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A REVIEW ON FLOATING DRUG DELIVERY SYSTEM

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ABSTRACT

Oral drug delivery system is the most preferred route of administration for drug delivery. The floating drug delivery systems (FDDS) become an additional advantage for drugs that are absorbed primarily in the upper segments of gastrointestinal (GI) tract, i.e., the stomach, duodenum and jejunum. The purpose of writing this review on floating drug delivery systems (FDDS) was to focus on the types of floating drug delivery systems, principal and mechanism of floatation to achieve gastric retention and polymers used in floating Drug delivery systems. Different types of Polymers used in the drug delivery system. These systems have some advantages and disadvantages. This article gives information about the different types of natural and synthetic polymer used in the drug delivery system. Natural polymers like guar gum, chitosan, xanthan gum, Gellan gum, sodium alginate and Synthetic polymers like HPMC, Eudragit, and Ethylcellulose are mentioned.

KEY WORDS: Floating drug delivery systems, Gastric retention, Mechanism, Classification of Fdds, Factors affecting and Polymers used in fdds, Novel methodologies, Evaluation of Fdds.

INTRODUCTION:

Drug delivery system represents pure crude form of the drugs either in solid, liquid or semi-solid form, which should be therapeutically efficient, safe and stable enough to deliver a required amount of the drug to the specified site in the body to reach instantly, to achieve the correct concentration and then retain the adapted concentration. Many of the drug delivery system commercialized is oral drug delivery systems [(1)]. Due to low treatment costs, increased patient compliance and ease of administration oral drug delivery is mostly preferred despite of the multiple benefits, the frequency of dosing of a medication should be increased as it gets easily emptied from the stomach [(2)]Floating drug delivery (FDDS)a invented to retain the drug in the stomach and applicable for drugs with poor solubility and low stability in intestinal fluids, The basis behind FDDS is making the dosage form less dense than the gastric fluids to make it float on them FDDS are Hydrodynamically controlled low density systems with sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. [(3)] Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying. Based on these approaches, classification of floating drug delivery systems (FDDS) has been described in detail. *In-vivo/In-vitro* evaluation of FDDS has been discussed by scientists to assess the efficiency and application of such systems. [(4)]

GASTRIC RETENTION

The presence or absence of food in the stomach influences the gastric retention time of the system. The presence of food increases the retention time and increases the absorption of the active agent by allowing it to stay at the absorption site for a longer time. Gastroretentive drug delivery systems are a good example; they emerged to enhance the bioavailability and effectiveness of drugs with a narrow absorption window in the upper gastrointestinal tract and/or to promote local activity in the stomach and duodenum. [(5)(6)]

Basic Gastrointestinal Tract Physiology

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following four phases;

1. Phase I (basal phase) lasts from 45 to 60 minutes with rare contractions.

2. Phase II (preburst phase) lasts for 30 to 45 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually. [(7)]

3. Phase III (burst phase) lasts for 5 to 15 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate. **(8)**

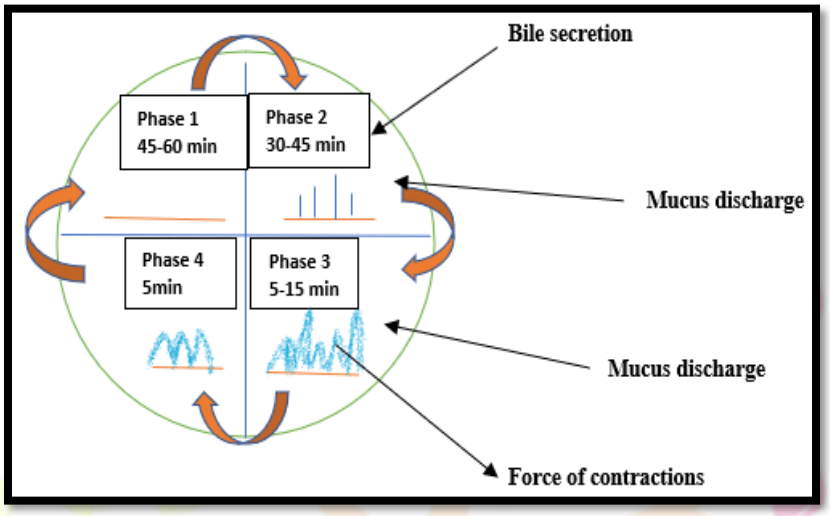

Figure 1: Motility pattern in GIT [9]

Mechanism of floating systems:

The drug is floating on the gastric contents (fig 2) the slow drug release is accompanied with requisite rate during the system flow on the gastric contents. The release is followed by removal of the residual system from the stomach. But, along with the appropriate level of floating force (F), minimum levels of gastric contents are needed to permit achievement of buoyancy retention principle and also to keep dosage form buoyant over meal surface. Its operation constitutes of measuring a force equivalent to F (with respect to time) which keeps the object submerged. The object floats better if RW (resultant weight) is on the higher positive side (fig 2(b)), this apparatus optimizes FDDS and prevents its drawbacks unforeseeable intragastric buoyancy capability variations, related to stability and durability.

F = F buoyancy - F gravity (Df - Ds) gv

Where, F= total vertical force,

Df = fluid density,

Ds = object density,

v = volume

g = acceleration due to gravity. [10]

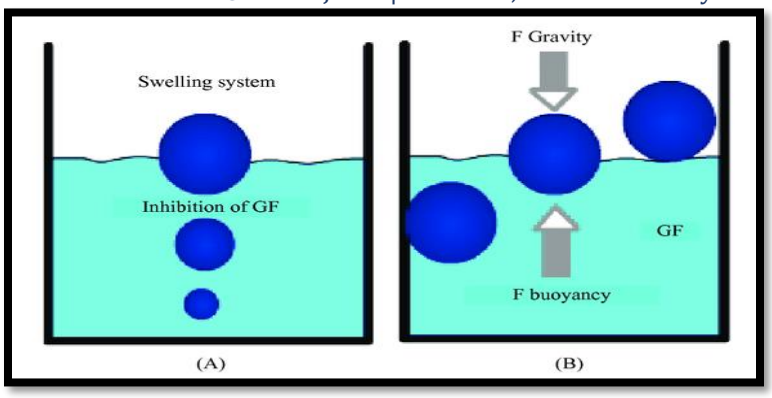

Figure2: Mechanism of drug action in FDDS [11]

ADVANTAGES: [12] [13] [14]

1. Floating dosage forms such as tablets or capsules will remain in the solution for prolonged time even at the alkaline pH of the intestine.
2. FDDS shows vigorous intestinal movement and in diarrhea to keep the drug in floating condition in stomach to get a relatively better response.
3. Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence; FDDS formulations may be useful for the administration of aspirin and other similar drugs.
4. Simple and conventional technique for formulation.
5. Controlled delivery of drugs. Delivery of drugs for residual action at a specific site in the stomach.
6. Site-specific drug delivery
7. Administration of prolonged release floating dosage forms, tablet or capsules, causes dissolution of the drug in the gastric fluid.
8. These FDDS maintain the drug floating condition in the stomach for better efficacy.
9. In treating gastro oesophageal reflux disorders (GERD).
10. Ease of administration with higher patient compliance.

DISADVANTAGES: [15] [16] [17]

1. Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.
2. Drug which is well absorbed along the entire GI tract and which undergo significant first-pass metabolism, may not be suitable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability.
   Ex: Nifedipine
3. In case of FDDS patient requires a sufficiently high level of fluids in the stomach to make the floating of drugs in stomach.

Application of Floating Drug Delivery System:

1. Enhanced bioavailability
2. Enhanced first-pass biotransformation
3. Sustained drug delivery/reduced frequency of dosing
4. Targeted therapy for local ailments in the upper GIT
5. Reduced fluctuations of drug concentration
6. Minimization of fluctuations in drug concentration
7. Reduced counter-activity of the body
8. Extended time over critical (effective) concentration
9. Minimized adverse activity at the colon
10 Site specific drug delivery [18] [19]

Classification of floating drug delivery system: [20] [21]

1. Single Unit Floating Dosage Systems

a) Effervescent Systems (Gas-generating Systems)

b) Non-effervescent Systems

2. Multiple Unit Floating Dosage Systems

a) Non-effervescent Systems

b) Effervescent Systems (Gas-generating Systems)

C) Hollow Microspheres

d) Raft Forming Systems.

e) Magnetic systems

1. Single unit floating dosage system

Single-unit dosage forms are simpler to manufacture, but because they empty completely or partially from the stomach, they run the risk of losing their effects too soon, resulting in high variability in bioavailability and local discomfort due to a large volume of drug administered at a specific location in the gastrointestinal tract.

(a)Effervescent Systems (Gas-generating Systems)

These are matrix forms of systems made with effervescent substances like sodium bicarbonate, citric acid, and tartaric acid, as well as swelling polymers like chitosan and methylcellulose. When CO_2 comes into contact with acidic gastric contents, it is generated and stuck in swollen hydrocolloids, giving dosage types buoyancy.

