as Chitosan and Carbopol. One of the approaches to the formulation of such floating dosage form involves intimate mixing of drug with a gel forming hydrocolloids, which swell in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier. The air trapped by swollen polymer confers buoyancy to this dosage forms and the gel structure act as a reservoir for the sustained release of the drug. Steurbel et al., developed a floating matrix tablet based on low-density foam powder. The tablet consists of polypropylene foam powder (Accurel MP 1002, MP 1000), matrix forming materials (HPMC, Carbopol, sodium alginate, corn starch, Noveon AA1, carragenan, Gum guar, Gum Arabic) and fillers like lactose, microcrystalline cellulose and dibasic calcium phosphate. The system when came in contact with the dissolution medium tends to floated due to incorporation of the highly porous foam powder in the matrix tablets which provides density (0.69 - 0.98 g/cm3) that are lower than the density of the release medium (1.00 g/cm3). They found that 17 % w/w of foam powder was sufficient to achieve proper in vitro floating behavior for 8 hours. Extended floating times

were achieved due to the air entrapped within the foam powder particles, which was slowly removed from the system upon contact with the dissolution medium.[29]

El - Kamel et al., developed floating microparticulate drug delivery system by emulsion solvent diffusion technique using four different ratios of Eudragit S 100 (ES) with Eudragit RL (ERL). The encapsulation efficiency was decreased with increase in ERL content. They demonstrated that formulation in a ratio of 2 - polymers (1:1) gave the best floating ability in the 3 - different media taken. This can be mainly due to its low bulk density obtained before and after tapping respectively. Moreover, its high packing velocity plus its high packing factor means that intervoid space is relatively low.[25]

S. Desai and S. Bolton developed controlled release floating tablets of Theophylline using agar and light mineral oil. Tablets were made by dispersing a drug/mineral oil mixture in a warm agar gel solution and pouring the resultant mixture into tablet moulds, which on cooling and air-drying formed floatable controlled release tablets. The air entrapped in the tablet gel network may reduce the density and enable the dosage form to float.[30]

Krogel and Bodmeier developed a multifunctional matrix drug delivery system surrounded by an impermeable cylinder. They prepared 3 - different types of configurationally cylinders in which case layer 2 - was composed of an impermeable cylinder with 2 - matrix tablets fixed within the 2 - orifices of the cylinder. The air filled space between the 2 - tablets resulted in a low density floating system. The device remained buoyant until at least 1 - matrix tablet was eroded/dissolved.

Applications of FDDS[30,31]

GRDFs can improve the pharmacotherapy of oral formulations and provide high and sustained drug concentrations along the gastric mucosa. For instance, the eradication of H. pylori requires the administration of various medications several times a day, which often results in poor patient compliance. More reliable therapy can be achieved by using GRDFs, by reducing the dose and frequency of drug administration. In another example, floating alginate beads have been used for the sustained release of Amoxicillin trihydrate for as long as 24 hours.

Desai and Bolton[30] compared the dissolution profiles of floating Theophylline CR tablets (300 mg) and a commercial SR tablet (theo-Dur® 300 mg). They found that floating tablets showed a more gradual release of the drug. The initial release rate was found to be comparatively faster, with a slower rate after 8 hrs. On the other hand, the release rate of Theo-Dur® was slower initially but increased later. However, these differences were not statistically significant and the 2 - formulations were regarded as bioequivalent.

The concept of FDDS has also been utilized in the development of various antireflux formulations. Washington et al., investigated the gastric distribution and residence time of a pectin-containing formulation. They observed that the formulation was able to float and form a discrete phase on top of the stomach contents. Indeed, the product emptied from the stomach more slowly than the food and more than 50 % of the formulation remained in the fundal region for 3 hours. Another therapeutic area in which FDDs can be explored is the eradication of H. Pylori, which is now believed to be the causative bacterium for chronic gastritis and peptic ulcers. Although the bacterium is highly sensitive to most antibiotic, its eradication from patients requires high concentration of drug to be maintained within the gastric mucosa for a long duration. Amiji M. and co-workers developed stomach specific drug delivery for the treatment of H. pylori which consisted of Tetracycline loaded Chitosan microspheres which released the drug for a period of 12 hrs residing the dosage form in stomach due to the inherent properties of Chitosan to form a gel in acidic medium as well as its bio adhesion characteristics.[32,33]

A floating dosage form is a feasible approach especially for drugs such as Furosemide, which has absorption sites in the upper small intestine. In fact, the absorption of Furosemide has been found to be site specific, the stomach being the major site of absorption followed by the duodenum. The property promoted the development of a monolithic floating dosage form for Furosemide, which would prolong the GRT and thus increase its bioavailability.[34] A bilayer - floating capsule has been used to achieve local delivery of Misoprostol at the gastric mucosa level. It is a synthetic prostaglandin - E analog approved and marketed in the US for the prevention of gastric ulcers caused by the non-steroidal anti-inflammatory drugs (NSAIDs). Thus, the controlled, slow delivery of Misoprostol to the stomach provides sufficient local therapeutic levels and limits the systemic and intestinal exposure to the drug. This reduces the side effects that are caused by the presence of the drug in the blood circulation or a combination of intestinal and systemic exposure while maintaining its antiulcer efficacy. In addition, the prolonged gastric availability of the Misoprostol from a site directed delivery system might also reduce the dosing frequency.[35] Apart from several applications, floating system are particularly useful for acid soluble drugs, which are poorly soluble or unstable in intestinal fluids and those which may undergo abrupt changes in their pH dependent solubility due to factors such as food, age and pathophysiological conditions of the GI tract.

Limitations[1,22,27,35]

GRDFs have great potential in improving the bioavailability of drugs that exhibit an absorption window, but with certain limitations. One of the major disadvantages of floating system is the requirement of high level of fluid in the stomach for the delivery system

to float and work efficiently. This system also requires the presence of food to delay their gastric emptying. In addition, there are limitations to the applicability of floating system for drugs that have the high solubility or solubility problem in highly acidic gastric environment or that irritant to gastric mucosa. Drugs, which are well absorbed along the entire GI tract and undergo significant 1st pass metabolism may not be desirable candidates for formulation as GRDFs since the slow gastric emptying may lead to reduced systemic bioavailability**.**

Suitability Criteria of the Drug and Excipients for FDDS[27,30,35]

Floating dosage forms would remain in stomach and upper part of GI tract for prolonged period of time. So the drug candidate that can be choosing for such dosage forms should have any of the following characteristics;

- Narrow absorption window in GI tract
- Primarily absorbed from stomach
- Poorly soluble at higher pH
- Higher solubility at acidic pH
- Act locally in stomach
- Degraded in colon

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