1 Introduction

1.1 Introduction to drug delivery

Historically, oral drug administration has been the predominant route for drug delivery due to the ease of administration, patient convenience and flexibility in formulations. However, it is a well accepted fact today that drug absorption throughout the GI tract is not uniform. Using currently utilized release technology, oral drug delivery for 12 or even 24 hr is possible for many drugs that are absorbed uniformly from GI tract. Nevertheless this approach is not suitable for a variety of important drugs characterized by narrow absorption window in the upper part of GI tract i.e. stomach and small intestine.\textsuperscript{1,2} The design of oral controlled drug delivery systems should be primarily aimed to achieve the more predictability and reproducibility to control the drug release, drug concentration in the target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose.\textsuperscript{3}

The controlled release systems for oral use are mostly solid and based on dissolution or diffusion or a combination of both the mechanisms in the control of release rate of drug. Depending upon the manner of drug release, these are classified as:

A. \textbf{Continuous release system:} These systems release the drug for a prolonged period of time along the entire length of Gastro Intestinal Tract (GIT) with normal transit of the dosage form. The various systems under this category are:

a) Dissolution controlled release systems

b) Diffusion controlled release systems

c) Dissolution and diffusion controlled release systems

d) Ion-Exchange resins – drug complexes

e) Slow dissolving salts and complexes

f) pH–dependent formulations

g) Osmotic pressure controlled systems

h) Hydrodynamic pressure controlled systems

B. \textbf{Delayed transit and continuous release system:} These systems are designed to prolong their residence in the GIT along with their release. Often, the dosage is fabricated to retain in the stomach and hence the drug present therein should be stable at gastric pH. Systems included in this category are:
a) Altered density systems

b) Mucoadhesive systems

c) Size-based systems

C. Delayed release systems: The design of such systems involve release of drug only at a specific site in the GIT. The drugs contained in such system have following category:

a) Destroyed in the stomach or by intestinal enzymes.

b) Known to cause gastric distress.

c) Absorbed from a specific intestinal site, or

d) Meant to exert local effect at a specific GI site.

The two types of delayed release systems are:

a) Intestinal release systems

b) Colonic release systems.

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available in the market are oral drug delivery systems. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate. Controlled-release drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time period, enhancement of activity of duration for short half-life drugs, elimination of side effects, reducing frequency of dosing and wastage of drugs, optimized therapy and better patient compliances.

The successful development of oral controlled drug delivery systems requires an understanding of the three aspects of the system, namely.

a) The physiochemical characteristics of the drug.

b) Anatomy and physiology of GIT and

c) Characteristics of dosage forms.
Good fundamental understanding of the anatomic and physiological characteristics of the human GIT is required to modulate the gastrointestinal transit time of a drug through Floating Drug Delivery System (FDDS) for maximal gastrointestinal absorption of drugs and site-specific delivery.

1.1.1 Stomach anatomy
The main function of the stomach is to process and transport food. It serves as a short-term storage reservoir, allowing a rather large meal to be consumed quickly. Substantial enzymatic digestion is initiated in stomach, particularly of proteins. Vigorous contractions of gastric smooth muscle mix and grind food stuffs with gastric secretions, resulting in liquefaction of food. As food is liquefied in the stomach, it is slowly released into the small intestine for further processing. Various approaches have been worked on to improve the retention of an oral dosage form in the stomach,

a) Floating system expanding system.

b) Bioadhesive system.

c) Modified shape system.

d) High-density system.

Anatomically the stomach is divided into 3 regions: Fundus, body and antrum (Pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions.
Figure 1.2: Gastro retentive drug delivery system to stomach

It has been reported that the mean value of pH in fasted healthy subjects is 1.1± 0.15. But when food comes into the stomach, the pH may rise to levels in the 3.0 to 4.0 level due to the buffering capacity of proteins. However, in fasted state, basal gastric secretion in women is slightly lower than that of men.

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the two states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hr. This is called the interdigestive myoelectric cycle or Migrating Myoelectric Cycle (MMC), which is further divided into following 4 phases.

Figure 1.3: Motility patterns of the GIT in fasted state

1. Phase I (Basal phase) lasts from 30 to 60 min with rare contractions.
2. Phase II (Preburst phase) lasts for 20 to 40 min with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 10 to 20 min. 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 min and occurs between phases III and I of two 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. Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically two complications that of short gastric residence time and unpredictable gastric emptying rate.

1.1.2 Factors affecting gastric retention

The Gastric Retention Time (GRT) of dosage form is controlled by several factors that affect their efficacy as a gastro retentive system.

a) **Density** – GRT is a function of dosage form buoyancy that is dependent on the density.

b) **Size** – Dosage form units with a diameter of more than 9.5 mm are reported to have an increased GRT.

c) **Shape of dosage form** – Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT. 90% to 100% retention at 24 hr compared with other shapes.

d) **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.

e) **Fed or unfed state** – Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hr. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.
f) **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.

g) **Caloric content** – GRT can be increased by four to 10 hr with a meal that is high in proteins and fats.

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

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

j) **Age** – Elderly people, especially those over 70, has a significantly longer GRT.

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

l) **Concomitant drug administration** – Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride.

m) **Biological factors** – Diabetes and Crohn’s disease.

1.1.3 **Approaches to gastric retention**

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

![Different gastric retention systems](image-url)
a) Floating systems

Floating Drug Delivery Systems (FDDS) 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, effervescent and non-effervescent systems.

b) Bio/muco-adhesive systems

Bio/Muco-adhesive systems are those which bind to the gastric epithelial surface or mucin and serve as a potential means of extending the GRT of drug delivery system in the stomach. 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:
   i. Hydration-mediated adhesion.
   ii. Bonding-mediated adhesion.
   iii. 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 longer. These systems may be named as “plug type system” since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state. Such polymeric matrices remain in the gastric cavity for several hr 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 and maintains 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 systems can be retained in the lower part of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert materials such as barium sulphate, zinc oxide, titanium dioxide, and iron powder.

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 $C_{10}$-$C_{14}$.

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.