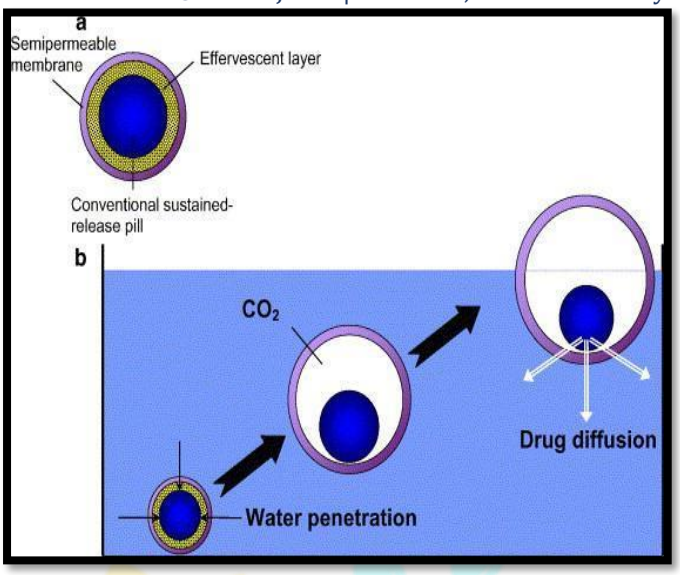

Figure 3: Effervacent systems (gas generating system) [22]

(b)Non-effervescent Systems

Polysaccharides, hydrocolloids, and matrix-forming polymers such as polyacrylate, polycarbonate, polystyrene, and polymethacrylate are used to generate a gel-forming or swelling cellulose type in non-effervescent floating dosage forms. A straight forward strategy to completely combine the medication and the hydrocolloid-forming gel is included in the formulation method. Following oral administration, this dosage form swells in contact with stomach juices and achieves a bulk density of 1. The air contained within the swelling matrix provides buoyancy to the dose form.

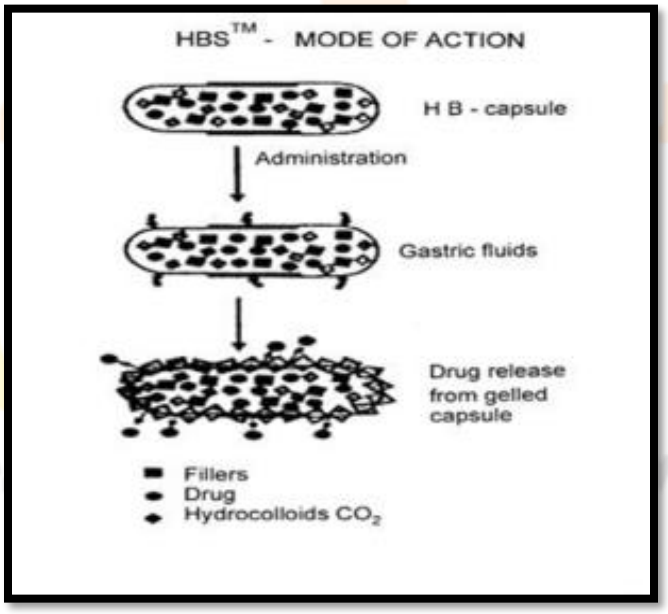

Figure 4: Non-Effervacent systems [23]

(2) Multiple unit dosage form

In spite of extensive research and development in hydro dynamically balanced systems and other floating tablets, these systems has an important drawback of high variability of gastrointestinal transit time, when orally administered, because of their all-or nothing gastric emptying nature. In order to overcome this problem, multiple unit floating

systems were developed, which reduces the inter-subject variability in absorption and lowers the probability of dose-dumping (Fig 5).

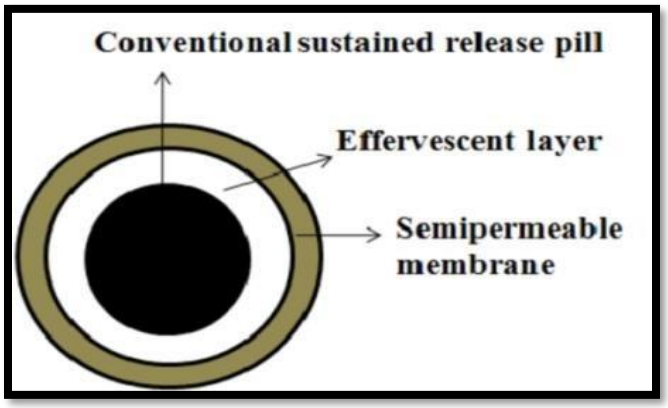

Figure 5: Multiple unit dosage forms [24]

(a) Non-effervescent Systems

Unlike effervescent systems, there is little research on effervescent multiple-unit systems in the literature. However, few researchers have investigated the feasibility of developing an indomethacin-containing technique employing chitosan as the polymeric excipient. A model drug manufactured using the extrusion procedure is a multiple HBS (Hydrodynamically Balanced System) unit containing indomethacin.

(b) Effervescent Systems

A calcium alginate core and a calcium alginate/PVA (poly vinyl alcohol) membrane were separated by an air compartment in a multi-unit system. In the presence of water, the PVA leaches out and increases the permeability of the membrane, preserving the integrity of the air compartment. The floating properties of the system have improved as the molecular weight and PVA content have increased. The freeze-drying procedure for making floating calcium alginate beads is also addressed. Due to the creation of calcium alginate, sodium alginate solution is dropped into an aqueous solution of calcium chloride, causing the droplet surface to quickly gel.

(c) Hollow Micro spheres

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 drug (tranilast or ibuprofen) and an enteric acrylic polymer were poured into an agitated aqueous solution of polyvinyl alcohol that was thermally controlled at 40 °C. The gas phase generated in the dispersed polymer droplet by the evaporation of dichloromethane formed an internal cavity in the microsphere of the polymer with the drug. The drugs incorporated in the solidified shell of the polymer were found to be partially or completely amorphous. The flow ability and pack ability of the resultant microballoons were much improved compared with the raw crystals of drug. The microballoons floated continuously over the surface of acidic dissolution media containing surfactant for > 12 h in vitro. The drug release behavior of the microballoons was characterized as an enteric property, and drug release rates were drastically reduced depending on the polymer concentration at pH 6.8

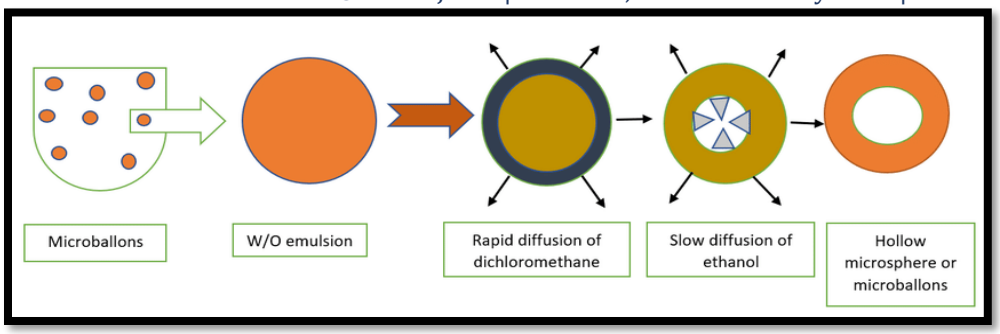

Figure 6: Hollow micro spheres [25]

(d) Raft Forming Systems:

Raft forming systems have received much attention for the delivery of antacids and drug delivery for GI infections and disorders. The basic mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with the gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft (Fig: 7). The raft floats because of the buoyancy created by the formation of CO_2 and act as a barrier to prevent the reflux of gastric contents like HCl and enzymes into the oesophagus. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation to make the system less dense and float on the gastric fluids have received much attention in the development of multiple unit systems.

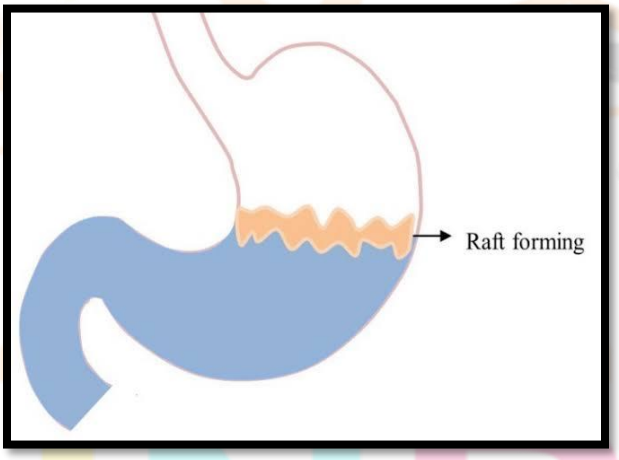

Figure 7: Raft forming systems [26]

(e)Magnetic systems:

In magnetic systems, a dosage form consists of active pharmaceutical ingredient, Excipients and also a small amount of internal magnet. An extracorporeal magnet is placed over the stomach to control the position of the dosage form containing internal magnet as presented in Figure 8. The position and the magnetic field intensity of the extracorporeal magnet can affect the GRT. Previous studies have reported that the GRT and bioavailability are improved by magnetic tablets. Groning et al. performed a study in human volunteers using magnetic acyclovir tablets with and without an external magnetic field. The authors observed that the GRT and plasma drug concentration were increased in the presence of an extracorporeal magnet. Ito et al. formulated bioadhesive granules containing ultra-fine ferrite and performed in vivo experiment in rabbits. They found that an external magnetic field intensity of 1700 G retained all granules in the stomach for more than 2 h. However, specific positioning of the magnet might be difficult and results in low patient compliance. Only a few studies have been conducted on magnetic systems and their clinical

significance has yet to be explored. Therefore, future research studies on these systems need to focus more on their clinical significance.

