CHAPTER 2: INTRODUCTION

2.1. CIRCADIAN RHYTHMS
Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 hours (Jha and Bapat, 2004). Interestingly, the term circadian is derived from the Latin circa which means "about" and dies which can be defined as "a day". Normally, circadian rhythms are synchronized according to internal biologic clocks related to the sleep-wake cycle. Our circadian rhythm is based on sleep-activity cycle and is influenced by our genetic makeup and thereby affects our body’s function throughout day and night (24 hour period). Circadian rhythm regulates many body functions in humans like metabolism, physiology, behavior, sleep pattern and hormone production (Arora et al., 2006). Hormones viz., progesterone, testosterone, dehydro-epi-amdrosteron, estriol and estradiol follow circadian rhythm and hence their concentration in blood varies over 24 h. Melatonin is also reported to be secreted mainly in the night. Some of the analogues and inhibitory substances for these hormones also follow a circadian rhythm. Examples of such classes include; antidiabetics, glucocorticoids, mineralocorticoids and antihistamines.

2.2. CHRONO BIOLOGY
Chronobiology is the study of biological rhythms and their mechanisms. There are three types of mechanical rhythms in our body (Veena et al., 2008). They are:

I. Circadian: This word comes from Latin word “circa” means about and “dies” means day.

II. Ultradian: Oscillation of shorter duration are termed as ultradian (more than one cycle per 24 h).

III. Infradian: Oscillations that are longer than 24 h (less than one cycle per day).

Every biological rhythm has a periodicity as shown in figure 1. Circadian rhythms have a periodicity of about 24 hours.

- 1:00 am - Post surgical death
- 2:00 am - Peptic ulcer
3:00 am - Blood pressure
4:00 am – Asthma

**Figure 1:** Diurnal changes of biological activities of human body

It is well known that circadian rhythms influence disease processes and physiological events as shown in figure 2. Diseases with established oscillatory rhythm in their pathogenesis are:

- **Asthma:** It is a chronic inflammatory disease of the airways, characterized by hyper responsiveness to a variety of stimuli. The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases progressively at night in asthmatic patients. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours (Gothoskar et al., 2004). The worsening of asthma or lung function at night, commonly referred to as nocturnal asthma (NA), which characterized by forced expiratory volume in one second (FEV1) of at least 20% is implicit. Lung function (e.g., peak expiratory flow rate or FEV1) is usually highest at 4 PM and lowest at 4 AM, the
latter time is generally when asthma symptoms are most prevalent. Approximately two-thirds of asthmatics suffer from nighttime symptoms and 53% of asthma deaths occurred during the nighttime hours (Martin and Schlegel, 1998). A drug delivery system administered at bedtime but releasing drug during morning hours would be ideal in this case (Skloot, 2002).

![Circadian rhythm of chronological disorders](image)

**Figure 2:** Circadian rhythms of chronological disorders

- **Rheumatoid arthritis:** The pathophysiology of arthritis and patients with osteoarthritis tend to have less pain in the morning and more at night; while those with rheumatoid arthritis, have pain that usually peaks in the morning and decreases throughout the day. There is circadian rhythm in the plasma concentration of C-reactive protein and interleukin-6 of patient with rheumatoid arthritis.

- **Duodenal ulcer:** Gastric acid secretion is highest during nights in peptic ulcer patients.

- **Diabetes:** Circadian variations of glucose and insulin in diabetes have been extensively studied and their clinical importance in case of insulin substitution in
type 1 diabetes has been well exploited. Blood sugar level is increase after meal. So, chances of hyperglycemia are high after meal. In cancer, the blood flow to tumors and tumor growth rate are up to three fold greater during each daily activity phase of the circadian cycle.

➢ **Attention deficit syndrome:** In children with attention deficit syndrome, DOPA level is found to be increase in afternoon.

➢ **Hypercholesterolemia:** A circadian rhythm occurs during hepatic cholesterol synthesis. Cholesterol synthesis is generally higher during the night time than during day light. The maximal production occurs early in the morning, i.e., 12 h after last meal (Maroni et al., 2005). Studies with 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG CoA) reductase inhibitors have suggested that evening dosing was more effective than morning dosing.

![Circadian rhythm of cardiovascular system](image)

**Figure 3:** Circadian rhythm of cardiovascular system
Cardiovascular disorders: In case of cardiovascular diseases, several functions (e.g. BP, heart rate, stroke volume, cardiac output, blood flow) of the cardiovascular system are subject to circadian rhythms as shown in figure 3. It has been reported that more shocks and heart attacks occur during morning hours (Shweta et al., 2008). The level of cortisol is higher in the morning hours, and its release is reported to decline gradually during the day. Blood pressure is also reported to be high in the morning till late afternoon, and then drops off during night (Lemmer, 1999). Capillary resistance and vascular reactivity are higher in the morning and decreases latter in the day. Platelet agreeability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hyper coagulability of the blood. Most myocardial infarctions occur in the early hours of the morning.

2.3. CHRONOPHARMACOTHERAPY

Chronopharmacotherapy or “Chronopharmaceutics” consist of two words chronobiology and pharmaceutics. Recent studies have revealed that there are number of conditions which show predictable circadian rhythms and advantage could be taken by timing and adjusting the administration of drugs according to the circadian rhythm of the disease (Youan, 2004). Diseases, such as cardiovascular, asthma, cancer, peptic ulcer, allergic rhinitis, rheumatoid arthritis, attention deficit syndrome in children, hypercholesterolemia etc., follow the body’s circadian rhythm. Coordination of biological rhythms and medical treatment is called chronotherapy. While, chronotherapeutics, is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. The potential benefits of chronotherapeutics have been demonstrated in the management of a number of diseases which follow circadian rhythm (Janugade et al., 2009).

Based on these findings, drug delivery and therapy should be modified to achieve an effective drug level at the required time. From the viewpoint of therapeutic optimization, maintaining a constant blood level for a drug in the human body is questionable. Long term constant drug concentration exposed in blood and tissues may induce many problems such as tolerance of drug and activation of physiological system. Recently,
chronotherapy has been extensively applied in clinical therapy by modifying the dosing regimen of drug administration according to physiological needs (Ashish et al., 2009).