1.1.4 Types of floating drug delivery system

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

a) Noneffervescent systems

b) Effervescent systems or Gas generating systems
A. Single unit

Single unit dosage forms are easiest to develop but suffers from the risk of losing their effects too early due to their all-or-none emptying from the stomach and, thus they may cause high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the gastrointestinal tract.24

a) Noneffervescent systems

One or more gel forming, highly swellable, cellulosic hydrocolloids (e.g. hydroxyl ethyl cellulose, hydroxyl propyl cellulose, hydroxypropyl methyl cellulose [HPMC] and sodium carboxy methyl cellulose), polysaccharides, or matrix forming polymers(e.g., polycarbophil, polyacrylates, and polystyrene) are incorporated in high level (20-75% w/w) to tablets or capsules.25 For the preparation of these types of systems, the drug and the gel forming hydrocolloid are mixed thoroughly. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

b) Effervescent systems or gas generating systems

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO₂ is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1.

B. Multiple units

Single unit formulations are associated with problems such as sticking together or being obstructed in gastrointestinal tract, which may have a potential danger of producing irritation. Multiple unit systems avoid the ‘all-or-none’ gastric emptying nature of single unit systems. It reduces the inter subject variability in absorption and the probability for dose dumping is lower.26

a) Noneffervescent systems

A little or no much report was found in the Lature on noneffervescent multiple unit systems, as compared to the effervescent systems. However, few workers have
reported the possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion process is reported. A mixture of drug, chitosan and acetic acid is extruded through a needle, and the extrudate is cut and dried. Chitosan hydrates float in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio.

b) Effervescent systems
A multiple unit system comprises of calcium alginate core and calcium alginate/PVA membrane, both separated by an air compartment was prepared. 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 technique is also reported for the preparation of floating calcium alginate beads. Sodium alginate solution is added drop wise into the aqueous solution of calcium chloride, causing the instant gelation of the droplet surface, due to the formation of calcium alginate. The obtained beads are freeze-dried resulting in a porous structure, which aid in floating. The authors studied the behavior of radio labeled floating beads and compared with nonfloating beads in human volunteers using gamma scintigraphy. Prolonged gastric residence time of more than 5.5 hr was observed for floating beads. The nonfloating beads had a shorter residence time with a mean onset emptying time of 1 h.27

c) Floating microspheres
A controlled release system designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of floating microspheres. Techniques involved in their preparation include simple solvent evaporation, and solvent diffusion and evaporation. The drug release and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers, such as polycarbonate, eudragit S and cellulose acetate, are used in the preparation of hollow microspheres, and the drug release can be modified by optimizing the amount of polymer and the polymer plasticizer ratio.28
C. Raft forming systems
The basic mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. The raft floats because of the buoyancy created by the formation of CO₂ and act as a barrier to prevent the reflux of gastric contents like hcl and enzymes into the esophagus. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of to make the system less dense and float on the gastric fluids.²⁹

1.1.5 Evaluation of floating drug delivery system
Various parameters that need to be evaluated in gastro-retentive formulations include floating duration, dissolution profiles, specific gravity, content uniformity, hardness, and friability in case of solid dosage forms. In the case of multiparticulate drug delivery systems, Differential Scanning Calorimetry (DSC), particle size analysis, flow properties, surface morphology, and mechanical properties are also performed.

a) **Buoyancy lag time** - It is determined in order to assess the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test.

b) **Floating time** - Test for buoyancy is usually performed in Simulated Gastric Fluid (SGF) maintained at 37°C. The time for which the dosage form continuously floats on the dissolution media is termed as floating time.³⁰

c) **Specific gravity / density** - Density can be determined by the displacement method using Benzene as displacement medium³¹.

d) **Swelling index** - After immersion of swelling dosage form into SGF at 37°C, dosage form is removed out at regular interval and dimensional changes are measured in terms of increase in tablet thickness / diameter with time.

e) **Gamma scientigraphy** - Gamma emitting radioisotopes compounded into CR-DFs has become the start-of-art for evaluation of gastroretentive formulation in healthy volunteers. A small amount of a stable isotope e.g. sm, is compounded into DF during its preparation. The main drawback of gamma scientigraphy is the associated ionizing radiation for the patient, the limited topographic information, low resolution inherent to the technique and the complicated and expensive preparation of radiopharmaceuticals.

f) **Radiolog** - The method is the state of art in preclinical evaluation of gastroretentivity. Its major advantages as compared to gamma scientigraphy are
simplicity and cost. However the use of X-ray is been declined due to strict limitations, regarding to the amount of exposure and it’s often requirement in high quantity. A commonly used contrast agent is barium sulphate.\textsuperscript{52}

g) Gastroscopy - It comprise of per oral endoscopy, used with a fibereioptic and video system. It is suggested that gastroscopy may be used to inspect stay in stomach milieu of the FDDS. Alternatively FDDS may be drawn out of the stomach for more detailed evaluation.

h) Ultrasonography - Ultrasonic wave reflected substantially different acoustic impedances across interface enable the imaging of abdominal organs.\textsuperscript{33} Most DFs do not have sharp acoustic mismatches across their interface with the physiological milieu. Therefore, ultrasonogrpphy is not routinely used for the evaluation of the FDDS. The characterization included assessment of the intragastric location of the hydrogels, solvent penetration in to the gel and interactions between the gastric wall and FDDS during peristalsis.

i) Magnetic resonance imaging - In the last couple of years, MRI was shown to be valuable tool in gastrointestinal research for the analysis of gastric emptying, motility and intragastric distribution of micronutrients and drug model. The advantages of MRI include high soft tissue contrast, high temporal and spatial resolution, as well as the lack of the ionizing irradiation.\textsuperscript{34}

1.1.6 Advantages of gastroretentive drug delivery systems\textsuperscript{35}

I. Enhanced bioavailability

The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.

II. Enhanced first-pass biotransformation

In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes in a sustained manner, rather than by a bolus input.

III. Sustained drug delivery/reduced frequency of dosing

For drugs with relatively short biological half-life, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing
frequency. This feature is associated with improved patient compliance, and thereby improves therapy.