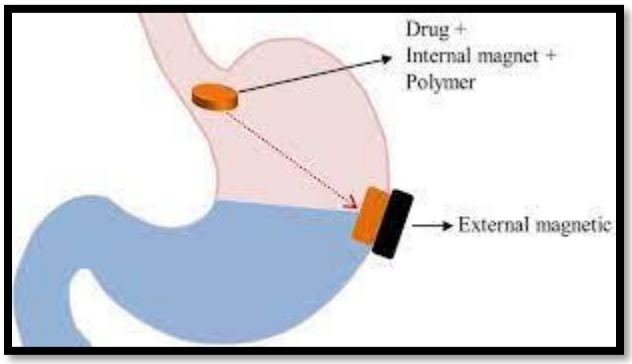

Figure 8: Magnetic systems

Factors affecting the floating drug delivery system: [27] [28] [29] [30] [31] [32]

1. Density:

The density of a dose form determines its buoyancy and, as a result, its floating efficiency. The dose form's density should be lower than the stomachic contents (1.004 gm/ml).

2. Shape of dosage form:

Tetrahedron and ring-shaped devices have a higher floating potential than other shapes. They have a 90-98 percent higher rate of 24-hour retention.

3. Fed or unfed state:

GI motility is characterized by periods of robust motor activity, or migrating myoelectric complexes (MMC), which occur every 1.5 to 2 hours under abstinence settings.

4. Formulation of a single or multiple units:

Multiple unit formulations permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

5. Nature of meal:

Feeding indigestible polymers or fatty acid salts to the stomach can cause it to shift its motility pattern to a fed state, slowing gastric emptying and prolonging medication release.

6. Calorie content:

A high-protein, high-fat meal can extend floating time by 4–10 hours.

7. Frequency of feed:

Because of the low frequency of migratory myoelectric complex, the GRT (Gastric Residence Time)will increase by over 40 minutes when successive meals are provided instead of a single meal (MMC).

8. Posture:

The GRT will differ between the patient's supine and upright ambulant stages. In the case of the floating systems, it was rumored that when individuals were kept in an upright ambulant position, the dosage type stayed consistent on stomachic content, as opposed to when they were in a supine position. As a result, the floating drug delivery system inside the upright position of the patients is safeguarded against post-prandial evacuation.

9. Age:

Elderly people, those over the age of 60, have a much longer floating time.

10. Biological factor:

Floating might vary depending on a person's health or physiological status. Diabetes and Crohn's illness, for example, affect floating time.

11. Concomitant drug administration:

Floating time is affected by anticholinergics like atropine, opiates like codeine, and prokinetic drugs like metoclopramide and cisapride.

POLYMERS USED IN FLOATING DRUG DELIVERY SYSTEM

Polymers have played an integral role in the advancement of drug delivery technology by providing controlled release of therapeutic agents in constant doses over long periods, Polymers are used in floating system so as to target the drug delivery at specific region in the GI tract i.e. stomach. Natural polymers used in floating system are Guar gum, Chitosan, xanthan gum, Gellan gum, Sodium alginate, etc. Synthetic polymers used for the floating drug delivery are HPMC, Eudragit, ethyl cellulose, etc.

Natural Polymers:

Natural gums (obtained from plants) are hydrophilic carbohydrate polymer of high molecular weight. They are generally insoluble in organic solvents, like hydrocarbon, ether. Gums either water soluble or absorb water and swell up or disperse in cold water to give a viscous solution or jelly.

Natural polymer has advantages over synthetic polymer.

- Biodegradable
- Biocompatible and non-toxic
- Low cost.
- Environment friendly
- Local availability.

Disadvantages:

They are as follows:

- Microbial contamination
- Batch to batch variation
- Uncontrolled rate of hydration
- Reduced viscosity on storage

1. Guar gum [33]

Functional Category:

Suspending Description agent; tablet binder; tablet disintegrant; viscosity increasing agent

Description:

Guar gum occurs as an odorless or nearly odorless, white to yellowish-white powder with a bland taste.

Typical Properties

Acidity/alkalinity pH = 5.0–7.0 (1% w/v aqueous dispersion)

Density 1.492 g/cm3

Solubility Practically insoluble in organic solvents, in cold or hot water, guar gum disperses and swells almost immediately to form a highly viscous, thixotropic sol. The optimum rate of hydration occurs at pH 7.5–9.0. Finely milled powders swell more rapidly and are more difficult to disperse. Two to four hours in water at room temperature are required to develop maximum viscosity.

Viscosity (dynamic) 4.86 Pas (4860 cP) for a 1% w/v dispersion. Viscosity is dependent upon temperature, time, concentration, pH, rate of agitation, and particle size of the guar gum powder. Synergistic rheological effects may occur with other suspending agents such as xanthan gum

Advantages of guar gum in floating drug delivery system:

It has been reported that polymer swelling play an important role in the pattern and amount of drug release. It was found that guar gum formulations were relatively insensitive to stirring speed during *in vitro* drug dissolution testing and dissolution profile was not affected significantly.

2. Chitosan [34]

Functional Category

Coating agent; disintegrant; film-forming agent; mucoadhesive; tablet binder; viscosity increasing agent.

Description

Chitosan occurs as odorless, white or creamy-white powder or flakes. Fiber formation is quite common during precipitation and the chitosan may look ‘cotton like’.

Typical Properties

Chitosan is a cationic polyamine with a high charge density at pH < 6.5, and so adheres to negatively charged surfaces and chelates metal ions. It is a linear polyelectrolyte with reactive hydroxyl and amino groups (available for chemical reaction and salt formation). The properties of chitosan relate to its polyelectrolyte and polymeric carbohydrate character. The presence of a number of amino groups allows chitosan to react chemically with anionic systems, which results in alteration of physicochemical characteristics of such combinations. The nitrogen in chitosan is mostly in the form of primary aliphatic amino groups. Chitosan therefore undergoes reactions typical of amines: for example, N-acylation and Schiff reactions. Almost all functional properties of chitosan depend on the chain length, charge density, and charge distribution. Numerous studies have demonstrated that the salt form, molecular weight, and

degree of deacetylation as well as pH at which the chitosan is used all influence how this polymer is utilized in pharmaceutical applications.

Acidity/alkalinity pH = 4.0–6.0 (1% w/v aqueous solution)

Density 1.35–1.40 g/cm3

Glass transition temperature 203°C

Moisture content

Chitosan adsorbs moisture from the atmosphere, the amount of water adsorbed depending upon the initial moisture content and the temperature and relative humidity of the surrounding air.

Particle size distribution 30 μm

Solubility

Sparingly soluble in water; practically insoluble in ethanol (95%) other organic solvents, and neutral or alkali solutions at pH above approximately 6.5 . Chitosan dissolves readily in dilute and concentrated solutions of most organic acids and to some extent in mineral inorganic acids (except phosphoric and sulfuric acids). Upon dissolution, amine groups of the polymer become protonated, resulting in a positively charged polysaccharide (RNH3 þ) and chitosan salts (chloride, glutamate, etc.) that are soluble in water; the solubility is affected by the degree of deacetylation. Solubility is also greatly influenced by the addition of salt to the solution. The higher the ionic strength, the lower the solubility as a result of a salting-out effect, which leads to the precipitation of chitosan in solution. When chitosan is in solution, the repulsions between the deacetylated units and their neighboring glucosamine units cause it to exist in an extended conformation. Addition of an electrolyte reduces this effect and the molecule possesses a more random, coil-like conformation.

Viscosity (dynamic)

A wide range of viscosity types is commercially available. Owing to its high molecular weight and linear, unbranched structure, chitosan is an excellent viscosity-enhancing agent in an acidic environment. It acts as a pseudo-plastic material, exhibiting a decrease in viscosity with increasing rates of shear. The viscosity of chitosan solutions increases with increasing chitosan concentration, decreasing temperature, and increasing degree of deacetylation.

Incompatibilities

Chitosan is incompatible with strong oxidizing agents.

Advantages of chitosan:

- It forms film that reduces effect of gastrointestinal transit time.
- Hallow microcapsule tend to float on gastric fluid for about 12hrs.
- Release rate of drug followed zero order kinetics.

3. Xanthan gum [35]

Functional Category

Gelling agent; stabilizing agent; suspending agent; sustained-release agent; viscosity-increasing agent

Description

Xanthan gum occurs as a cream- or white-colored, odorless, free-flowing, fine powder.

Typical Properties

Acidity/alkalinity pH = 6.0–8.0 for a 1% w/v aqueous solution.

Freezing point 0C for a 1% w/v aqueous solution

Heat of combustion 14.6 J/g (3.5 cal/g)

Melting point Chars at 270°C

Refractive index nD 20 = 1.333 (1% w/v aqueous solution)

Solubility

Practically insoluble in ethanol and ether; soluble in cold or warm water

Specific gravity 1.600 at 258 °C

Viscosity (dynamic) 1200–1600 mPa s (1200–1600 cP) for a 1% w/v aqueous solution at 258°C

Advantages of Xanthan gum:

- It is used to increase or decrease rate of release of drug from formulation
- Soluble in water
- High viscosity at low concentration
- It has potential advantage of drug release at zero order kinetics.
- Some tablet containing xanthan gum and citric acid show buoyancy for more than 24hrs.