Among modified-release oral dosage forms, increasing interest has currently turned to system designed to achieve time specific (delay, pulsatile, time clock system) and site specific delivery of drugs (Howard et al., 2002, Lemmer, 2007). In particular, pulsatile drug delivery systems (PDDS) are gaining importance as these systems deliver the drug at specific time as per the pathophysiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. These systems constitute a relatively new class of device, beneficial for the drugs having chronopharmacological behaviour (where night time dosing is required), first pass effect, having specific site of absorption in gastrointestinal tract (GIT), targeting to colon; and cases where night time dosing is required. The pulsatile effect, i.e., the release of drug as a “pulse” after a lag time has to be designed in such a way that a complete and rapid drug release should follow the lag time (figure 4). Such systems are also called time-controlled as the drug released is independent of the environment. Consequently, the administration of a drug formulated in such a delivery system, i.e. taken at bedtime with a programmed start of drug release in early morning hours, could offer a more effective therapy than a typical controlled release drug delivery system (Efentakis et al., 2006). Pulsatile drug delivery system is the one type of drug delivery system, where the delivery device is capable of releasing drug after predetermined time-delay (i.e. lag time). These systems have a peculiar mechanism of delivering the drug rapidly and completely after a "lag time," i.e., a period of "no drug release" (Basak, 2005). Thus, the efficacy and tolerability of a therapy could notably be improved by delivery systems intended to timely release the drug few hours after bedtime administration, thus providing pharmacological protection when it is especially required without involving an unnecessarily extended patient exposure to the active molecule nor impairing the overall treatment compliance. Oral pulsatile administration could be useful for the treatment of certain diseases, such as asthma, gastric ulcer, hypertension, ischemic heart disease, duodenal ulcer, cancer, arthritis, etc., which exhibit circadian rhythms.

Pulsatile drug delivery denotes the capability of a controlled release preparation to deliver the drug at varying rates from very low to high over a desirable time. Though most delivery systems are designed for constant drug release over a prolonged period of time,
pulsatile delivery systems are characterized by a programmed drug release, as constant blood levels of a drug may not always be desirable (figure 4). It also should be capable of releasing its drug content at either a predetermined time or at a specific site in the gastrointestinal tract. Pulsatile systems are designed in a manner that the drug is available at the site of action at the right time in the right amount. A pulsatile drug delivery system administered at bedtime, but releasing drug as a burst during morning hours. According to gastrointestinal transit time, in early morning pulsatile or time release drug delivery system is present in colon. Thus, it is necessity to protect the drug during the transit time in gastro intestine and to allow its release only in the colon. So, developing colon-specific pulsatile or time release drug delivery system (CDDS) has been advantageous, when a delay in absorption is desirable from a therapeutic point of view as for the treatment of diseases that have a peak symptom in the early morning and that exhibit circadian rhythm, such as cardiovascular diseases, angina, asthma and rheumatoid arthritis (Ravi and Pramod, 2008). So by developing the pulsatile device for colonic delivery, plasma peak is obtained at an optimal time, number of doses per day can be reduced (Mastiholimath et al., 2007, Krishnaiyah et al., 1998, Laila et al., 2009).

2.4. INTRODUCTION TO PULSATILE DRUG DELIVERY SYSTEM

With the advancement of the technologies in the pharmaceutical field, drug delivery systems have drawn an increasing interest over the last few decades. Nowadays, the emphasis of pharmaceutical galenic research is turned towards the development of more efficacious drug delivery systems with already existing molecule rather going for new drug discovery because of the inherent hurdles posed in drug discovery and development process (Sachin and Neeraj, 2007). Till early nineties efforts have been made to design the drug delivery system which will release the drug at fairly constant rate. In fact these systems turned to be one of the most successful systems in delivering the drug molecule (Maroni et al., 2005). But still for many of the drugs, use of such systems is not suitable because of a number of reasons. This is particularly true in cases where the drug is subjected to large metabolic degradation. Due to ‘first pass effect’ there will be reduction in the bioavailability of the drug because of gradual release can result in greater degradation. Secondly drugs with short half-life need to be administered repeatedly which results in patient non-compliance. Further, in case of chronic treatment, where the
drug is given in sustained release dosage form, continuous exposure of the drug to body may lead to adverse effect. Lastly, drugs which exhibit tolerance should not be delivered at a constant rate, since the drug effect decreases with time at constant drug level. In addition drug toxicity increases with time when drug levels are held constant. In such cases, it is preferable to develop a dosage form, which will provide desired concentration of drug at particular time point only. The dependence of several diseases and body function on circadian rhythm is well known. A genetic control of a “master clock” located in the nucleus supra-chiasmaticus has been recently proposed (Bjorm, 1991). Numerous studies conducted, suggest that pharmacokinetics, drug efficacy and side effects can be modified by following therapy matching the biological rhythm (Lemmer, 1999). Nowadays, concept of chronopharmaceutics has been emerged, chronopharmacotherapy or “chronopharmaceutics” consist of two words chronobiology and pharmaceutics. Recent studies have revealed that there are number of conditions which show predictable circadian rhythms and research is devoted to the design and evaluation of chronotherapeutic drug delivery systems that release a therapeutic agent at a rhythm to maintain the adequate drug concentration according to the needs of the physiological states of patient’s body and the cardiac rhythm (Youan, 2004). Various diseases following the body’s circadian rhythm are listed in table 1. Thus, chronotherapeutics, is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. Based on these findings, diseases where a constant drug levels are not preferred, but needs a pulse of therapeutic concentration in a periodic manner acts as an initiator for the development of “Pulsatile Drug Delivery Systems” (Skloot, 2005).

Pulsatile drug delivery system is time and site-specific drug delivery system, thus providing special and temporal delivery and increasing patient compliance. Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of molecules within a short time period immediately after a predetermined/programmable off-release period, i.e., lag time (Figure 4) (Kikuchi and Okano, 2002). They are predictable resonating dynamic systems, which require different amounts of drug at predictably different times within the circadian cycle which will maximize desired and minimize undesired drug effects. In short, pulsatile release systems are designed to
deliver the drug at the right site, at right time and in right concentration after a predetermined lag time.