**IV. Targeted therapy for local ailments in the upper GIT**
The prolonged and sustained administration of the drug from GRDF to the stomach may be advantageous for local therapy in the stomach and small intestine. By this mode of administration, therapeutic drug concentrations may be attained locally while systemic concentrations, following drug absorption and distribution, are minimal.

**V. Reduced fluctuations of drug concentration**
Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

**VI. Improved selectivity in receptor activation**
Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

**VII. Reduced counter activity of the body**
In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

**VIII. Extended time over critical (effective) concentration**
For certain drugs that have non-concentration dependent pharmacodynamics, such as beta-lactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration. The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

**IX. Minimized adverse activity at the colon**
Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for beta-
lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism’s resistance.

X. Site specific drug delivery

A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper small intestine. Controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency.

1.1.7 Limitations/disadvantages of floating drug delivery system

a) These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently—coat, water.

b) Not suitable for drugs that have solubility or stability problem in GIT.

c) Drugs such as nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.

d) Drugs which are irritant to Gastric mucosa are also not desirable or suitable.

e) The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.

f) The dosage form should be administered with a full glass of water (200-250 mL).

g) These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract.

1.1.8 Application of floating drug delivery system

a) Recent study indicated that the administration of diltiazem floating tablets twice a day might be more effective compared to normal tablets in controlling the blood pressure of hypertensive patients.

b) Modapar® HBS containing L-dopa and benserazide, here the drug was absorbed over a period of 6-8 hr and maintained substantial plasma concentration for parkinsonian patients.

c) Cytotech® containing misoprostol, a synthetic prostaglandin –EL analogue, for prevention of gastric ulcer caused by non-steroidal anti-inflammatory drugs (NSAIDS). As it provides high concentration of drug within gastric mucosa, it is used to eradicate H. pylori (a causative organism for chronic gastritis and peptic ulcers).
d) 5-fluorouracil has been successfully evaluated in the patients with stomach neoplasm.

e) Developing HBS dosage form for tacrin provide better delivery systems and reduced its GI side effects.

f) Treatment of gastric and duodenal ulcer.

1.1.9 Future potential of floating drug delivery system

a) Floating dosage form offers various future potential as evident from several recent publications. The reduced fluctuations in the plasma level of drug results from delayed gastric emptying.

b) Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailability.

c) Buoyant delivery system considered as a beneficial strategy for the treatment of gastric and duodenal cancers.

d) The floating concept can also be utilized in the development of various anti-reflux formulations.

e) Developing a controlled release system for the drugs, which are potential to treat the Parkinson’s disease.

f) To explore the eradication of halico-bector pylori by using the narrow spectrum antibodies.

### Table 1.1: Marketed product of FDDS

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Brand name</th>
<th>Active ingredient</th>
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<tbody>
<tr>
<td>1</td>
<td>Madopar ®</td>
<td>L-DOPA and benserazide</td>
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<tr>
<td>2</td>
<td>Cifran OD ®</td>
<td>Ciprofloxacin</td>
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<td>3</td>
<td>Valrelease ®</td>
<td>Diazepam</td>
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<td>4</td>
<td>Topalkan ®</td>
<td>Aluminum -magnesium antacid</td>
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<tr>
<td>5</td>
<td>Almagate FlatCoat ®</td>
<td>Aluminum -magnesium antacid</td>
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<td>Liquid Gavison ®</td>
<td>Aluminium hydroxide,</td>
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<td>7</td>
<td>Conviron ®</td>
<td>Ferrous sulfate</td>
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<td>8</td>
<td>Cytotec®</td>
<td>Misoprostal</td>
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<td>Sr. no.</td>
<td>Dosage forms</td>
<td>Drugs</td>
</tr>
<tr>
<td>--------</td>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>1</td>
<td>Floating Tablets</td>
<td>Acetaminophen, acetylsalicylic acid, ampicillin, amoxicillin trihydrate, atenolol, captopril, cinnerzine, chlorpheniramine maleate, ciprofloxacin, diltiazem, fluorouracil, ilosorbide dinitrate, ilosorbide mononitrate, p-aminobenzoic acid (PABA), prednisolone, nimodipine, Sotalol, theophylline, verapamil</td>
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<td>Floating Capsules</td>
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<td>3</td>
<td>Floating Microspheres</td>
<td>Aspirin, griseofulvin, p-nitro aniline, ibuprofen, terfenadine, tranilast</td>
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<tr>
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<td>Floating Granules</td>
<td>Diclofenac sodium, indomethacin, prednisolone</td>
</tr>
<tr>
<td>5</td>
<td>Powders</td>
<td>Several basic drugs</td>
</tr>
<tr>
<td>6</td>
<td>Films</td>
<td>Cinnerzine</td>
</tr>
</tbody>
</table>

### 1.2 Introduction to immediate drug delivery

Oral route of drug administration is perhaps the most appealing route for the delivery of drugs. Amongst the various dosage forms administered orally, the tablet is one of the most preferred dosage forms because of its ease of manufacturing, convenience in administration, accurate dosing, stability compared with oral liquids, and because it is more tamperproof than capsules. The bioavailability of drug is dependent on in vivo disintegration, dissolution, and various physiological factors. In recent years, scientists have focused their attention on the formulation of quickly disintegrating tablets. The task of developing rapidly disintegrating tablets is accomplished by using a suitable diluent and superdisintegrants.

The gastrointestinal tract provides sufficient fluid to facilitate disintegration of the dosage form and dissolution of the drug. The large surface area of gastric mucosa favors the drug absorption. Banker and Anderson stated that at least 90% of all drugs used to produce systemic effect are administered orally. Rapidly disintegrating tablets have received much attention in recent years, as they are preferred by pediatric and geriatric patients. Moreover, the drug dissolution is facilitated by the tablets quick
disintegration. Bioavailability of a drug depends in absorption of the drug, which is affected by solubility of the drug in gastrointestinal fluid and permeability of the drug across gastrointestinal membrane. The drugs solubility mainly depends on physical-chemical characteristics of the drug. However, the rate of drug dissolution is greatly influenced by disintegration of the tablet.

