INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance, and cost-effective manufacturing process.¹

The dissolution rate of a drug from its dosage form is considered as an important parameter in the bio-availability. Dissolution is the rate limiting step in the absorption of drugs from solid dosage forms, especially when the drug is poorly soluble.

DISSOLUTION RATE LIMITED ABSORPTION:

The poor dissolution characteristics of relatively insoluble drugs have long been a problem to the pharmaceutical industry. When an insoluble or sparingly soluble drug is administered orally, the rate and extent of absorption are controlled by the dissolution rate in the gastrointestinal fluids.

The process of dissolution is primarily dependent on pharmaceutical variables with the possible exception of pH dependency which may be patient variable.

A quantitative description of dissolution rate is given by the Noyes-Whitney² equation based on diffusion layer model.

\[
\frac{dc}{dt} = \frac{DS(C_s - C)}{h}
\]

where, \(\frac{dc}{dt}\) is the rate of diffusion,
S is the surface area,
D is the diffusion coefficient,
h is the thickness of the diffusion layer ,
C_s is the saturation solubility and
C is the concentration of the drug in the solvent at time ‘t’.

In dissolution rate limited absorption ‘C’ is negligible when compared to ‘C_s’. Under these conditions ‘D’ and ‘h’ remain constant and cannot be altered to any degree by the product formulation. Hence,

\[
\frac{dc}{dt} = K.S.C_s
\]

Thus, the dissolution rate of a poorly soluble drug can be increased by increasing either solubility or surface area or both.
STUDIES ON SOLUBILITY IMPROVEMENT\textsuperscript{2,6}:

The most important property of a dosage form is its ability to deliver the active ingredient to its site of action at a rate and amount sufficient to elicit the desired pharmacological response. If the drug is administered by an extravascular route and acts systemically, its potency will be directly related to the amount of drug the dosage form delivers into the blood.

Methods Used For Increasing the Dissolution Rate of Poorly Soluble Drugs:

Poor aqueous solubility and/or slow dissolution rate in the biological fluids.

1. Poor stability of the dissolved drug at the physiologic pH.
2. Inadequate partition coefficient and thus poor permeation through the biomembrane.
3. Extensive presystemic metabolism.

The three approaches in overcoming the bioavailability problems due to such causes are:

1. **The Pharmaceutical Approach** which involves modification of formulation, manufacturing, process or the physicochemical properties of drugs without changing the chemical structure.

2. **The Pharmacokinetic Approach** in which the pharmacokinetics of drugs is altered by modifying its chemical structure.

3. **The Biological Approach** where by the route of drug administration may be changed such as changing from oral to parenteral route. The second approach of chemical structure modification has a number of draw backs like very expensive and time consuming, require repetition of studies and a long for regulatory approval. The attempts, whether optimizing the formulation, manufacturing process or physicochemical properties of the drug, are aimed at enhancement of dissolution rate.

The methods are:

1. **Micronization**: The process involves reducing the size of the solid drug particles to 1 to 10 microns commonly by spray drying or by use of air attrition methods. Examples of drugs whose bioavailability have been increased by micronization include griesofulvin and several steroidal and sulfa drugs.

2. **Use of surfactants**: The surface-active agents enhance dissolution rate primarily by promoting wetting and penetration of dissolution fluid into the solid particles. They are generally used in concentration
below their (CMC) values since above CMC, the drug entrapped in the micelle structure fails to partition in the dissolution fluid. Nonionic surfactants like polysorbates are widely used. Examples of the drugs whose bioavailability have been increased by use of surfactants in the formulation include steroids like spironolactone.

3. Use of salt Forms: Salts have improved solubility and dissolution characteristics in comparison to the original drug. Alkali metal salts of acidic drugs like penicillins and strong acid salts of basic drugs like atropine are more water soluble than the parent drug.

4. Alteration of pH of the Drug Microenvironment: This can be achieved in two ways— in situ salt formation, and addition of buffers to the formulation. e.g. buffered aspirin tablets.

5. Use of Metastable polymorphs: A metastable polymorphs is more soluble than the stable polymorph of a drug that exhibit polymorphism—for example, the B form of chloramphenicol palmitate is more soluble than A and C forms.

6. Solute-Solvent complexation: Solvates of drugs with organic solvents have higher aqueous solubility than their respective hydrates or the original drug. Much higher solubility can be attained by freeze drying such as solute in solution with an organic solvent with which it is known to form a solvate. E.g.1:2 griesofulvin-benzene solvate.