**Table 1:** List of diseases that depends on circadian rhythm

<table>
<thead>
<tr>
<th>Disease condition</th>
<th>Chrobiology</th>
<th>Drugs used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcer</td>
<td>Acid secretion is high in the afternoon and at night</td>
<td>H$_2$ blockers</td>
</tr>
<tr>
<td>Asthma</td>
<td>Precipitation of attacks during night or at early morning hour</td>
<td>β$_2$ agonist, Antihistaminics</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period</td>
<td>Nitroglycerin, Calcium channel blocker, ACE inhibitors etc.</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Pain in the morning and more pain at night</td>
<td>NSAIDs, Glucocorticoids</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Blood sugar level increase after meal</td>
<td>Sulfonylurea, Insulin, Biguanide</td>
</tr>
<tr>
<td>Attention deficit</td>
<td>Increase in DOPA level in afternoon</td>
<td>Methylphenidate</td>
</tr>
<tr>
<td>Syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Cholesterol synthesis is generally higher</td>
<td>HMG CoA reductase inhibitors</td>
</tr>
</tbody>
</table>

**Figure 4:** Drug release profile of pulsatile systems
Such a novel drug delivery has been attempted for the following:

- **Chronopharmacotherapy** of diseases which shows circadian rhythms in their pathophysiology i.e., their activity increases or decreases with time. A number of hormones like rennin, aldosterone, and cortisol show daily as well as timely fluctuations in their blood levels. Circadian effects are also observed in case of pH and acid secretion in stomach, gastric emptying, and gastro-intestinal blood transfusion (Drayer et al., 1985).

- Severity of diseases like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer and hypertension is time dependent. Sharp increase in asthmatic attacks during early morning hours have been reported (Lemmer, 1999). Such a condition demands supplement of drug at particular time rather than maintaining constant plasma drug level. A drug delivery system administered at bedtime, but releasing drug as a burst after the time of administration (during morning hours), would be ideal in this case.

- For drugs which develop biological tolerance, where the constant presence of drug at the site of action diminishes the therapeutic effect, for such drugs pulsatile systems with special pharmacokinetic features designed according to the circadian rhythm of human. The efficacy and tolerability of a therapy could notably be improved by delivery systems intended to timely release the drug few hours after bedtime administration, thus providing pharmacological protection when it is especially required without involving an unnecessarily extended patient exposure to the active molecule nor impairing the overall treatment compliance.

- Avoiding degradation in upper gastrointestinal tract, so, it is currently used as a potential approach to increase the oral bioavailability of peptides, proteins, oligonucleotides and nucleic acids (Rubinstein et al., 1997, Bourgeois et al., 2005).

- For time-programmed administration of hormones and many drugs such as isosorbide dinitrate, respectively, to avoid suppression of hormones in the body that can be hampered by constant release of hormone from administered dosage form and development of resistance.

- Pulsatile drug delivery system is desirable for the drug with extensive first pass metabolism e.g., β-blockers and for drug the drugs acting or having an absorption
window in the gastro-intestinal tract e.g., vitamins, to targeted at specific site in the intestinal tract mostly colon.

- Pulsatile colon targeted delivery has proved advantageous in the management of inflammatory bowel disease (IBD) (Friend, 2005).

### 2.4.1. CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEMS

Pulsatile systems can be classified into single- and multiple-unit systems. Based on methodologies for the pulsatile drug delivery system can be broadly classified into three classes;

1. Time controlled
2. Stimuli induced
3. Externally regulated

The design of pulsatile delivery systems, which have been presented in the form of reservoir, capsular and osmotic devices (Maroni et al., 2005). Reservoir formulations contain drug core which is coated with one or more coating layers. According to the inherent characteristics of the coating materials, they are also further classified in erodible, rupturable and diffusive systems. Delayed release is, respectively, enabled by disruption and erosion of the coat layer or by drug diffusion phenomena through the coat layer itself. Disruption may in turn be promoted by an osmotic or swelling-induced increase in the core volume or result from the membrane strain produced by carbon dioxide that is formed from effervescent excipients (Bussember et al., 2001, Gazzaniga et al., 2006).

For most aforementioned formulation types, swellable hydrophilic polymers indeed play a pivotal role in the composition of key items susceptible to solvent activation. Water swellable polymers are highly hydrophilic materials that, upon contact with aqueous fluids, typically undergo a glassy–rubbery thermodynamic transition, which is related to a distension of their macromolecular chains (Colombo et al., 1993). As a consequence of the hydration process, polymeric volume increases (swelling). Swollen polymeric substrates may erode because of mechanical attrition phenomena and/or dissolve in the medium at a rate that mostly depends on the relevant physicochemical properties and
solvent concentration (Caramella et al., 1989). In contrast to erodible polymers, cross-linked macromolecular networks (hydrogels) fail to dissolve even after extensive water uptake. When water penetrates into swellable polymeric matrices, two differing phenomenon occurs: the swelling, which is the boundary between glassy and rubbery matrix regions, and the erosion, that is the interface between the rubbery polymer and outer medium (Colombo et al., 1987, Conte et al., 1988). Due to these two phenomenons, a gelled layer of varying thickness is formed. In insoluble hydrogel systems, such a layer keeps thickening until the swelling process is completed (Colombo et al., 2000). Such inherent characteristics have drawn remarkable interest to swellable hydrophilic materials such as hydrophilic cellulose derivatives, polysachharides, alginic acid, carrageenans, polyvinyl alcohol (PVA) and polyethylene oxide (PEO) which have widely been employed in the pharmaceutical area over the past decades, especially as far as polysaccharidic compounds (guar, xanthan and locust bean gums) are concerned. Due to their consolidated safety, versatility and broad availability profiles, cellulosic ethers, such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC) and calcium or sodium carboxymethylcellulose (CMC), have particularly been exploited in the pharmaceutical manufacturing either as conventional binding, film-coating and viscosity-building excipients or as functional formulation adjuvants governing drug release from advanced delivery systems (Li et al., 2005). In the specific field of oral modified release, used to to the design and preparation of hydrophilic matrix systems for prolonged delivery. More recently, a further interesting application has been highlighted in connection with the accomplishment of pulsatile (delayed) release performances. Only inner release mechanisms are operating in time-based release, which is expected to be independent of environment variables such as pH, ionic strength and temperature. Therefore, time-based pulsatile delivery can also be referred to as delayed release. After the lag phase, the drug liberation may be prompt and quantitative, sustained over a prolonged period of time or else repeated when multiple dose fractions are delivered following prefixed lag intervals (Andrea et al., 2008).

2.4.2. TIME CONTROLLED SINGLE UNIT PULSATILE SYSTEMS

The principle of time controlled drug delivery systems is that the release of the drug happens according to a predetermined rate after a lag phase (delayed release
systems) to achieve maximum therapeutic and minimum toxic effect. These are subclassified as capsule-based systems, osmotic systems. Single-unit systems are designed by coating the system either with eroding/soluble or rupturable coating.