The drug will dissolve at a slower rate from a nondisintegrating tablet due to exposure of limited surface area to the fluid. The disintegration test is an official test and hence a batch of tablet must meet the stated requirements of disintegration. Disintegrants, an important excipients of the tablet formulation, are always added to tablet to induce breakup of tablet when it comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which induce this process are known as disintegrant. The objectives behind addition of disintegrants are to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together in a tablet.

1.2.1 Introduction to superdisintegrant

A disintegrant is a substance in a tablet formulation that enables the tablet to break up into smaller fragments upon contact with gastrointestinal fluids. Such a rapid rupture of the tablet matrix increases the surface area of the tablet particles, thereby increasing the rate of absorption of the active ingredient and producing the desired therapeutic action. The disintegrants are substances or mixture of substances added the drug formulation that facilitate the breakup or disintegration of tablet or capsule content into smaller particles that dissolve more rapidly than in the absence of disintegrants.

Superdisintegrants are generally used at a low level in the solid dosage form, typically 1-10% by weight relative to the total weight of the dosage unit. Examples of superdisintegrants are cross carmelose, crosspovidone, sodium starch glycolate which represent example of a cross linked cellulose, cross linked polymer and a cross linked starch respectively. Tablet disintegration has received considerable attention as an essential step in obtaining fast drug release. The emphasis on the availability of drug highlights the importance of the relatively rapid disintegration of a tablet as a criterion for ensuring uninhibited drug dissolution behavior. Number of factors affects the disintegration behavior of tablets. The development of fast dissolving or disintegrating tablets provides an opportunity to take an account of tablet disintegrants. Recently new materials termed as superdisintegrant have been
developed to improve the disintegration processes. Selecting appropriate formulation excipients and manufacturing technology can obtain the design feature of fast disintegrating tablet. The disintegrants have the major function to oppose the efficiency of the tablet binder and the physical forces that act under compression to form the tablet. The stronger the binder, the more effective must be the disintegrating agents in order for the tablet to release its medication. Ideally, it should cause the tablet to disrupt, not only into the granules from which it was compressed, but also into powder particles from which the granulation was prepared.

1.2.2 Mechanism of tablet superdisintegrant\textsuperscript{45}

The tablet breaks to primary particles by one or more of the mechanisms listed below:

a) Capillary action
b) Swelling
c) Heat of wetting
d) Disintegrating particle/particle repulsive forces
e) Deformation
f) Release of gases
g) Enzymatic action

a) Capillary action

Disintegration by capillary action is always the first step\textsuperscript{46}. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drugs/excipients and on tableting conditions. For these, types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid are necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

b) Swelling

Perhaps, the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.
The superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

![Granules with superdisintegrants](image1) → ![Swelling of granules due to superdisintegrants in aqueous media](image2)

**Figure 1.5: Mechanism of superdisintegrant by swelling**

c) Because of heat of wetting (air expansion)
When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

d) Disintegrating particle/particle repulsive forces
Another mechanism of disintegration attempts to explain the swelling of tablet made with ‘non-swellable’ disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

e) Deformation
Hess had proved that during tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied.
f) Release of gases
Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

<table>
<thead>
<tr>
<th>Table 1.3: List of disintegrating enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enzymes</strong></td>
</tr>
<tr>
<td>Amylase</td>
</tr>
<tr>
<td>Protease</td>
</tr>
<tr>
<td>Cellulase</td>
</tr>
<tr>
<td>Invertase</td>
</tr>
</tbody>
</table>

**Deformation**

- Particle swell to precompression size and break up the matrix

**Repulsion**

- Water is drawn into the pores and particles repel each other because of the resulting electrical force

*Figure 1.6: Disintegration by deformation and repulsion*[^1]

[^1]: Image reference for Figure 1.6
g) Enzymatic reaction
Here, enzymes present in the body act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration.

1.2.3 Methods of addition of disintegrant
The method of addition of disintegrant is also a crucial part. Disintegrating agent can be added either prior to granulation (intragranular) or prior to compression (after granulation i.e. extragranular) or at the both processing steps. Extragranular fraction of disintegrant (usually, 50% of total disintegrant requires) facilitates breakup of tablets to granules and the intragranular addition of disintegrants produces further erosion of the granules to fine particles.

1.2.4 Factors affecting disintegration
a) Effect of fillers
The solubility and compression characteristics of fillers affect both rate and mechanism of disintegration of tablet. If soluble fillers are used then it may cause increase in viscosity of the penetrating fluid which tends to reduce effectiveness of strongly swelling disintegrating agents and as they are water soluble, they are likely to dissolve rather than disintegrate. Insoluble diluents produce rapid disintegration with adequate amount of disintegrants.
b) Effect of binder
As binding capacity of the binder increases, disintegrating time of tablet increases and this counteract the rapid disintegration. Even the concentration of the binder can also affect the disintegration time of tablet.
c) Effect of lubricants
Mostly lubricants are hydrophobic and they are usually used in smaller size than any other ingredient in the tablet formulation. When the mixture is mixed, lubricant particles may adhere to the surface of the other particles. This hydrophobic coating inhibits the wetting and consequently tablet disintegration.
Lubricant has a strong negative effect on the water uptake if tablet contains no disintegrants or even high concentration of slightly swelling disintegrants. On the contrary, the disintegration time is hardly affected if some strongly swelling disintegrants are present in the tablet.
d) Effect of surfactants

<table>
<thead>
<tr>
<th>Surfactants</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium lauryl sulfate</td>
<td>Good- various drugs, Poor- various drugs</td>
</tr>
<tr>
<td>Polysorbate 20</td>
<td>Good</td>
</tr>
<tr>
<td>Polysorbate 40 &amp; 60</td>
<td>Poor</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>Good</td>
</tr>
<tr>
<td>Tweens</td>
<td>Poor</td>
</tr>
<tr>
<td>Poly ethylene glycol</td>
<td>Poor</td>
</tr>
</tbody>
</table>

(Good – decrease in disintegration time, Poor – increase in disintegration time)

Sodium lauryl sulphate increased absorption of water by starch or had a variable effect on water penetration in tablets. Surfactants are only effective within certain concentration ranges. Surfactants are recommended to decrease the hydrophobicity of the drugs because the more hydrophobic the tablet the greater the disintegration time.