4. Gellan gum [36] [37]

Gellan gum is an anionic, high molecular weight, deacetylated extracellular, linear polysaccharide. This gum has an outstanding flavor release, high gel strength, an excellent stability, process flexibility, high clarity, good film former and thermally reversible gel characteristics. Gellan gum is produced as a fermentation product from spingomonas elodea.

Advantages of Gellan gum:

- It has excellent flavor release, high gel strength, and excellent stability.
- It forms gel when positively charged ions are added
- It is used in food product as thickening agent or stabilizing agent

5. Sodium alginate [38]

Functional Category

Stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity increasing agent

Description

Sodium alginate occurs as an odorless and tasteless, white to pale yellowish-brown colored powder.

Typical Properties:

Acidity/alkalinity ph-7.2 (1% w/v aqueous solution)

Solubility: Practically insoluble in ethanol (95%), ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30%. Also, practically insoluble in other organic Solvents and aqueous acidic solutions in which the pH is less than 3. Slowly soluble in water, forming a viscous colloidal Solution.

Viscosity (dynamic): Various grades of sodium alginate are commercially available that yield aqueous solutions of varying Viscosity. Typically, a 1% w/v aqueous solution, at 208C, will have a viscosity of 20–400mpa s (20–400cp). Viscosity may vary depending upon concentration, pH, temperature, or the Presence of metal ions. Above pH 10, viscosity decreases.

Applications of sodium alginate

Sodium alginate is used as a gel in pharmaceutical preparations. Sodium Alginate (E401) is extracted from brown seaweed. It is also used as a stabilizer, thickener and emulsifier for food products such as ice cream, yogurt, cream, and cheese.

Synthetic Polymers:

Synthetic polymers are becoming increasingly important in pharmaceuticals. Uses of synthetic polymer are as binder, film coating agent, etc. Polymer are macromolecule having very large, contain a variety of functional group. Synthetic polymers are either purely synthetic or they are modified form of natural polymer know as semi-synthetic. List of synthetic polymer used is as follows:

1. Hydroxypropyl methyl cellulose [HPMC]
2. Eudragit
3. Ethyl cellulose

Disadvantages:-

- High cost toxicity environmental pollution
- Acute and chronic adverse effect
- Poor biocompatible
- Inflammatory response and local reaction

1. Hydroxypropyl methyl cellulose [HPMC] [39] [40] [41]

Hydroxypropyl methylcellulose ethers belong to an extensive family of white to off-white, odorless, water soluble polymers that bind, retain water, thicken, form films, lubricate. It is a semi synthetic, inert, viscoelastic polymer, used as an excipient and controlled-delivery component in oral medicaments, found in a variety of commercial products.

Functional category:

Bioadhesive material, coating agent, controlled-release agent, dispersing agent, dissolution enhancer, emulsifying agent, emulsion stabilizer, extended-release agent, film-forming agent, foaming agent, granulation aid, modified-release agent, mucoadhesive, release modifying agent, solubilizing agent, stabilizing agent, suspending agent, sustained release agent, tablet binder, thickening agent, viscosity-increasing agent .

General properties

Common to the Hypremellose are listed below. Individual type exhibits these properties to varying degrees and may have additional properties that are desirable for specific applications.

- Apparent density: 0.25~0.70g/cm3
- The refractive index=1.336
- Surface tension: 42 to 56mn/m

Solubility: Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of HPMC are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents. Some grades are swellable in ethanol .

Advantages

- Water soluble and most abundant polymer in nature
- Used as a thickener, film former and water retension agent
- Hydrophilic matrix is the simplest sustained release technology for oral dosage form

2. Eudragit [(42)]

Functional category:

Film former; tablet binder; tablet diluent

Description:

Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. Several different types are commercially available and may be obtained as the dry powder, as an aqueous dispersion, or as an organic solution. A (60: 40) mixture of acetone and propan-2-ol is most commonly used as the organic solvent. Eudragit S 100 is available as powder and solvents used for this is 95 % Acetone and alcohols which is soluble in intestinal fluid from pH 7 and used as an enteric coating material.

Eudragit L and S also referred to as methacrylic acid copolymers in the USPNF 23 monograph, are anionic copolymerization products of methacrylic acid and methyl methacrylate. The ratio of free carboxyl groups to the ester is approximately 1:1 in Eudragit L (Type A) and approximately 1: 2 in Eudragit S (Type B). Both polymers are readily soluble in neutral to weakly alkaline conditions (pH 6– 7) and form salts with alkalis, thus affording film coats that are resistant to gastric media but soluble in intestinal fluid. Eudragit L-100 and Eudragit S-100 are white free-flowing powders with at least 95 % of dry polymers.

3. Ethyl cellulose [43]

Functional Category

Coating agent ; flavoring agent; tablet binder; tablet filler; viscosity increasing agent.

Description

Ethylcellulose is a tasteless, free-flowing, white to light tan-colored powder.

Typical Properties

Density (bulk) 0.4 g/cm3

Glass transition temperature 129–133°C

Moisture content Ethylcellulose absorbs very little water from humid air or during immersion, and that small amount evaporates readily.

Specific gravity 1.12–1.15 g/cm3

Solubility:

Ethylcellulose is practically insoluble in glycerin, propylene glycol, and water. Ethylcellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%). Ethylcellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene.

Viscosity

The viscosity of ethylcellulose is measured typically at 258°C using 5% w/v ethylcellulose dissolved in a solvent blend of 80% toluene: 20% ethanol (w/w). Grades of ethylcellulose with various viscosities are commercially available; see Table IV. They may be used to produce 5% w/v solutions in organic solvent blends with viscosities nominally ranging from 7 to 100 mPa s (7–100 cP). Specific ethylcellulose grades, or blends of different grades, may be used to obtain solutions of a desired viscosity. Solutions of higher viscosity tend to be composed of longer polymer chains and produce strong and durable films. The viscosity of an ethylcellulose solution increases with an increase in ethylcellulose concentration; e.g. the viscosity of a 5% w/v solution of Ethocel Standard 4 Premium is 4 mPa s (4 cP) and of a 25% w/v solution of the same ethylcellulose grade is 850 mPa s (850 cP).

4. Carbopol [44]

Nur and Zhang developed floating tablets of captopril using HPMC (4000 and 15,000 cps) and carbopol 934P. In vitro buoyancy studies revealed that tablets of 2 kg/cm^2 hardness after immersion into the floating media floated immediately and tablets with hardness 4 kg/cm^2 sank for 3-4 minutes and then came to the surface. Tablets in both cases remained floating for 24 hours. The tablet with 8 kg/cm^2 hardness showed no floating capability. It was concluded that the buoyancy of the tablet is governed by both the swelling of the hydrocolloid particles on the tablet surface when it contacts the gastric fluids and the presence of internal voids in the center of the tablet (porosity).

A prolonged release from these floating tablets was observed as compared with the conventional tablets and a 24 hour CR from the DF of captopril was achieved. Admixtures containing Carbopol 940, 941 and NaCMC were assessed for bioadhesive delivery of metronidazole. The bioadhesive properties of the admixtures were estimated by

using the adhesion of polymer coated glass beads on a biological tissue and the modified Lecomte Du Nouy tensiometer.

The rheological behaviors of the polymers and their admixtures were studied as well. The bioadhesive, swelling and release characteristics of tablet compacts formulated with the polymers and their admixtures, which contained metronidazole, were also determined. Results obtained indicated that although all single polymers and their admixtures had high bioadhesive potentials, Carbopol 940 and 941 admixtures (2:1) showed the best performance and NaCMC/Carbopol 940 admixture (2:1) exhibited the least bioadhesive strength.

Table 1: Carbopol Products for Oral Pharmaceutical Applications [44]

Carbopol Polymer	Polymerization Solvent	Carbomer Product Type	Viscosity, cP (0.5 wt% at pH 7.5)
71G NF	Ethyl Acetate	Homopolymer	4,000 - 11,000
971P NF	Ethyl Acetate	Homopolymer	4,000 - 11,000
974P NF	Ethyl Acetate	Homopolymer	29,400 - 39,400
980 NF	Cosolvent[1]	Homopolymer	40,000 - 60,000
981 NF	Cosolvent[1]	Homopolymer	4,000 - 10,000
5984 EP	Cosolvent[1]	Homopolymer	30,500 - 39,400
ETD 2020 NF	Cosolvent[1]	Interpolymer	47,000 - 77,000[2]
Ultrez 10 NF	Cosolvent[1]	Interpolymer	45,000 - 65,000
934 NF	Benzene	Homopolymer	30,500 - 39,400
934P NF	Benzene	Homopolymer	29,400 - 39,400
940 NF	Benzene	Homopolymer	40,000 - 60,000
941 NF	Benzene	Homopolymer	4,000 - 10,000
1342 NF	Benzene	Copolymer	9,500 - 26,500[2]

Table 2: Polymers used in FDDS drugs and their floating effect

S.NO	Name of the drug	Polymers used	Method adopted	Inference [BUOYANCY TIME]
1.	Famotidine [45]	Eudragit s100 Methocel k100 Methocel k15M	Effervescent	6-10hrs
2.	Salbutamol sulphate [46]	HPMC (K100M) (K4M) Methyl cellulose	Effervescent	8-12 hrs
3.	Ondosteron [47]	Eudragit 100	Non- Effervescent	8-12hrs