**Time controlled single unit capsule based systems with release controlling plug**

Single-unit systems are mostly developed in capsule form. The lag time is controlled by a plug, which gets pushed away by swelling or erosion, and the drug is released as a “Pulse” from the insoluble capsule body i.e., Pulsincap®.

Pulsincap® was developed by R. P. Scherer International Corporation, Michigan, US, and is one such system that comprises of a water-insoluble capsule enclosing the drug reservoir. A highly swellable, erodible or, alternatively, lipophilic matrix plug made of approved substances such as hydrophilic polymers or lipids was used to seal the drug contents into the capsule body (Mc Neill et al., 1993). This plug undergoes a timed removal either because of its water swelling and/or erosion processes or following a pressure rise that is caused by water uptake inside the capsule body. As shown in figure 5, when this capsule come in contact with the dissolution fluid, it swelles; and after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug. The plug matrix was originally composed of cross-linked polyethylene glycol (PEG 8000) hydrogel in the Pulsincap®, which was the very first capsule-shaped pulsatile delivery system described in the literature (Wilding et al., 1992). Various types of polymers used for designing of the hydro gel plug are hydroxyl propyl methyl cellulose (HPMC), polyvinyl alcohol (PVA), poly methyl methacrylates, polyvinyl acetate and polyethylene oxide. The length of the plug and its point of insertion into the capsule controlled the lag time. When capsule made an enteric coating, the system was evaluated for time-dependent colon delivery as well. In this respect, scintigraphic investigations indicated that a selective plug ejection in the large bowel could be achieved (Gang et al., 2004).

Steven et al., developed a Pulsincap® system with erodible compressed tablet (Stevens et al., 1995). Krogel and Bodmeier prepared impermeable cylinder system for ibuprofen. The system consists of hollow, impermeable polypropylene cylinder in which the matrix tablet is inserted (Krogel and Bodmeier, 1999). Ross et al., used low substituted
hydroxypropylcellulose for the expulsion system for the release of propranolol over a time period of 2-10 h. This could be controlled using compressed erodible tablets made of lactose and HPMC (Ross et al., 2009). Krogel and Bodmeier studied the release of chlorpheniramine utilizing the erodible plugs fitted in the capsules (Krogel and Bodmeier, 1998).

Figure 5: Design of Pulsincap® system

**Time controlled single unit pulsatile systems based on osmosis**

The Port™ system was developed by Therapeutic system research laboratory Ann Arbor, Michigan, USA, and consists of a capsule coated with a semi permeable membrane. Inside the capsule was an insoluble plug, osmotically active agent and the drug formulation (Crison et al., 1995). When this capsule came in contact with the dissolution fluid, the semipermeable membrane allowed the entry of water, which caused the pressure to develop and the insoluble plug expelled after a lag time (figure 6). Pulsatile
port system was utilized to deliver methylphenidate used in the treatment of attention
deficit hyperactivity disorder. This system avoided second time dosing, which was
beneficial for school children during daytime.

![Plan of Port system](image)

**Figure 6:** Plan of Port system

Barzegar and Siyahi developed osmotic hard gelatin capsule filled with acetaminophen
and osmotic agent (sorbitol) coated with semipermeable cellulose acetate membrane
containing hydrophobic plasticizer (castor oil) and sealed with wax of white bees. They
notified that when capsule sink water, water penetrates the membrane, dissolves the
osmotic agent and increases the osmotic pressure inside the capsule. When the latter
pressure is high enough, then it expels out the plug and the drug release commences. The
lag time depends on thickness of semipermeable membrane and plug thickness (Barzegar
and Siyahi, 2006).

Linkwitz et al., invented an expandable orifice technology based osmotic systems. The
system is in the form of capsule from which the osmotic delivery of the drug was driven
by the osmotic infusion of the moisture by the capsule from a physiological environment.
The orifice forms in the capsule wall, which is constructed of an elastic material, such as
elastomer (e.g., styrene-butadiene copolymer) and the delivery orifice opens
intermittently to achieve pulsatile delivery effect. The orifice is small enough that, when
the elastic wall is relaxed, release of the drug through the orifice is substantially zero.
But, when the elastic wall is stretched, because of pressure rise inside the capsule, the
orifice expands sufficiently to allow the release of the drug at a required rate (Linkwitz et al., 1994).

Niwa et al., prepared a capsule made from ethyl cellulose with varied thickness for time-controlled release of drugs in the colon. The ethyl cellulose capsules contained a large number of mechanically made micropores (400 μm) at the bottom. A swellable layer consisting of low substituted hydroxy propyl cellulose (L-HPC) was located at the bottom of capsule body. Above the swellable layer was the drug reservoir which contained mixture of model drug and bulking agent, such as lactose and starch. The capsule was then capped and sealed with a concentrated ethyl cellulose solution. After administration of the capsule, water molecules penetrated the capsule through the micropores in the bottom of the capsule body. L-HPC hydrates and swells to increase internal osmotic pressure, which resulted in the “explosion” of the capsule and a burst drug release was achieved. The lag time of the drug release could be altered by altering the thickness of the capsule (Niwa et al., 1995).

**Time controlled single unit pulsatile system with eroding or soluble barrier coating**

The chronotropic system is an oral dosage form that is designed to achieve time controlled delivery. This system has been developed keeping in view interaction between gastrointestinal fluids and the coating polymer, which causes time and site-controlled release. These systems comprise reservoir devices coated with a soluble barrier layer that dissolves with time, and the drug releases at once after a specified lag time. Hydrophilic derivatives such as HPMC, HEC (hydroxyethyl cellulose), HPC (hydroxypropyl cellulose), PEO, macrogol 6000, xanthan gum, locust bean gum and sodium alginate/chitosan complexes have been employed to prepare most reservoir pulsatile delivery systems provided with erodible coating (Matsuo et al., 1995, Fukui et al., 2000, Takeuchi et al., 2000). Press-coating technique has chiefly used for their application onto drug-containing core. However, organic and aqueous spray-coating, dipping and, more recently, powder-layering have been attempted as well. The mechanism by which hydrophilic cellulosic barriers delay release of drug as shown in figure 7 depends on progressive hydration, the swelling of the polymer, increasing the permeability and dissolution/erosion phenomena, when exposed to the aqueous medium. In Pulsatile tablet
containing immediate release drug cores, even the disintegrant activation that is possibly induced by water penetration through the gelled polymeric layer may contribute to a complete removal of coat polymeric residues adhering to the inner drug formulation. Lag times of erodible reservoir systems depend on the physicochemical properties of the applied polymer and on the coating level.