**1.3 Introduction to sustained release dosage forms**

Modified release dosage form is a general term used to describe the dosage forms having drug release features based on time, course and/or location and which are designed to accomplish therapeutic or convenience objectives not offered by conventional or immediate release forms. There are several terms which are used interchangeably with respect to modified release dosage forms, viz., controlled release, sustained release, prolonged release, extended release and other such dosage forms. Controlled release system differs from other systems which simply prolong the drug release and hence the plasma drug levels for an extended period of time. Controlled release systems are those which can provide some control, whether this is of a temporal or spatial nature, or both, of the drug release in the body. An ideal controlled release system aims at delivering the drug at a predetermined rate, locally or systemically, for a specified period of time.

**1.3.1 Repeat action versus sustained action drug therapy**

A repeat action tablet or hard gelatin capsule maybe distinguished from its sustained-released counterpart by the fact that the repeat-action product does not release the drug in a slow controlled manner, and consequently does not give a plasma
concentration-time curve which resembles that of a sustained release product. A repeat action tablet usually contains two doses of drug, the first being released immediately following peroral administration in order to provide a rapid onset of the therapeutic response. The release of the second dose is delayed, usually by means of an enteric coat. Consequently, when the enteric coat surrounding the second dose is breached by the intestinal fluids, the second dose is released immediately. Figure 1.1 shows that the plasma concentration-time curve obtained following the administration of one repeat-action preparation exhibits the peak and valley profile associated with the intermittent administration of conventional dosage forms. The primary advantage provided by a repeat action tablet over a conventional one is that two (or occasionally three) doses are administered without the need to take more than one tablet.

For developing matrix tablet, various materials like waxes, hydrophilic and hydrophobic polymers and gums have been employed in the formulation. Among these polymers, the use of hydrophilic matrices has been extremely popular in controlling the release of drug from solid dosage forms. Among the hydrophilic polymers, swellable and hydrophilic property of hydroxypropyl methylcellulose (HPMC) and polyoxyethylene (PEO) have been paid considerable attention for the preparation of matrix tablets as sustained release formulation of various drugs. Further, various research on HPMC has been studied and reported by several research groups.

1.3.2 Advantages of sustained release formulations

a) Reduction in dosing frequency
b) Reduced fluctuation in circulatory drug levels
c) Avoidances of night time dosing
d) Increased patient compliance
e) More uniform effect
f) Decreased side effects like reduced GI irritation
g) Effective utilization of drug

1.3.3 Disadvantages of sustained release formulations

a) High cost
b) Unpredictable or poor in-vivo in-vitro correlation
c) Dose dumping
d) Reduced potential for dosage adjustments
e) Increased first pass clearance and poor systemic availability in general
1.4 Introduction to dosage form

Tablets are solid preparations each containing a single dose of one or more active substances and usually obtained by compressing uniform volumes of particles. Tablets are intended for oral administration. Some are swallowed whole, some after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth where active substance is liberated.

The particles consist of one or more active substances with or without excipients such as diluents, binders, disintegrating agents, glidants, lubricants, substances capable of modifying the behavior of the preparation in the digestive tract, coloring matter authorized by the component authority and flavoring substances.\textsuperscript{51,52}

---

**Figure 1.7:** Plasma concentration-time curves obtained following peroral administration of repeat action dosage form containing two doses and sustained dosage form containing the same drug\textsuperscript{50}
<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Types</th>
<th>Classes of Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oral tablets for Ingestion</td>
<td>Compressed tablets or standard compressed tablets (CT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple compressed tablets (MCT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Layered tablets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Compression-coated tablets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Repeat action tablets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delayed-action and enteric coated tablets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sugar and chocolate coated tablets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Film coated tablets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chewable tablets</td>
</tr>
<tr>
<td>2</td>
<td>Tablets used in oral cavity</td>
<td>Buccal tablets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sublingual tablets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Troches and lozenges</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dental cones</td>
</tr>
<tr>
<td>3</td>
<td>Tablets administered by other routes</td>
<td>Implantation tablets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vaginal tablets</td>
</tr>
<tr>
<td>4</td>
<td>Tablets used to prepare solutions</td>
<td>Effervescent tablets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dispensing tablets (DT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypodermic tablets (HT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tablet triturates (TT)</td>
</tr>
</tbody>
</table>

1.4.1 Introduction to dual retard bi-layer tablet

Bi-layer tablets are tablets made by compressing several different granulations fed into a die in succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet presses can be set up for two or three layers. More are possible but the design becomes very special. Ideally, a slight compression of each layer and individual layer ejection permits weight checking for control purposes. Figure 1.5 show picture of bi-layer tablet. The layered tablet concept has been utilized to develop controlled-release formulations. Such a tablet is considered as a biphasic delivery system that is designed to release the
drug at two different rates and is usually composed of a fast-release layer combined with single or double sustained-release layers. Generally, conventional controlled-release dosage forms delay the release of drugs and do not provide a rapid onset of action after oral administration. Hence, the layered tablets offer a pharmacokinetic advantage over conventional controlled-release dosage forms as the drug is quickly released from the fast-release layer leading to rapid rise of drug plasma concentration followed by continuation of drug release from the sustained-release layer.

Figure 1.9: General concept of dual retards bi-layer tablets

This release pattern is required for successful treatment in many therapies, primarily when maximum relief needs to be achieved as soon as possible, and is followed by a sustained-release phase to avoid repeated drug administration. It is reported that the NSAIDs are suitable candidate drugs for this type of administration.\textsuperscript{53,54}

Figure 1.10: Drug release mechanism from bi-layer tablet
1.4.2 Advantages of bi-layer tablets

a) Incompatible substances can be separated by formulating them in separate layers as a two-layer tablet or separating the two layers by a third layer of an inert substance as a barrier between the two.

b) Two layer tablets may be designed for sustained release, one layer for immediate release of the drug and the second layer for extended release, thus maintaining a prolonged blood level.

c) Layers may be colored differently to identify the product.