4.	Captopril [48]	Eudragit	Non- Effervescent	Less than 6hrs
5.	Risperidone [49]	Eudragit	Effervescent	6hrs
6.	Ofloxacin [50]	Ethyl cellulose EU RT 30D	Effervescent	More than 24 hrs
7.	Cephalexin [51]	HPMC	Effervescent	Less than 12 hrs
8.	Hydralazine [52]	HPMC	Effervescent	Less than 12 hrs
9.	Simvastatin [53]	HPMC	Effervescent	More than 12hrs
10.	Cefpodoxime Proxetil [54]	HPMC, Guar gum	Effervacent	More than 12hrs
11.	Atenolol [55]	Locust bean gum, HPMC	Effervescent	10-12hrs
12.	Pantaprazole [56]	Ethylcellulose, HPMC	Non- Effervescent	7-8 hrs
13.	Lafutidine [57]	Guar gum, Methocel K14 Methocel K 15m	Effervescent	More than 12hrs
14.	Metoclopramide Hydrochloride [58]	HPMC, Methyl cellulose, Carbopol 934 P, Sodium alginate, Guar gum	Effervescent	4-8hrs
15.	Indomethacin [59]	HPMC 5cps	Effervescent	12hrs
16.	Felodipine [60]	Ethylcellulose HPMC (K4M) (K15M) Carbopol 934 P	Effervescent	24hrs
17.	Metformin [61]	HPMC K4M Ethyl cellulose	Effervescent	8-10 hrs
18.	Procynanidins [62]	Chitosan	Effervescent	50-60 mins
19.	Clarithromycin [63]	HPMC K4M	Non- Effervescent	12 hrs
20.	Acyclovir [64]	HPMC K4M Carbopol 934 & PVP	Effervescent	14.4 hrs
21.	Diltiazem [65]	Sodium Alginate Beads	Effervescent	Less than 12 hrs
22.	Ciprofloxacin [66]	Ethylcellulose HPMC (K100 M) (K15 M)	Effervescent	4-7hrs
23.	Propranolol [67]	Polyvinyl acetate	Non- Effervescent	12hrs
24.	Itraconazole [68]	chitosan	Non- Effervescent	12hrs
25.	Norfloxacin hydrochloride [69]	Eudragit ^{R} L100 Eudragit ^{R} RS100	Effervescent	8.5 hrs
26.	Nifedipine [70]	Ethylcellulose	Effervescent	12hrs
27.	Piretanide [71]	HPMC [K4M] [K15M] [K100M]	Effervescent	10hrs
28.	Levodopa [72]	Gelatin Ethylcellulose Carbidopa L-Polylactic acid Eudragit S 100	Effervescent	More than 12 hrs
29.	Riboflavin [73]	Eudragit L & S Plasticized with triethyl citrate	Effervescent	Less than 48 hrs
30.	Anthocyanin [74]	Calcium alginate Eudragit RS 30 D Chitosan	Effervescent	3-6 hrs
31.	Ketoprofen [76]	Eudragit S 100 Eudragit RL 100	Effervescent	12hrs

32.	Fluconazole [77]	Carbopol 934	Effervescent	1-2hrs
33.	Ketoconazole [78]	HPC Carbopol 934 & 940 Xanthan gum	Effervescent	2hrs
34.	Rantidine [79]	Poly acrylate HPMC Chitosan gel	Effervescent	More than 12 hrs

Excipients Incorporated in Different Floating Dosage Form: [80]

- **Effervescent Agents:** E.g. citric acid, tartaric acid, sodium bicarbonate, Di-SGC (Disodium glycine carbonate), CG (Citroglycine).
- **Release rate Retardants:** Talc, Dicalcium phosphate, Magnesium stearates are used for retarding the release rate.
- **Inert Fatty Materials:** E.g. Long chain fatty alcohols, Beeswax, Fatty acids, Gelucires 39/01 ,44/14 and 43/01
- **Release rate Accelerants**: E.g. Mannitol, lactose, etc.
- **Hydrocolloids:** E.g. Acacia, β-cyclodextrin, Gelatin, Alginates, Pectin, HPMC, carbopol etc.
- **Buoyancy increasing Agents:** E.g. Ethyl Cellulose and Polypropylene Foam Powder (Accurel MP 1000).

Methods of Developing Floating Drug Delivery System: [81] [82] [83] [84]

(1)Direct compression technique:

It means compressing tablets directly from powder content without altering the substance's physical structure itself. Dicalcium trihydrate phosphate, tricalcium phosphate, etc. are the most widely used carriers.

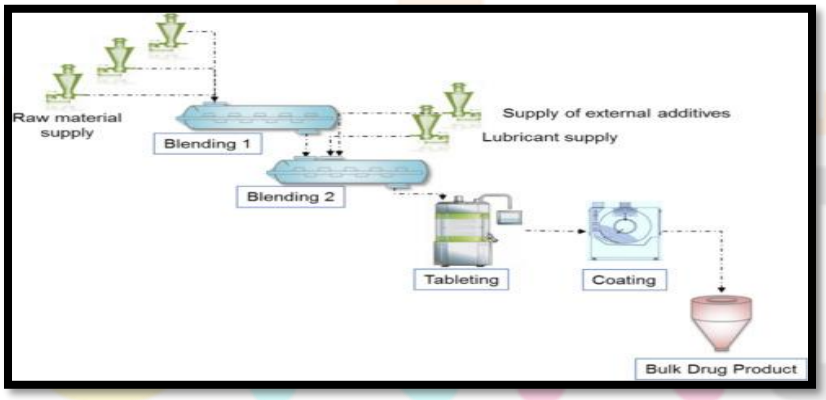

FIG 8: Direct compression technique [85]

(2) Effervescent Technique:

An effervescent reaction between organic acid (citric acid) and bicarbonate salts will fill the floating chamber of the drug delivery system with inert gas (CO^2). Effervescent tablets were designed to produce solutions that release carbon dioxide simultaneously. Usually, these tablets are prepared by compressing the active ingredients with mixture of sodium bicarbonate and organic acids such as citric and tartaric acid.

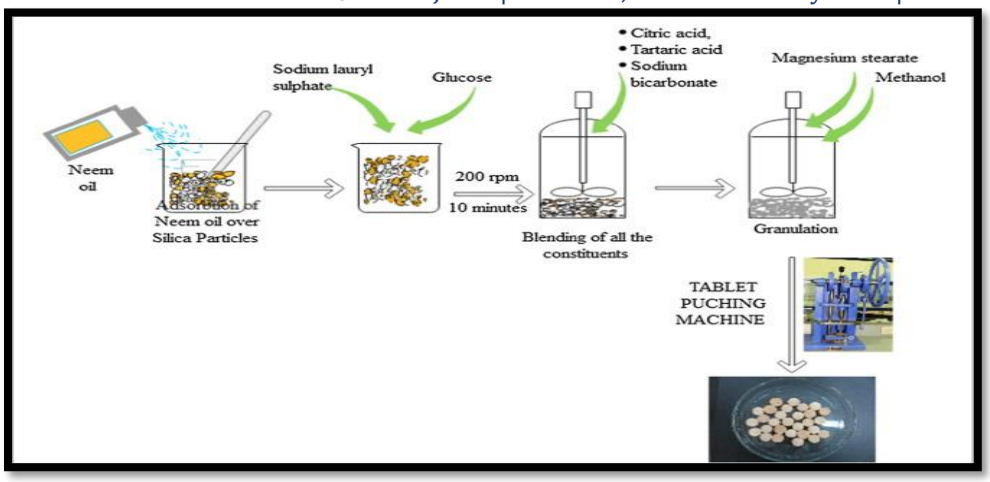

Figure 9 : Effervacent technique[86]

(3) Wet granulation technique:

Wet granulation involves the massing of a mix of dry primary powder particles using a granulating fluid. The fluid contains a solvent which can be removed by drying, and should be non-toxic. Typical solvents include water, ethanol and isopropanol and methylene chloride either alone or in combination. It involves wet powder massaging, milling or drying. Wet granulation shapes the granules by binding the powders together with an adhesive rather than compacting them.

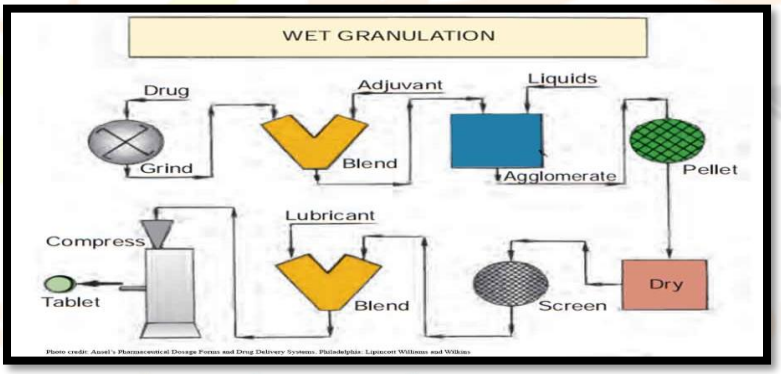

Figure 10: Wet granulation technique [87]

(4)Ionotropic Gelation Technique:

The ionic gelation technique is a chemical method to synthesize microparticles or Nano particles (NP) based on electrostatic interactions between ions with different charges that was discovered by Calvo et al. (1997). This technique requires polymeric, usually insoluble calcium salt (CS) and alginate. Gelation of anionic polysaccharide sodium alginate, the primary polymer of natural origin, was accomplished with opposite charged calcium ions (counter-ions) with the objective of forming instantaneous micro particles.