![Diagram](image.png)

**Figure 7**: Release profile of reservoir system with swellable/erodible or soluble barrier coating

Chronotropic® system consists of a core containing drug reservoir coated by a hydrophilic polymer HPMC using aqueous spray coating procedure as shown in figure 8 (Gazzaniga et al., 1994). An additional enteric-coated film is given outside this layer to overcome intra-subject variability in gastric emptying rates. Here, the drug core is coated with soluble ingredients; shell dissolution/disintegration becomes the key factor in controlling the lag time. So, the lag time and the onset of action are controlled by the thickness and the viscosity grade of HPMC (Gazzaniga et al., 1995).

Time release three-layer tablet consisting of two drug-containing layers, separated by a drug-free gellable polymeric barrier layer, release drug in two pulses. The three-layer
tablet was coated on three sides with a water insoluble ethyl cellulose coating and the top side of the tablet remained uncoated. Upon contact with dissolution fluids, the initial dose incorporated into the top layer was released rapidly from the uncoated surface of the tablet. The second pulse was obtained from the bottom layer after the gelled barrier layer (HPMC) has been eroded and dissolved (Veena et al., 2008).

Figure 8: Schematic diagram of pulsatile system with erodible coating layer

The Time Clock® system is a delivery device based on solid dosage form that is coated by an aqueous dispersion. This coating is a hydrophobic-surfactant layer to which a water-soluble HPMC polymer is added to improve adhesion to the core. Once in contact with the dissolution fluid, the dispersion film rehydrates and redisperses. The lag time could be controlled by varying the thickness of the film. After the lag time, i.e., the time required for rehydration, the core immediately releases the drug. The lag time was studied in vivo using gamma scintigraphy. The mean lag time of drug release was 345 min (Sangalli et al., 2001). Another, the Time Clock® Tablet system was prepared by coating drug core with a hydrophobic dispersion of carnauba wax, beeswax, poly(oxyethylene) sorbitan monooleate and HPMC in water. The lag time could be proportionally modulated by altering the thickness of the coating (Pozzi et al., 1995).

Recently, the SyncroDose® delivery technology was developed, which envisaged a drug-containing tablet core and an erodible dry-coating layer composed of xanthan and locust bean gum mixtures (Sawada et al., 2003). By varying the ratio between these polysaccharides, the lag phase could be modulated according to differing chronotherapeutic needs.
Time controlled single unit pulsatile system with rupturable layers/membranes

These systems are based upon a reservoir system coated with a rupturable membrane. These systems comprising at least one water soluble swelling excipient and above which water insoluble but permeable polymer film coating adapted to rupture mechanically at predetermined period of time after administration (figure 9). The outer membrane ruptures due to the pressure developed by effervescent agents or swelling agents in the reservoir. Sungthongjeen et al., designed a pulsatile drug delivery system where the tablets of buflomedil HCL prepared by direct compression with varying amounts of spray-dried lactose and microcrystalline cellulose were coated with an inner swelling layer using croscarmellose sodium and an outer rupturable layer using ethyl cellulose. It was observed that by increasing the amount of ethyl cellulose coating, the lag time could be prolonged. Ethyl cellulose, being water insoluble, retarded the water uptake (Sungthongjeen et al., 2004).

Bussemer et al., worked on a pulsatile system with rupturable coating on hard gelatin capsules containing drug. These capsules were first coated with a swelling layer and then with an insoluble but water-permeable outer coating. These coated capsules when immersed in the release media could take up the media at a constant rate up to a point when the outer coating would rupture because of the pressure caused by the swelling layer. It could be concluded that by increasing the swelling layer, the lag time could be shortened. However, by increasing the outer coating, the lag time could be prolonged (Bussemer et al., 2003).

Bussemer and Bodmeier, studied the effect of various swelling agents and the outer polymeric coating on the lag time and the drug release. It could be concluded from this study that croscarmellose sodium was a better swelling agent as compared to HPMC (E5 and K100 M). Also, cellulose acetate propionate and ethyl cellulose gave better rupturing by virtue of their brittle nature when compared to Eudragit RS, which gave a flexible polymer coating. Cellulose acetate propionate coated capsules gave better drug release as compared to those coated with ethyl cellulose (Bussemer and Bodmeier, 2003).
Intestinal Pulsatile release tablet was developed by coating drug core containing swelling agent with mixture of ethyl cellulose and Eudragit L. Eudragit L dissolves in an environment of pH above 6 and creates pores in the coating film. Penetration of water molecules from the surroundings through the pores into the core causes expansion of the swelling agent, bursting the film and releasing the drug with a single pulse (Fan et al., 2001).

2.4.3. TIME CONTROLLED MULTIPLE UNIT PULSATILE SYSTEMS

Multiparticulate systems (e.g., pellets, beads) offer various advantages over single-unit systems. These systems have no risk of dose dumping, they provide flexibility of blending units with different release patterns, and provide reproducible and short gastric residence time. But the drug-carrying capacity of multiparticulate systems is lower due to presence of higher quantity of excipients. In multiple-unit systems, the pulsatile release is induced by changing membrane permeability or by coating with a rupturable membrane coating.

Time controlled multiparticulate pulsatile system based on change in membrane permeability

The capsule has the capability of delivering multiple units containing therapeutic agent into the body in a time controlled pulsatile release fashion. The dosage form comprises of multiple coated particulates. The time-controlled series of pulses occur several hours after oral administration, with or without immediate release. The coating membranes may be composed of an enteric polymer or a mixture of water-insoluble polymer and an enteric
polymer. The composition and thickness of the polymeric membranes determine the lag time and the duration of the drug release from each of the coated particulates (Veena et al., 2008).