![Figure 1.11: Compression cycle of dual retard bilayer tablet](image)

1.4.3 Steps of compression of bi-layer tablet

a) Filling of first layer.

b) Compression of first layer.

c) Ejection of upper punch.

d) Filling of second layer.

e) Compression of both layer together.

f) Ejection of bi-layer tablet.

1.5 Introduction to drugs

1.5.1 Introduction of salbutamol sulphate

**Generic name**

Salbutamol sulphate IP

**IUPAC name**

-[2-(tert-butylamino)-1-hydroxyethyl]-2-hydroxymethyl) phenol

**Empirical formula**

C$_{13}$H$_{21}$NO$_3$
Molecular weight
239.3107 gm/mol

Melting point
157-158°C

Structural formula

Solubility
Soluble in water, ethanol and most organic solvent.

Absorption
Readily absorbed from GIT.

Cmax
2.5 to 3 hrs.

Half Life
1.6 hr.

Total renal clearance
Excretion in urine about 24 hr.

Log P
1.44

pKa
10.3

Mechanism of action
Salbutamol is a moderately selective beta (2)-receptor agonist similar in structure to terbutaline, is widely used as a bronchodilator to manage asthma and other chronic obstructive airway diseases. It is believed that salbutamol increases cAMP production by activating adenylate cyclase, and the actions of salbutamol are mediated by cAMP. Increased intracellular cyclic AMP increases the activity of cAMP-dependent protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular calcium concentrations. A lowered intracellular calcium concentration leads to a
smooth muscle relaxation. Increased intracellular cyclic AMP concentrations also cause an inhibition of the release of mediators from mast cells in the airways.

1.5.2 Introduction of theophylline

**Generic name**
Theophylline IP

**IUPAC name**
1,3-dimethyl-7H-purine-2,6-dione

**Empirical formula**
C\(_7\)H\(_8\)N\(_4\)O\(_2\)

**Molecular weight**
180.1640

**Melting point**
272°C

**Structural formula:**

![Structural formula of theophylline]

**Absorption**
Rapidly and completely absorbed after oral administration

**C\(_{\text{max}}\)**
1-2 hr

**Half Life**
6 hr

**Total renal clearance**
15% excreted unchanged in urine

**Log P**
0.8

**pK\(_a\)**
8.81
Mechanism of action
Theophylline relaxes the smooth muscle of the bronchial airways and pulmonary blood vessels and reduces airway responsiveness to histamine, methacholine, adenosine, and allergen. Theophylline competitively inhibits type III and type IV phosphodiesterase (PDE), the enzyme responsible for breaking down cyclic AMP in smooth muscle cells, possibly resulting in bronchodilation. Theophylline also binds to the adenosine A2B receptor and blocks adenosine mediated bronchoconstriction.¹

1.5.3 Introduction of amlodipine besylate⁶⁵-⁶⁸
Generic name
Amlodipine besylate I.P.

Chemical name
3-Ethyl-5-methyl (±) - 2- [(2-aminoethoxy) methyl]- 4 - (2 chlorophenyl)-1, 4-di hydro -6 - methyl-3, 5-pyridine di-carboxylate, mono benzene sulfonate.

CAS number
88150-42-9

Empirical formula
C₂₀H₂₅CIN₂O₅•C₆H₆O₃S

Molecular weight
567.1 gm/mol

Appearance
White crystalline powder

Melting point
195-204 °C

Solubility
It is slightly soluble in water and sparingly soluble in ethanol.

Category Long-acting calcium channel blocker.

Structural formula
**Half Life**
30-50 hr.

**Mechanism of action**
Amlodipine is a long-acting calcium channel blocker. Like other calcium channel blockers, Amlodipine acts by relaxing the smooth muscle in the arterial wall, decreasing total peripheral resistance and hence reducing blood pressure; in angina it increases blood flow to the heart muscle. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

**1.5.4 Introduction of atenolol**

**Generic name**
Atenolol I.P.

**Chemical name**
(RS)-2-{4-[2-hydroxy-3-(propan-2ylamino) propoxy] phenyl} acetamide

**CAS number**
29122-68-7

**Empirical formula**
C_{14}H_{22}N_{2}O_{3}

**Molecular weight**
266.336 g/mol

**Appearance**
White crystalline powder

**Melting point**
146-148°C

**Solubility**
Soluble in ethanol, sparingly soluble in water, slightly soluble in dichloromethane and practically insoluble in ether.

**Structural formula**

![Structural formula of atenolol](image)

**Category**
Beta-adrenoceptor antagonist.
Half Life
6-7 hr

Mechanism of action
Atenolol is a selective $\beta_1$ receptor antagonist, a drug belonging to the group of beta blockers (sometimes written $\beta$-blockers), a class of drugs used primarily in cardiovascular diseases. It blocks beta receptor; primarily affecting cardiovascular system (decrease heart rate, decrease contractility, decrease BP), and lungs (promotes bronchospasm).

1.6 Introduction to excipients
1.6.1 Sodium starch glycolate\textsuperscript{71}

Nonproprietary name
USP-NF /BP: Sodium starch glycolate

Synonyms
Carboxymethyl starch, sodium salt; explosol; explotab; glycolys; primojel

Chemical name
Sodium carboxymethyl starch.

Molecular weight
The molecular weight is typically 500000–1000000

Functional category
Tablet and capsule disintegrant

Structural formula

Applications in pharmaceutical formulation or technology
Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct-compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% insufficient.
Chapter 1

Description
White or almost white free-flowing very hygroscopic powder.

Typical properties
a) Density (bulk): 1.48 g/cm³.
b) Solubility: Practically insoluble in methylene chloride. It gives a translucent suspension in water.
c) Swelling capacity: In water, sodium starch glycolate swells to up to 300 times its volume.

1.6.2 Croscarmellose sodium

Nonproprietary name
USP/BP: Croscarmellose sodium

Synonyms
Ac-di-sol; crosslinked carboxy methyl cellulose sodium; explocel.

Chemical name
Cellulose, carboxymethyl ether, sodium salt, crosslinked

Functional category
Tablet and capsule disintegrant

Structural formula

Applications in pharmaceutical formulation
Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.
Description
Crocarmellose sodium occurs as an odorless, white or grayish white powder.