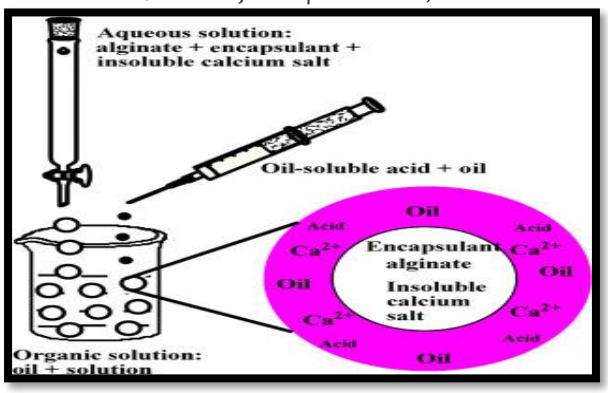

Figure 11: Ionotropic Gelatin Technique [88]

(5)Solvent evaporation technique:

Solvent evaporation technique is a flexible method of particle preparation, in which various macromolecules and drugs may be employed. Parameters of emulsion obtained as first step of particle preparation are crucial in terms of particle size, drug loading, and morphology. Continuous phase ability is inadequate to remove the entire amount of liquid dispersal solvent. Solvent evaporates from the dispersal surface to receive hardened microspheres.

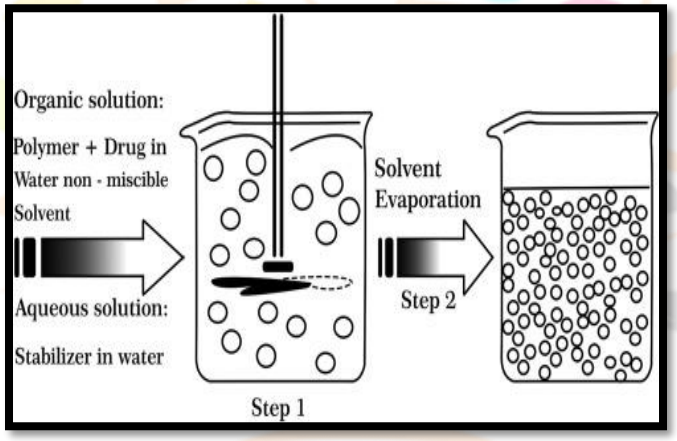

Figure 12: Solvent evaporation technique [89]

(6)Spray Drying Technique:

Spray drying process involves pumping the powder/solvent slurry through a nozzle to aerate and create a spray of the slurry in a counter or concurrent flow of hot gases, such that droplets of the slurry are dried in flight before falling to the bottom of the vessel. It is critical to maintain slurry uniformity from the time slurry is discharged from the mill to the time it is actually sprayed. This is done by maintaining the slurry in a state of constant agitation in a feed tank prior to spraying. Often wax or other additives may be added to the slurry prior to spraying, thus slurry in the feed tank must be kept in constant agitation to mix the ingredients and avoid any sedimentation or separation of different ingredients of the powder

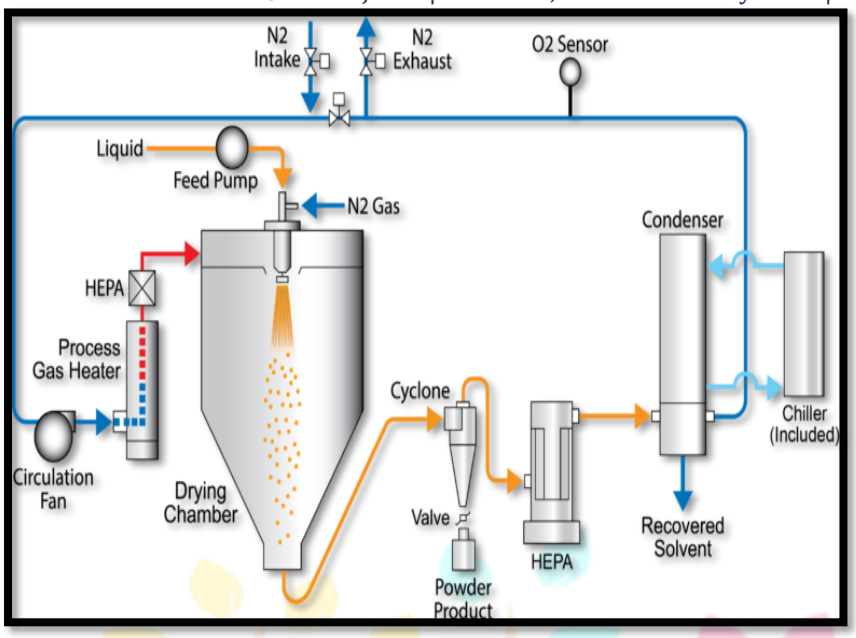

Figure 13: Spray drying technique [90]

(7)Melt Solidification Technique:

Melt solidification technique is defined as a process where there is no relative motion between adjacent polymer layers, such as in the case of extrudate cooling, and flow solidification where the melt solidifies during shear flow in the filling stage in injection molding. This method involves emulsifying the molten mass in the aqueous phase followed by cooling it to solidify. Lipids, waxes, polyethylene glycol, etc. are the carriers used for this technique.

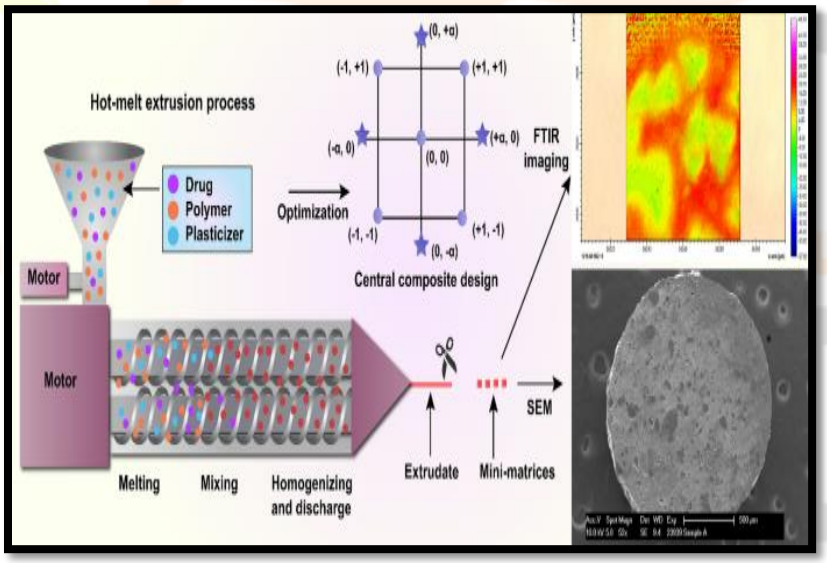

Figure 14: Melt solidification technique [91]

(8)Melt Granulation Technique:

Melt granulation or thermoplastic granulation is a technique that facilitates the agglomeration of powder particles using meltable binders, which melts or softens at relatively low temperature (50–90 °C). Fig 15 represents the schematic diagram of melt granulation. Cooling of the agglomerated powder and the consequent solidification of the molten or soften binder complete the granulation process. Low melting binders can be added to the granulation process either in the form of solid particles that melt during the process (melt-in procedure or in situ melt granulation) or in the form of molten liquid, optionally containing the dispersed drug (spray-on or pump-on procedure), which

displays a variety of options to design final granular properties. More specifically, the melt-in procedure of melt granulation process includes heating a mixture of drug, binder and other Excipients to a temperature within or above the melting range of the binder. On the contrary, the spray-on procedure encompasses spraying of a molten binder, optionally containing the drug, onto the heated powders.