7. Solvent deposition: In this method, the poorly aqueous soluble drug such as nifedipine is dissolved in an organic solvent like alcohol and deposited on an inert, hydrophilic, solid matrix such as starch or micro-crystalline cellulose by evaporation of solvent.

8. Selective Adsorption on Insoluble Carriers: A highly active adsorbent such as the inorganic clays like bentonite can enhance the dissolution rate of poorly soluble drugs such as griesofulvin, indomethacin and prednesolone by maintaining the concentration gradient at its maximum. The two reasons suggested for the rapid release of drugs from the surface of clay are— the weak physical bonding between the adsorbate and the adsorbent, and hydration and swelling of the clay in the aqueous media.

9. Solid solutions: The three means by which the particle size of a drug can be reduced to submicron level are—
   a) Use of solid solution,
   b) Use of eutectic mixtures, and
   c) Use of solid dispersions.
In all these cases, the solute is frequently a poorly water-soluble drug acting as the **guest** and the solvent is highly water-soluble compound or polymer acting as a **host** or **carrier**.

**a) A solid solution** is the binary system comprising of a solid solute molecularly dispersed in a solid solvent. Since the two components crystallize together in a homogeneous one phase system, solid solutions are also called as molecular dispersions or mixed crystals. Because of reduction in particle size to the molecular level, solid solution show greater aqueous solubility and faster dissolution than eutectics and solid dispersion. They are generally prepared by fusion method where by a physical mixture of solute and solvent are melted together followed by rapid solidification. Such system, prepared by fusion, is often called as melts. E.g. griseofulvin-succinic acid, the griesofulvin from such solid solution dissolves 6 to 7 times faster than pure griesofulvin.

The two mechanisms suggested for enhanced solubility and rapid dissolution of molecular dispersions are:

1. When the binary mixture is exposed to the water, the soluble carrier dissolves rapidly leaving the insoluble drug in a state of micro-crystalline dispersion of very fine particles,
2. When the solid solution, which is said to be in a state of randomly, arranged solute and solvent molecules in the crystalline lattice, is exposed to dissolution fluid, the soluble carrier dissolves rapidly leaving the insoluble drug stranded at almost molecular level.

**b) Eutectic Mixture:** These systems are also prepared by fusion method. Eutectic melts differ from solid solution in that the fused melt of solute-solvent show complete miscibility but negligible solid-solid solubility i.e. such systems are basically intimately blended physical mixture of two crystalline components.

Examples of eutectics include paracetamol-urea, griesofulvin-urea, griseofulvin-succinic acid, etc. Solid solutions and eutectics, which are basically melts, are easy to prepare and economical with no solvents involved. The method however cannot be applied to:

- drugs which fail to crystallize from the mixed melt,
- thermolabile drugs, and
- Carriers such as succinic acid that decompose at their melting point. The eutectic product is often tacky, intractable or irregular crystals.

**c) Solid dispersions:** These are generally prepared by **solvent** or **co-precipitation** method where by both the guest solute and the solvent are dissolved in a common volatile liquid solvent such as alcohol. The liquid solvent is removed by evaporation under reduced pressure or by freeze drying which results in amorphous precipitation of guest in a crystalline carrier. Example is griesofulvin – PVP.
10. Molecular Encapsulation with Cyclodextrins:3,4,5 The beta- and gamma-Cyclodextrins and several of their derivatives are unique in having the ability to form molecular inclusion complexes with hydrophobic drugs having poor aqueous solubility. These cyclodextrin molecules are versatile in having a hydrophobic cavity of size suitable enough to accommodate the lipophilic drugs as guest; the outside of the host molecule is relatively hydrophilic. Thus molecularly encapsulated drug has greatly improved aqueous solubility and dissolution rate. Among the possibilities, the preparation of inclusion complexes with cyclodextrin is of particular interest.

Gastroretentive Dosage Form (GRDF):7,8

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDF or GRDS).

GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form.

Dosage form with prolonged GRT, i.e. gastro retentive dosage form (GRDF), will bring about new and important therapeutic options such as9 –

1) This application is especially effective in sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To override this problem, erodible, gastroretentive dosage forms have been developed that provide continuous, controlled administration of sparingly soluble drugs at the absorption site.

2) GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa. (For e.g. Eradicating Helicobacter pylori from the submucosal tissue of stomach) making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis, reduce the risk of gastric carcinoma and administer non-systemic controlled release antacid formulations (calcium carbonate).