Typical properties
a) Density (bulk): 1.43 g/cm³.
b) Melting point: Does not melt, but chars at approximately 200°C.
c) Solubility: Practically insoluble in methylene chloride. It gives a translucent suspension in water.
d) Specific surface area: 0.24 m²/g.

1.6.3 Kyron T-314

Nonproprietary names
USP-NF: Polacrilin potassium

Synonyms
Amberlite IRP-88; potassium salt; polacrilinum kalii.

Chemical name
2-Methyl-2-propenoic acid polymer with divinylbenzene, potassium salt

Functional category
Tablet and capsule disintegrant

Structural formula

Applications in pharmaceutical formulation or technology
a) Polacrilin potassium is a cation-exchange resin used in oral pharmaceutical formulations as a tablet disintegrant. Concentrations of 2-10% w/w have been used for this purpose, although 2% w/w of polacrilin potassium is usually sufficient.

b) Other polacrilin ion-exchange resins have been used as excipients to stabilize drugs, to mask or modify the taste of drugs, and in the preparation of sustained-release dosage forms and drug carriers.

c) Polacrilin resins are also used in the analysis and manufacture of pharmaceuticals and food products.
Description
Polacrilin potassium occurs as a cream-colored, odorless and tasteless, free flowing powder. Aqueous dispersions have a bitter taste.

1.6.4 Microcrystalline cellulose

Non Proprietary Names

Synonym
Avicel PH, Celex, Cellulose gel, Celphere, Emcocel etc.

Chemical Name and CAS Registry Number
Cellulose [9004-34-6]

Empirical formula
(C₆H₁₀O₅)ₙ, Where n≈220.

Molecular weight
≈ 36000.

Solubility
Slightly soluble in 5% w/v Sodium hydroxide solution, practically insoluble in water, dilute acids and most of the organic solvents.

Structural Formula

Typical properties
a) Angle of repose: 35°
b) Density: Bulk: 0.32 g/cm³, Tapped- 0.45 g/cm³
c) Flowability: 1.41 g/s
d) Moisture content: Less than 1.5 %
e) Particle size: 100 µm
Use

It is used as adsorbent, anti-adherent, capsule binder/diluents, tablet binder/diluents and tablet disintegrant in concentration range from 20-90%, 5-20%, 20-90%, 20-90% and 5-15% respectively.

**Application of microcrystalline cellulose**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avicel PH -101</td>
<td>Standard grade with medium particle size</td>
<td>For conventional applications, especially in wet granulation</td>
</tr>
<tr>
<td>Avicel PH -102</td>
<td>Standard grade with large particle size</td>
<td>For improved flow in direct compression, the dry phase of wet granulation and dry granulation</td>
</tr>
<tr>
<td>Avicel PH -103</td>
<td>Low moisture content with fine particle size</td>
<td>Well suited to moisture-sensitive drugs</td>
</tr>
<tr>
<td>Avicel PH -105</td>
<td>Extra fine particle size</td>
<td>For use in direct compression of coarse or hard-to-compress materials</td>
</tr>
<tr>
<td>Avicel PH -112</td>
<td>Very low moisture content with large particle size</td>
<td>For increased flow in direct compression with moisture-sensitive ingredients</td>
</tr>
<tr>
<td>Avicel PH -113</td>
<td>Very low moisture content with fine particle size</td>
<td>Helps extend shelf life and improve final product stability especially with moisture-sensitive drugs</td>
</tr>
<tr>
<td>Avicel PH -200</td>
<td>Largest particle size</td>
<td>For best flow rate in direct compression</td>
</tr>
<tr>
<td>Avicel PH -200LM</td>
<td>Largest particle size with very low moisture content</td>
<td>For best flow rate in direct compression with moisture-sensitive ingredients</td>
</tr>
</tbody>
</table>

**Stability and storage conditions**

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

1.6.5 Hydroxypropyl methylcellulose

**Nonproprietary names**

USP /BP: Hypromellose

**Synonyms**

Hydroxypropyl methylcellulose; HPMC; Methocel; Metolose;

**Chemical name**

Cellulose hydroxypropyl methyl ether
**Functional category**

Controlled-release agent, dispersing agent, dissolution enhancer; emulsifying agent, emulsion stabilizer, extended-release agent, modified-release agent, mucoadhesive, release-modifying agent.

**Structural formula**

![Structural formula diagram]

Where R is H, CH3, or CH3CH (OH) CH2

**Molecular weight**

Molecular weight is approximately 100000–1500000.

**Viscosity**

| Table 1.7: Viscosity values for 2% (w/v) aqueous solutions of methocel |
|--------------------------|-----------------|-------------------|
| Methocel products        | JP/PhEur/USp Designation | Nominal viscosity (mPas) |
| Methocel K3 Premium LV   | 2208             | 3                 |
| Methocel K100 Premium LVEP | 2208          | 100               |
| Methocel K4M Premium     | 2208             | 4000              |
| Methocel K15M Premium    | 2208             | 15000             |
| Methocel K100M Premium   | 2208             | 100000            |
| Methocel E3 Premium LV   | 2910             | 4000              |
| Methocel E3 Premium LV   | 2910             | 100000            |
| Methocel F50 Premium     | 2906             | 4000              |

**Applications in pharmaceutical formulation or technology**

Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder in film-coating and as a matrix for use in extended release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Hypromellose is
also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0%.

1.6.6 Introduction of eudragit

EUDRAGIT® polymers are copolymers derived from esters of acrylic and methacrylic acid, whose physicochemical properties are determined by functional groups.

Nonproprietary names

Synonyms
Acryl-EZE; Acryl-EZE MP; Eastacryl 30D; Eudragit; Kollicoat MAE 30 D; Kollicoat MAE 30 DP; polymeric methacrylates.

Chemical name
Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride)

Structural formula

![Structural formula of Eudragit](image)

Solubility
Soluble in acetone, ethanol, dichloro methan and ethyl acetate while insoluble in water, sodium hydroxide and petroleum ether.