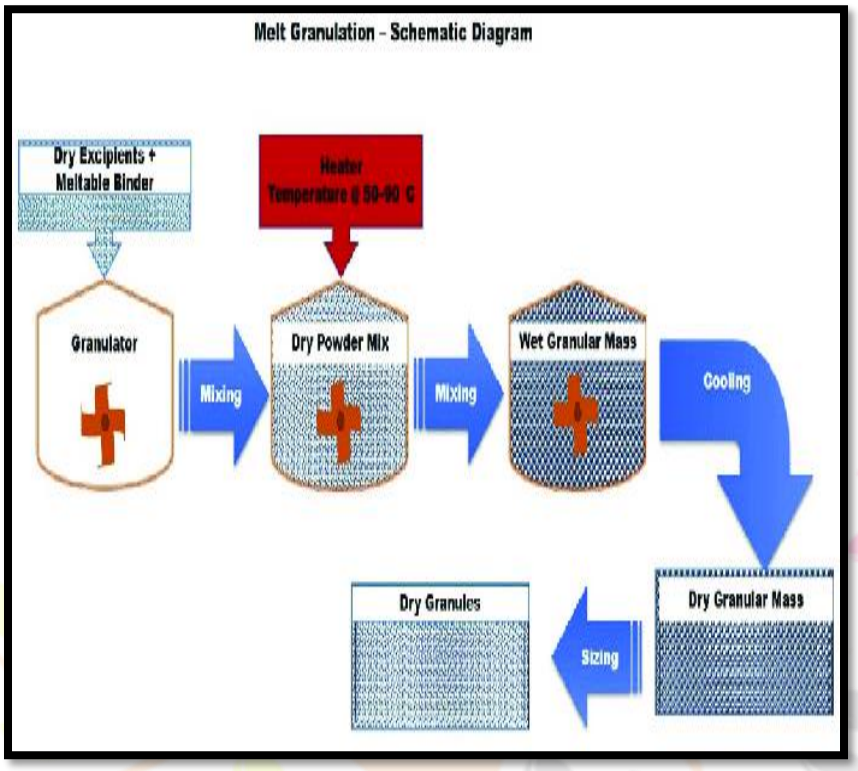

Figure 15: Melt granulation technique [92]

NOVEL METHODOLOGIES ADOPTED IN FDDS

1. Oleotec™ and Soctec™ :[93]

Oleotec™ and Soctec™ gastro retentive capsule technology are innovated by Skyepharma Company. For Drugs having high therapeutic doses, Oleotac ™ technique is designed but it is not suitable for the conventional dosage form. Drugs that show effect primarily in the proximal part of the gastro intestinal tract are developed by this technique. Oleotec system is basically a gel incorporated in the form of stick pack that forms a continuous layer at walls of the stomach. Soctec ™ system is designed for the drugs that should be administered as controlled release and should be absorbed in the proximal part of intestine for increasing the bioavailability of drug. Soctec is an elongated capsule fill with drug. It can be used with a range of drugs that have a short absorption window and are preferably absorbed in the proximal intestine fragment. It can also improve the bioavailability of drugs that are degraded by the basic pH of the distal part of GIT.

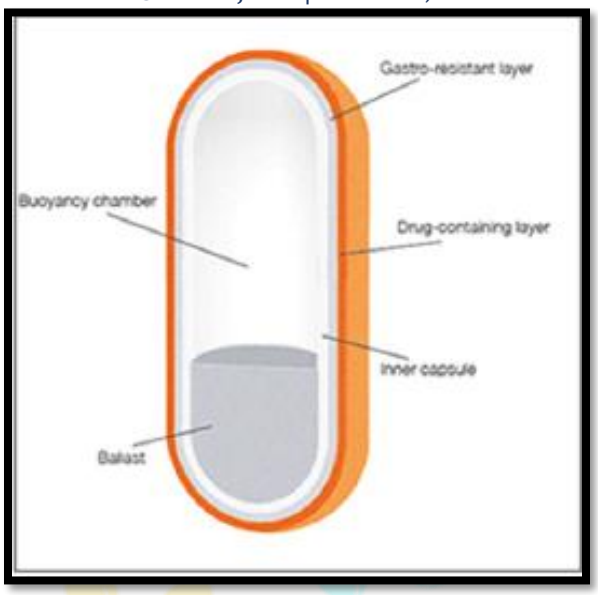

Figure 16: Soctec ™ Gastro- retentive Elongated Capsule

2. Accordion Pill™ Technology: [93]

This is a versatile gastro adhesive formulation composed of the biodegradable polymers. It is a multi-layer, planar structure, folded to an accordion shape into regular standard size capsule. When capsule reaches to the stomach, it dissolves; the folded pill unfolds and is sustained in the stomach last up to 12 hours. During it is in the stomach, the pill releases the drug in a controlled manner towards the proximal part of the GI tract which gives prolonged and continuous absorption phase of the drug in the upper part of the GI tract, resulting in increased efficacy and safety profiling, as well as reducing frequency dosing. The drug release mechanism is not dependent on the Accordion pill™ retention mechanism. After the Accordion Pill™ is expelled from the stomach; it is get degraded in the intestinal media. Drugs which are belonging to the BCS Class II and BCS Class IV are more preferable for this system.

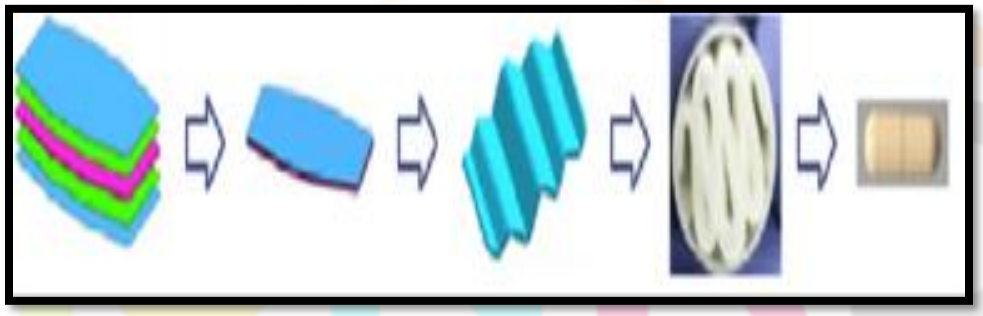

Figure 17: Accordion Pill™

3. Gastro Retentive Innovative Device (GRID): [93]

Gastro Retentive Innovative Device (GRID) is an ideal once-a- day system for drugs that are otherwise absorbed only in stomach or small intestine. GRID is designed so that drug is retained in the stomach for over an eight-hour span. Longer retention in stomach improves the drug absorption. The tablet offers a combination of instant and sustained drug release profiles, and being once a day improves patient compliance. This innovative system is a dosage form with specialized multiple coatings. On ingestion of the dosage form along with food, it floats instantaneously on the gastric contents. GRID's coatings are activated by gastrointestinal fluid, eventually leading to swelling, to about eight

to eleven times its initial volume. Plasma concentrations for medicines are thus maintained in the therapeutic range for a prolonged period; hence this dosage form can be used as a "Once-a- day" system. Specific release profiles for drugs can be tailored to achieve combination of immediate and slow release using this innovative dosage form. Retention of the dosage form close to its site of absorption may help in reducing the dose and thus the side effects.

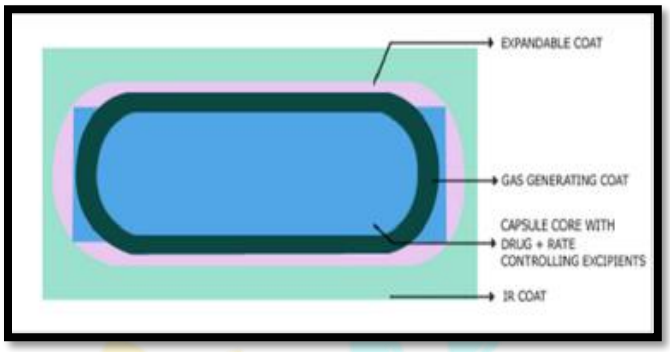

Figure 18: GRID Device

4. Multiple Polymers Hydrophilic Matrix Technology: [93]

Multiple polymer hydrophilic matrix technology is a sustained gastro drug delivery system. Cetapin XR is a formulation of this system patented by Sanofi which contain Metformin XR as a drug, to achieve extended release of Metformin hydrochloride. The polymers are made by combining non-ionic and ionic hydrophilic polymers. The drug release from the matrix pore occurs through a process of dissolution of the drug and undergoing diffusion through the gel matrix in a sustained manner. This technology gives consistent and reproducible results with good optimal absorption, minimum irritation, increased plasma drug levels and good bioavailability.

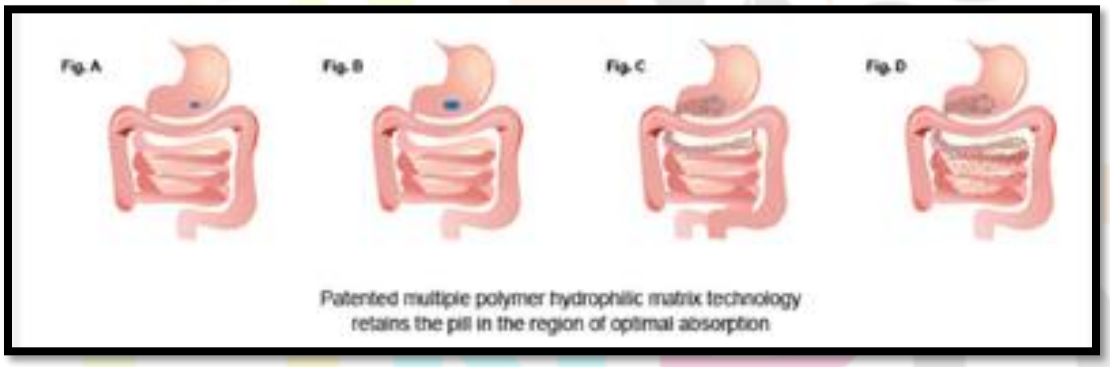

Figure 19: Multiple polymers Hydrophilic Matrix Technology

5. Gastrointestinal Permeation Enhancement Technology: [93]

Gastrointestinal Permeation Enhancement Technology (GIPET) is developed by Merrion Pharmaceutical's and it is unique approach which allows drugs that now can only be injected by parenterally (injectable). For to converted into oral solid forms e.g. tablet/capsule, as well as enhance the absorption of oral drugs. Gastrointestinal Permeation Enhancement Technology uses selectively formulated oral formulations absorption enhancers which activate micelle formation undergoing transport of drug and increasing absorption with good reproducibility and a strong safety profile.