3) GRDFs can be used as carriers for drugs with so-called absorption windows. These substances for e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides, tetracyclines etc.), are taken up only from very specific sites of the GI mucosa.
APPROACHES TO GASTRIC RETENTION\textsuperscript{10}

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 –

\textbf{a) Floating Systems:}

\textit{Floating Drug Delivery Systems} (FDDS)\textsuperscript{11} have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, 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 release of the drug, the residual 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 classified into two distinct categories, non-effervescent and effervescent systems.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{buoyant-tablet.jpg}
\caption{Graphic of Buoyant tablet that is less dense than the stomach fluid and therefore remains in the fundus.}
\end{figure}

\textbf{b) Bio/Muco-adhesive Systems:} \textsuperscript{12}

Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the GRT of drug delivery system (DDS) in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane.

The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS 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 can be divided into three broad categories:–

- Hydration-mediated adhesion.
- Bonding-mediated adhesion.
- Receptor-mediated adhesion.
c) Swelling and Expanding Systems:  

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 long period of time. 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. The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity. Such polymeric matrices remain in the gastric cavity for several hours even in the fed state.

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 of the system maintaining its physical integrity for prolonged period.

d) High Density Systems:  

These systems with a density of about 3 g/cm³ are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm³ acts as a threshold value after which such systems can be retained in the lower part of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc.

e) Incorporation of Passage Delaying Food Agents:

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 largely caused by saturated fatty acids with chain length of C₁₀-C₁₄.

f) Ion Exchange Resins:

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival 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 towards the top of gastric
content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

g) Osmotic Regulated Systems:  

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release 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 consists of two components – drug reservoir compartment and osmotically active compartment.

TYPES OF FLOATING DRUG DELIVERY SYSTEMS (FDDS)  

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS that are:  
A. Effervescent System, and  
B. Non-Effervescent System.

A. EFFERVESCENT SYSTEM: -  

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO$_2$) gas, 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 evaporate at body temperature. These effervescent systems further classified into two types.  
I. Gas Generating systems  
II. Volatile Liquid/Vacuum Containing Systems.

I. Gas – Generating Systems:  

I. Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS):  

These are as shown in Fig.8 and formulated by intimately mixing the CO$_2$ generating agents and the drug with in the matrix tablet. 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. The drug is
slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

2. Intra Gastric Bilayer Floating Tablets:

These are also compressed tablet as shown in Fig 6 and containing two layer i.e.,

i. Immediate release layer and
ii. Sustained release layer.

3. Multiple Unit type floating pills:

These systems consist of sustained release pills as ‘seeds’ surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO\textsubscript{2} within the system.

II. Volatile Liquid / Vacuum Containing Systems:

1. Intragastric Floating Gastrointestinal Drug Delivery System:

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

2. Inflatable Gastrointestinal Delivery Systems:

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid.

3. Intragastric Osmotically Controlled Drug Delivery System:

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release 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 pressure controlled drug delivery devices consist of two components; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the 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 in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice.

The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.

B. NON EFFERVESCENT SYSTEMS:

The Non-effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol. The various types of this system are as:

1. Single Layer Floating Tablets:

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

2. Bilayer Floating Tablets:

A bilayer tablet contain two layer one immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.
3. Alignate Beads:  

Multi unit floating dosage forms were developed from freeze-dried calcium alginate. 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 hours. When compared with solid beads, which gave a short residence, time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hour.

4. Hollow Microspheres:

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol:dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40°C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug. The microballoons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours in vitro.

Factors Controlling Gastric Retention Time of Dosage Form:  

The gastric retention time (GRT) of dosage form is controlled by several factors that affect their efficacy as a gastroretentive system.

- **Density** – GRT is a function of dosage form buoyancy that is dependent on the density.
- **Size** – Dosage form units with a diameter of more than 9.5mm are reported to have an increased GRT.
- **Shape of dosage form** – Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilopounds per square inch (KSI) are reported to have better GRT. 90% to 100% retention at 24 hours compared with other shapes.
- **Single or multiple unit formulation** – Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.
- **Nature of meal** – Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.
Caloric content – GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.

Frequency of feed – The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

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

Age – Elderly people, especially those over 70, have a significantly longer GRT.

Posture – GRT can vary between supine and upright ambulatory states of the patient.

Biological factors – Diabetes and Crohn’s disease.

Advantages of GDDS: 22, 23

Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery.

These advantages include:

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
2. Controlled delivery of drugs.
3. Delivery of drugs for local action in the stomach.
4. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
5. Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
6. Simple and conventional equipment for manufacture.
7. Ease of administration and better patient compliance.
8. Site-specific drug delivery.

Disadvantages of GDDS:

1. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
2. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
3. High variability in gastric emptying time due to its all or non-emptying process.
4. Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diametrical size. Therefore patients should not be dosed with floating forms just before going to bed.