Application

a) Eudragit RL, RS, RD 100, NE 30 D and NE 40 D are used to form water-insoluble film coats for sustained-release products.

b) As binders in both aqueous and organic wet-granulation processes.

c) As control release matrix former in larger quantities (5–20%).

d) As direct-compression processes in quantities of 10–50%.

e) Used to form the matrix layers of transdermal delivery systems

f) Used to prepare novel gel formulations for rectal administration
Properties

<table>
<thead>
<tr>
<th>Eudragit Polymer</th>
<th>Availability</th>
<th>Dissolution properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>RL 100</td>
<td>Granules</td>
<td>High permeability, pH independent swelling</td>
</tr>
<tr>
<td>RLPO</td>
<td>Powder</td>
<td></td>
</tr>
<tr>
<td>RL 30 D</td>
<td>30% Aqueous dispersion</td>
<td></td>
</tr>
<tr>
<td>RL 12.5</td>
<td>12.5% Organic solution</td>
<td></td>
</tr>
<tr>
<td>RS 100</td>
<td>Granules</td>
<td>Insoluble</td>
</tr>
<tr>
<td>RSPO</td>
<td>Powder</td>
<td>Low permeability</td>
</tr>
<tr>
<td>RS 30 D</td>
<td>30% Aqueous dispersion</td>
<td>pH independent swelling</td>
</tr>
<tr>
<td>RS 12.5</td>
<td>12.5% Organic solution</td>
<td></td>
</tr>
<tr>
<td>NE 30 D</td>
<td>30% Aqueous dispersion</td>
<td>Insoluble, low permeability, pH independent swelling</td>
</tr>
<tr>
<td>NE 40 D</td>
<td>12.5% Organic solution</td>
<td>pH independent swelling, no plasticizer required, highly flexible</td>
</tr>
<tr>
<td>NM 30 D</td>
<td>30% Aqueous dispersion</td>
<td></td>
</tr>
</tbody>
</table>

1.6.6 Introduction of Ethyl cellulose

Nonproprietary names
BP: Ethylcellulose, PhEur: Ethylcellulosum, USPNF: Ethylcellulose

Synonyms
Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.

Chemical name
Cellulose ethyl ether [9004-57-3]

Structural formula

Empirical formula
\[ C_{12}H_{23}O_6 \text{ (C}_{12}H_{23}O_5 \text{n C}_{12}H_{23}O_5 \]
**Functional category**
Coating agent, flavoring fixative; tablet binder; tablet filler, viscosity-increasing agent.

**Application**

<table>
<thead>
<tr>
<th>Table 1.9: Application of ethyl cellulose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Use</strong></td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>Microencapsulation</td>
</tr>
<tr>
<td>Sustain release tablet coating</td>
</tr>
<tr>
<td>Tablet coating</td>
</tr>
<tr>
<td>Tablet granulation</td>
</tr>
</tbody>
</table>

**Typical properties**

a) Density (bulk): 0.4 g/cm³

b) Glass transition temperature: 129–133°C.

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

d) Solubility: It 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%).

**1.6.7 Introduction of xanthan gum**

The USPNF 23 describes xanthan gum as a high molecular weight polysaccharide gum. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid, and is prepared as the sodium, potassium, or calcium salt.

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

**Nonproprietary names**
BP/ USPNF: Xanthan gum, PhEur: Xanthani gummi

**Synonyms**
Corn sugar gum; E415; Keltrol; polysaccharide B-1459; Rhodigel; Vanzan NF; Xantural.
Chapter 1

Chemical name and CAS registry number
Xanthan gum [11138-66-2]

Functional category
Stabilizing agent, suspending agent and viscosity increasing agent.

Structural formula

Applications
a) It is widely used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending and stabilizing agent.
b) It is used as a thickening and emulsifying agent.
c) It is used to prepare sustained-release matrix tablets.
d) Xanthan gum has been incorporated in an ophthalmic liquid dosage form,
e) It is used as an excipient for spray drying and freeze-drying processes for better results.
f) It is used to increase the bioadhesive strength in vaginal formulations and as a binder in colon specific drug delivery systems.
g) It is also used as a hydrocolloid in the food industry,

Pharmacopeial specification:

a) pH: 6.0–8.0
b) Viscosity: 600 mPas
c) Loss on drying: 15.0%
d) Total ash: 6.5–16.0%
e) Assay: 91.0–108.0%

Typical Properties
a) Melting point: 270°C.
b) Solubility: Practically insoluble in ethanol and ether; soluble in cold or warm water.

c) Viscosity (dynamic): 1200–1600 mPas (1200–1600 cP) for a 1% w/v aqueous solution at 25°C.

1.6.8 Introduction of carbomer

Description
Carbomers are white-colored, fluffy, acidic, hygroscopic powders with a slight characteristic odor.

Nonproprietary names
BP: Carbomers, PhEur: Carbomera, USPNF: Carbomer

Synonyms
Acritamer, acrylic acid polymer, Carbopol, carboxy polymethylene, polyacrylic acid, carboxyvinyl polymer, Pemulen, Ultrez.

Functional category
Bioadhesive, emulsifying agent, release-modifying agent, suspending agent, tablet binder, viscosity-increasing agent.

Structural formula

![Structural formula of carbomer]

Application
a) It is mainly used in liquid or semisolid pharmaceutical formulations as suspending or viscosity-increasing agents. Formulations include creams, gels, and ointments.
b) In tablet formulations, carbomers are used as dry or wet binders and as a rate controlling excipient.
c) In wet granulation processes, water or an alcohol–water blend is used as the granulating fluid.
d) It is also employed as emulsifying agents in the preparation of oil-in-water emulsions for external use.
It is used as emulsifying agent, gelling agent, suspending agent and tablet binder in concentration range of 0.1–0.5%, 0.5–2.0%, 0.5–1.0% and 5.0–10.0% respectively.

**Typical properties**

a) Density (bulk): 1.76–2.08 g/cm³
b) Melting point: 260°C.
c) Moisture content: Up to 2% w/w.
d) Solubility: Remain undissolve in water.

### 1.7 References

56. Indian Pharmacopoeia. 2007. Ministry of Health and Family Welfare, Govt. of India, Ghaziabad. 3:1689-1690
70. http://www.drugs.com/atenolol.html