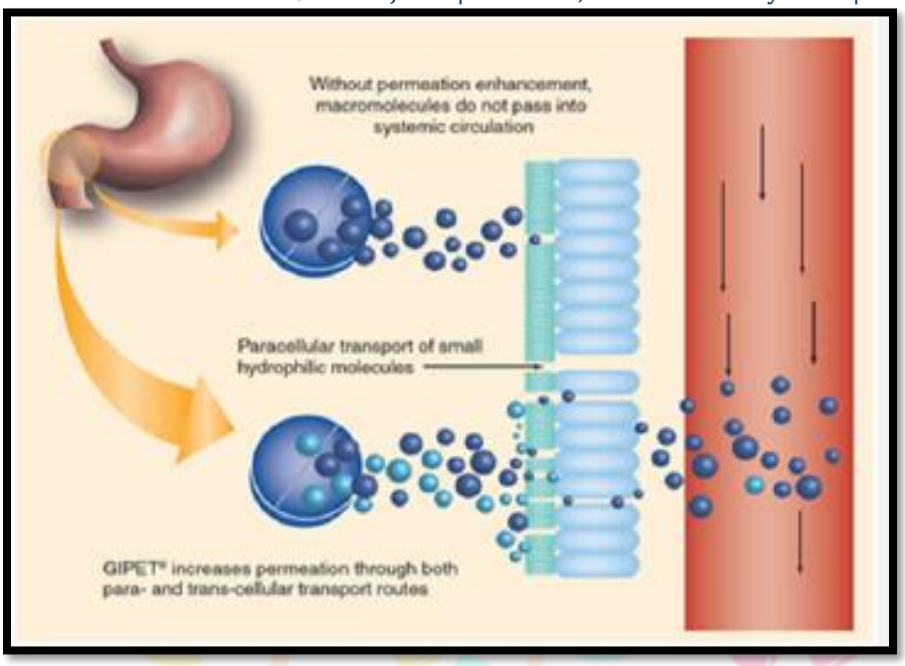

Figure 20: GIPET Technology

6. Aciform® technology: [93]

Aciform® is formulated patented by Depomed's. It is a polymer-based technology formulated to optimize drug delivery in GIT. This technology permit targeted and controlled delivery of drug to the proximal (upper) GIT which is the preferable absorption site for many oral drugs. In particular, for drugs that are absorbed in the upper GI region this technology is an effective delivery solution. It is also valuable for drugs insoluble in water, irritating for mucosa of the small intestines or not safe in the distal GIT region and it is more effective when plasma drug levels have less fluctuation.

7. Micropump technology [93]

Flamel's Micropump® platform permits either extended, or both delayed and extended, delivery of small molecule drugs via the oral route. Micropump consists of a multiple-particulate system containing 5,000 to 10,000 microparticles per capsule or tablet. The 200-500 microns diameter-sized microparticles release the drug at an adjustable rate and over an extended period of time. Micropump's key attributes includes extended release in the GI tract allowing mean plasma residence times to be extended for up to 24 hours, potentially improved efficacy (by extending therapeutic coverage), potentially reduced toxicity and/or side effects (by reducing Cmax or peak drug concentration in the plasma, or by reducing intra- and interpatient variability), improved patient compliance (by reducing frequency of administration), applicable to poorly soluble (<0.01mg/L) as well as highly soluble (>500g/L) and to low dose (e.g. 4mg) or high dose (e.g. 1,000mg) drugs, excellent mouth feel, taste masking properties.

8. Gastro Dose technology [93]

Gastro dose is retained in the stomach for extended periods of time used for the treatment of disorders of the stomach or upper gastrointestinal tract. It is also suited for drugs that are readily absorbed into the circulation from the stomach or upper small intestine. For instance, Alza Corporation has developed a gastro-retentive platform for the OROS™

system, which showed prolonged gastric residence time in a dog model as the product remained in the canine stomach at 12 hours post dose and was frequently present at 24 hours. In humans, in the fasted state, the average gastric residence time for the same system was 33 minutes. DepoMed has developed technology that consists of a swellable tablet. After ingestion of the tablet, it swells and achieves sufficient size to resist gastric emptying, while simultaneously providing controlled release of the drug. Two of the products that DepoMed is developing include Metformin GR™ and Ciprofloxacin GR™.

Evaluation of floating drug delivery system [94] [95] [96] [97]

❖ **Shape of tablets**

Compressed tablets designed for FDDS are examined under the magnifying lens for the determination of its shape consistency.

❖ **Tablet dimensions**

As per official compendia, the thickness and diameter of tablets in FDDS form are measured using an Automated calibrated Vernier calipers same with that of conventional tablets. six tablets of each formulation are picked randomly, and thickness is measured individually.

❖ **Friability test**

Friability testing is a laboratory technique used by the pharmaceutical industry to test the durability of tablets during transit. This testing involves repeatedly dropping a sample of tablets over a fixed time, using a rotating wheel with a baffle.

❖ **Hardness of the tablet**

Randomly sampled twenty tablets in each batch of formulations should be used for the determination of hardness with the help of Monsanto type hardness tester.

❖ **Weight variation**

Twenty tablets selected at random are weighed accurately, and the average weight of the tablet is calculated. Then the deviation of individual weight from the average weight is calculated**.**

Weight Variation = (Iw -Aw)/Aw x 100%

where,

Iw = Individual weight of tablet;

Aw = Average weight of tablet

❖ **Thickness of the tablet**

The individual crown to crown thickness of ten tablets is determined using slide calipers for each batch.

❖ **Measurement of the density of the formulation**

The apparent densities of the tablets are calculated from their volumes and masses in triplicate. The volume V of the cylindrical tablets are calculated from their height h and radius r (both determined with a micrometer gauge) using the mathematical equation for a cylinder ($V = A \times r2 \times h$).

❖ **Drug content in tablets**

Ten tablets from each batch are selected randomly and transferred to a 100 ml volumetric flask filled up with 0.1(N) HCl. Stir and Keep it aside for 2 h then take 1 ml from the volumetric flask and transfer it to the test tube. Samples are then filtered, suitably diluted and analyzed spectrophotometrically at a suitable wavelength.

❖ **In vitro dissolution study**

USP Apparatus II is the most commonly used dissolution apparatus for solid oral dosage forms and are versatile in enabling the development of many types of dissolution methods. The paddle apparatus (USP Apparatus II): It is used for capsules or tablets, suppositories, floating dosage forms and a delayed release. This apparatus is specially made and it comes with a coated paddle that reduces the disturbance from the stirring. Apparently, it has a blade that comes in contact with the bottom of the shaft.

❖ **Buoyancy/Floating test**

The time between introduction of the dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant are measured. The time taken for the dosage form to emerge on the surface of a medium called floating lag time (FLT) or buoyancy lag time (BLT) and total duration of time by which dosage form remain buoyant is called total floating time (TFT).

❖ **Swelling study**

The swelling behavior of a dosage form is measured by studying its weight gain or water uptake. The dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake can be measured in terms of percent weight gain, as given by the equation.

Where, $WU = (Wt - Wo) \times 100 / Wo$

WU = Water uptake

Wt = Weight of dosage form at time t

Wo = Initial weight of dosage form.

Table 3: List of FDDS drugs commercially available in market [98]

S.NO	Brand Name	Active Ingredients	Dosage form	Manufacturer
1.	Zanocin OD	Ofloxacin	Tablets	Ranbaxy , India
2.	Riomet OD	Metformin hydrocholride	Tablets	Ranbaxy , India
3.	Prazopress XL	Prazosin hydrochloride	Tablets	Sun pharma
4.	Metformin-HCl LP	Metformin hydrochloride	Tablets	Galenix ,France
5.	Cafeclor LP	Cefaclor	Tablets	Galenix , France
6.	Tramadol LP	Tramadol	Tablets	Galenix ,France
7.	Modopar HBS	Benserazide,Levodopa	Tablets	Roche products,USA
8.	Inon Ace tabs	Simethicone	Tablets	Sato pharm , India
9.	Gabapentin GR	Gabapentin	Tablets	Depomed ,USA
10.	ProQuin XR	Ciprofloxacin	Tablets	Depomed ,USA

11.	Glumetza	Metformin HCl	Tablets	Depomed ,USA
12.	Cipro XR	Ciprofloxacin	Tablets	Bayer ,USA
13.	Metformin GR	Metformin HCl	Tablets	Depomed,USA
14.	Baclofen GRS	Baclofen	capsule	Sun pharma, India
15.	Cytotec	Misoprostol	Capsule	Pharmacia ,USA
16.	Valrelease	Diazepam	Capsule	Hoffmann-LaRoche USA
17.	Cifran OD	Ciprofloxacin	Capsule	Ranbaxy ,India
18.	Coreg CR	Carvedilol	Capsule	Glaxosmith kline
19.	Gaviscon	Aluminum Hydroxide, Magnesium carbonate	Liquid suspension	Glaxo smith kline ,India
20.	Topalkan	Aluminium hydroxide Magnesium carbonate	Liquid suspension	Pierre fabre drugs, India
21.	conviron	Ferrous sulphate, folic acid	Colloidal soluntion	Ranbaxy ,India

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