Sigmoidal release system consists of pellet cores having drug and succinic acid coated with ammonio-methacrylate copolymer. The water in the medium dissolves succinic acid. The drug inside and the acid solution increase the permeability of the polymer film. This system was used to design an acid containing core. Chen developed an osmotic multiparticulate drug delivery system with a Sigmoidal release system (SRS) for diltiazem. It was designed in such a way that the drug released in divided doses over timed intervals throughout the day to produce a pulsatile blood concentration curve with time. The dosage form comprised of a gelatin capsule containing three types of pellets. Each pellet contained a core that comprised of drug and water-soluble modulating agent such as NaCl. Each pellet was enclosing with a water-insoluble and water-permeable film-forming agent and a hydrophilic agent. The thickness of this coating varied in each kind of pellet. In one kind of pellets, the thickness was the least; in the second kind of pellets, a thicker coating was given; and in the third kind of pellets, the thickest coating was given. When the dosage form was exposed to the physiological environment, the capsule dissolved and the pellets were exposed to the gastric environment. The rate of release was controlled by the relative thickness of the coating on the respective kind of pellets, the proportion of hydrophobic agent in the coating, and the proportion of osmotic agent in the pellet. To ensure that pH doesn’t disturb the preset release time intervals, the coating given was of pH-independent material (Chen, 1993).

**Time controlled multiparticulate pulsatile systems with rupturable coating**

Similar to single-unit system, the rupturing effect is achieved by coating the individual units with effervescent or swelling agents. Bai invented a pulsatile capsule or tablet comprising of a large number of pellets, each having the same therapeutic drug and a water-soluble osmotic agent (e.g., NaCl). A water permeable, water-insoluble polymer encloses each pellet. A hydrophobic water-insoluble agent that alters the permeability (e.g., wax, fatty acid or salt of fatty acids) is incorporated into the polymer film. The water passes from the film coating to the core and osmotic agent dissolves in water,
which causes the pellets to swell, rupture due to osmotic pressure and thereby diffusion of the drug from the pellet. Drug delivery was controlled by the rupture of the membrane and timing of release was controlled by the thickness of coating (Bai, 1998).

2.4.4. STIMULI INDUCED SITE SPECIFIC PULSATILE SYSTEMS

In these systems there is release of the drug after stimulation by any biological factor like temperature, or any other chemical stimuli. These systems are further classified in to temperature induced systems and chemical stimuli induced system, on the basis of stimulus.

**Temperature induced pulsatile systems**

Thermo-responsive hydrogel systems have been developed for pulsatile release. In this pulsatile system, polymer undergoes swelling or deswelling phase in response to the temperature which modulate drug release in swollen state. The use of temperature as a signal has been justified by the fact that body temperature often deviate from the physiological temperature (37°C) in presence of pathogens or pyrogens. This temperature deviation sometimes can be useful stimulus that activates the release of drug from temperature sensitive hydrogel or micelle type pulsatile system for disease accompanying fever. Hydrogel undergoes reversible volume changes in response to change in temperature (Anita and Santani, 2008). Hydrogels shrink at a transit temperature that is related to lower critical solution temperature (LCST) from which the gel is made. Thermosensitive hydrogels absorb water and swell at temperature below transition temperature, whereas they expel water and shrink/deswell at temperature above transition temperature. Poly(N-isopropyl acryl amide) (PIPAAm) cross-linked gel shows thermo responsive discontinuous swelling/deswelling phenomenon. It swells and forms gel at a temperature below 32°C and drug release controlled by diffusion, while above this temperature drug release stop completely because gels shrink and form dense shrunken layer over skin surface, which hindered water permeation from inside gel into environment. A rapid deswelling is achieved by adding polyethylene glycol into PIPAAm cross linked hydrogels.

**Chemical stimuli induced pulsatile systems**
Glucose-responsive insulin release devices
There is rhythmic increase in the levels of glucose in the body in diabetes mellitus, requiring injection of the insulin at proper time. Several systems have been developed which are able to respond to changes in glucose concentration. The system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases, glucose oxidase converts glucose into gluconic acid, which changes the pH of the system. This pH change induces swelling of the polymer which results in insulin release. Examples of the pH sensitive polymers include N, N-dimethylaminoethyl methacrylate, chitosan and polyolete (Sershen et al., 2000, Gutowska et al., 1997).

Inflammation-induced pulsatile release
Upon any physical or chemical stress, such as injury, fracture etc., inflammation takes place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation-responsive cells. Degradation via hydroxyl radicals however, is usually dominant and rapid when Hyaluronic acid gel is injected at inflammatory sites (Yui et al., 1992). Thus, it is possible to treat patients with inflammatory diseases like rheumatoid arthritis; using anti-inflammatory drug incorporated HA gels as new implantable drug delivery systems.

pH sensitive drug delivery system
This type of PDDS contains two components. The first is fast release type while the other is pulsed release which releases the drug in response to change in pH. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, and sodium carboxymethylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine (Sachin and Neeraj, 2007).

2.4.5. EXTERNAL STIMULI INDUCED PULSATILE SYSTEMS
Electro responsive pulsatile release
Electrically responsive delivery systems are prepared from polyelectrolytes (polymers which contain relatively high concentration of ionisable groups along the backbone chain), which release drug upon generation of electric impulse externally due to
reversible deswelling/swelling of polymers. Examples of naturally occurring polymers include hyaluronic acid, chondroitin sulphate, agarose, carbomer, xanthan gum and calcium alginate. The synthetic polymers are generally acrylate and meth acrylate derivatives such as partially hydrolyzed polyacrylamide, polydimethylaminopropyl acrylamide (Sachin and Neeraj, 2007).

Table 2: Marketed products of pulsatile system

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Drug</th>
<th>Company Name</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxatag®</td>
<td>Amoxicillin</td>
<td>Advancis Pharmaceutical Corp., USA</td>
<td>Shweta et al., 2008</td>
</tr>
<tr>
<td>Uniphyl®</td>
<td>Theophylline</td>
<td>Purdue Pharmaceuticals Products Pvt. Ltd., USA</td>
<td>Urwitz et al., 1987</td>
</tr>
<tr>
<td>Ritalina®</td>
<td>methylphenidate</td>
<td>Novartis International AG, Switzerland</td>
<td>Shweta et al., 2008</td>
</tr>
<tr>
<td>Verelan®</td>
<td>Verapamil HCl</td>
<td>Alkermes Gainesville LLC, USA</td>
<td>Youan, 2004</td>
</tr>
<tr>
<td>Innopran®</td>
<td>Verapamil HCl, Propranolol HCl</td>
<td>SmithKline Beecham Corporation, Vandalia</td>
<td>Harshida et al., 2013</td>
</tr>
<tr>
<td>Pulsincap®</td>
<td>Dofetilide</td>
<td>R. P. Scherer International Corporation, Michigan, USA</td>
<td>Anamika et al., 2012</td>
</tr>
<tr>
<td>Invega®</td>
<td>Diclofenac sodium</td>
<td>Janssen Pharmaceuticals Inc., New Jersey, USA</td>
<td>Urwitz et al., 1987</td>
</tr>
<tr>
<td>OPANA®</td>
<td>Oxymorphone</td>
<td>Endo Pharmaceuticals, New Jersey, USA</td>
<td>Shidhaye et al., 2010</td>
</tr>
<tr>
<td>Cardiazem®</td>
<td>Diltiazem HCl</td>
<td>sanofi-aventis, USA</td>
<td>Youan, 2004</td>
</tr>
<tr>
<td>Procardia®</td>
<td>Nifedipine</td>
<td>Pfizer labs, NY, USA</td>
<td>Harshida et al., 2013</td>
</tr>
</tbody>
</table>

Magnetically regulated pulsatile system
The use of an oscillating magnetic field to modulate the rates of drug release from polymer matrix was one of the old methodologies. Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials such as Magnetite,
Iron, Nickel, Cobalt etc. For biomedical applications, magnetic carriers must be water-based, biocompatible, non-toxic and non-immunogenic mechanistic approach based on magnetic attraction is the slowing down of oral drugs in the gastrointestinal system. This is possible by filling an additional magnetic component into capsules or tablets. The speed of travel through the stomach and intestines can then be slowed down at specific positions by an external magnet, thus changing the timing and/or extent of drug absorption into stomach or intestines (Chen and Langer, 1997).

Commercial products
Now a day, many drug products available in marketed in form of pulsatile system. Table 2 listed the marketed products with drug and company manufacturing it.

2.5. INTRODUCTION TO COLON TARGETED DRUG DELIVERY SYSTEM
To date in ongoing research, oral delivery is still the preferred route of drug administration, especially for chronic therapies where repeated administration is required. Oral administration offers patients less pain, greater convenience, higher likelihood of compliance, and reduced risk of cross infection and needle stick injuries. Thus, formulations of oral drug delivery continue to dominate more than half of the drug delivery market share (Chourasia and Jain, 2003). Despite these advantages, the oral route is not suitable to the administration of drugs which are destroyed and inactivated in acidic environment of the stomach and/or by pancreatic enzymes in the small intestine, poor absorption, and their limited ability to transport across the intestinal epithelial barrier. As a result, new strategies of drug delivery have been developed to overcome obstacles encountered by oral delivery. Among these strategies, colon-specific delivery has been extensively studied from the last two decades (Ramprasad et al., 1995). Colon specific drug delivery has gained a more importance for the delivery at colonic region by use of various drugs to treat the both local and systemic diseases listed in table 3. Local diseases include ulcerative colitis, crohn’s disease, irritable bowel syndrome, inflammatory bowel disease (IBD) and colorectal carcinomas. Other serious disorders like nocturnal asthma, Hypertension, arthritis and angina can also be cured by these techniques (Nirav et al., 2008). In addition, the colon can also be utilized as a portal for the entry of drugs into the systemic circulation. Colonic delivery is a good candidature
for delivery of proteins peptides and vaccines, where, the enzymatic degradation and the hydrolysis of proteins can be minimized and increases the systemic bioavailability. Colon an area where protein drugs are free from the attack of numerous proteases is thought to be an ideal location to direct the drugs into the blood stream and the immune system (Liu et al., 2003). The colon specific delivery of drugs to the target receptor sites has a lot of benefits in terms of improving safety and reducing toxicity when treating local or systemic chronic diseases. Colonic delivery can be accomplished by oral or rectal administration. Rectal administration offers the shortest route for targeting drugs to the colon. However, reaching the proximal part of colon via rectal administration is difficult. Rectal administration is uncomfortable to patients and compliance may be less than optimal. Oral route is the most convenient route of administration for colon targeting.

<table>
<thead>
<tr>
<th>Target Sites</th>
<th>Disease Conditions</th>
<th>Symptoms</th>
<th>Drugs and active agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local action</td>
<td>Inflammatory Bowel Disease</td>
<td>Diarrhea, Abdominal pain and cramping, blood in stool, ulcers, reduced appetite</td>
<td>Hydrocortisone, Budenoside, Prednisolone, Olsalazine, Mesalazine.</td>
</tr>
<tr>
<td></td>
<td>Ulcerative colitis</td>
<td>abdominal pain or cramping, a bloated feeling, flatulence</td>
<td>Dicyclomine, Hyoscine, Propantheline, Cimetropium,</td>
</tr>
<tr>
<td></td>
<td>Irritable bowel syndrome</td>
<td>A change in bowel habits, narrow and bloody stool, abdominal discomfort, cramps, gas or pain</td>
<td>Leucovorin, Oxaliplatin, Irinotecan, bevacizumab, cetuximab, Metronidazole</td>
</tr>
<tr>
<td></td>
<td>Colorectal cancer</td>
<td>Formation of pouches on the outside of the colon due to bacterial infection.</td>
<td>5-Flourouracil, Pseudoephedrine, Glucagon, Epoetin</td>
</tr>
<tr>
<td>Systemic action</td>
<td>Oral delivery of peptides</td>
<td>--</td>
<td>Insulin</td>
</tr>
<tr>
<td></td>
<td>Oral delivery of vaccines</td>
<td>----</td>
<td>Typhoid</td>
</tr>
</tbody>
</table>

Most of the oral conventional drug delivery systems for treating the colon disorders are failing as the drugs do not reach the site of action in appropriate concentrations. Thus, an
effective and safe therapy of these colonic disorders, using site specific drug delivery system is a challenging task to the pharmaceutical technologists. Absorption or degradation of the active ingredient in the upper part of the GIT is the major obstacle and must be circumvented for successful colonic drug delivery. Colon specific oral drug delivery is being developed by taking advantage of the luminal PH conditions and the presence of microbial enzymes such as azoreductase, pectinase, and dextranase. Targeted drug delivery to the colon, by means of combination of one or more controlled release mechanisms, hardly releases drug in the upper part of the GIT but rapidly releases in the colon following oral administration (Kumar et al., 2009). The therapeutic advantage of targeting drug to the colon includes:

- Colon is an ideal site for the delivery of agents to cure the local diseases of the colon (e.g., Diclofenac, Metaprolol) (Rubenstein, 2005).
- Delayed systemic absorption of drugs via colonic delivery is advisable for Chronotherapy of diseases such as asthma, hypertension, rheumatoid arthritis, which are affected by circadian rhythms. These diseases are characterized by night time or early morning symptoms. These types of approaches are beneficial for nocturnal release of drug, which in turn may provide considerable relief to the patients while they are resting. Colon targeting provides delivery of drug in its intact form as close as possible to the target site and improved therapy of diseases.
- The ability to cut down the conventional dose and reduces dosage frequency. Hence, lower cost of expensive drugs.
- Targeted drug delivery to the colon would ensure direct treatment at the disease site, possibly leading to a reduced incidence of side effects and drug interactions (e.g., 5-Aminosalicylic acid, Prednisolone, Vasopressin) (Ravi et al., 2009).
- The colon is an attractive site where poorly absorbed drug molecules may have an improved bioavailability (e.g., Ibuprofen, Theophylline, Isosorbides, Cyclosporine, Desmopressin) (Asghar and Chandran, 2006).
- The longer residence time, less peptidase activity, natural absorptive characteristics and high response to absorption enhancers make the colon a promising site for the delivery of protein and peptide drugs, oral vaccines, insulin, and growth hormones for systemic absorption (Maestrelli et al., 2008).
Reduce gastric irritation caused by many drugs (e.g., NSAIDS).

Bye pass initial first pass metabolism (e.g., Steroids, Nimustine, Bleomycin, Sermorelin, Saloatonin).

Colonic residence time is high. So, it’s desirable to achieve extended drug release in colonic fluid. Thus, improve patient compliance.

Limitations of colon targeting drug delivery system

Multiple manufacturing steps involved in preparation of colonic dosage form.

The colonic microflora causes metabolic degradation of the drug.

Lower surface area and relative tightness of the tight junctions in the colon can restrict drug transport across the mucosa into the systemic circulation.

Incomplete release of drug may be from dosage form (Rubinstein, 2000).

Bioavailability of drug may be low due to potentially binding of drug in a nonspecific way to dietary residues, intestinal secretions, mucus or faecal matter.

Drug should be in solution form before absorption. But, Colonic fluid volume is low as compared to stomach and intestinal fluid and therefore, dissolution is rate limiting step for poor soluble drugs (Jose et al., 2009).

Non availability of an appropriate dissolution testing method to evaluate in-vitro drug release from the dosage form (Chourasia and Jain, 2003).

An important limitation of the pH sensitive coating technique is the uncertainty of the location and environment in which the coating may start to dissolve. Normal in patients with ulcerative colitis (Manjanna et al., 2010).

2.5.1. ANATOMY AND PHYSIOLOGY OF COLON

The Gastrointestinal tract, also called the alimentary canal, which functions to digest dietary food, to absorb nutrients, electrolytes and fluid, and to prevent the absorption of potentially harmful substances. The digested materials that reach the large intestine contain few nutrients, but the residues remain here for 12-24 h. Major regions of the large intestine are the cecum, colon, rectum and anal canal as shown in figure 10. The colon forms the lower part of the GIT extends from the ileo caecal junction to the anus. The entire colon is about 5 feet (150cm) long. The major function of the colon is the consolidation of the intestinal contents into faeces by the absorption of water and
electrolytes and to store the faeces until excretion. The absorptive capacity is very high; each day about 2000 ml of fluid enters the colon from which more than 90 % of the fluid is absorbed. pH of the colon is 6.0–7.6 (Sarasija and Hota, 2000, Watts and Illum, 1997).

![Figure 10: Structure of Colon](image)

2.5.2. FACTORS TO BE CONSIDERED IN THE DESIGN OF COLON SPECIFIC DRUG DELIVERY SYSTEMS

Various factors affect the absorption of the drug molecules from the Colon. These factors include physiological, pathological and pharmaceutical factors.

**Physiological factors**

The physiological factors include:

- Barriers in Colonic absorption
- Gastrointestinal transit
- Gastric emptying time
- pH of the GI tract
- Colonic micro flora

**Barriers in Colonic absorption**

Drug absorption from the Colon can be limited by a number of barriers. The mucus layer at the epithelial surface, due to its highly charged and sieve-like nature, presents a formidable thermodynamic barrier to the transit of large, negatively-charged drug molecules. Although removal of the mucus barrier using mucolytic agents might seem
attractive, this may implicate in a variety of disease processes. Another physical barrier to drug absorption is at the level of epithelium, the drugs intending to pass from the epithelial barrier must do by passing through either Colonocytes (the transcellular route) or between adjacent Colonocytes (the paracellular route). Transcellular absorption involves passage of the drugs through cells and this is the route for lipophilic drugs takes, whereas paracellular absorption involves the transport of drug through the tight junctions between cells and is the route for most of the hydrophilic drugs takes. The poor paracellular absorption of many drugs is due to the fact that the epithelial cell junctions are very tight. Colon is a more selective site for the drug absorption than small intestine for many drugs (Vandamme et al., 2002). Co-administration of absorption enhancer such as dimethyl sulfoxide, Surfactants such as Polyoxyethylene lauryl ether, Chelating agents such as EDTA and Bile salts such as Taurocholate are increased transcellular and paracellular transport of drugs (Niibuchi et al., 1986).

**Gastrointestinal transit**

The average overall transit time from the mouth to the anus in humans is 24–72 h. In general, the transit time from the mouth to the small intestine in healthy human adults is 0.5–2 h, whereas it can be delayed to 3–6 h and 5–8 h after the intake of light meals and heavy meals, respectively. It is longer for solid meals than for liquids. The transit time from the stomach to the large intestine is 2–4 h, and that from the small intestine to the anus is 6–48 h. The transit time through the GI tract varies depending on various factors such as the GI motility, the quality and quantity of food ingested, dietary fiber content, mobility, stress, disease and drugs. Studies have shown that drugs that act on the parasympathetic or sympathetic nervous system affect the propulsive motor activity, thereby influencing the Colonic transit time (Mrsny, 1992).

**pH of the GI tract**

There is large variation of pH along entire GI tract. In the stomach pH ranges between 1 and 2 during fasting but increases to 5–6 after ingestion of a meal. Once the dosage form is discharged from the stomach it reaches small intestine where pH ranges from 6.5 in the proximal part and about 7.5 in the distal portion. From the ileum to the Colon pH declines significantly, it is about 6.4 in the caecum, because of the acidification of colonic contents by the products of bacterial fermentation (Vandamme et al., 2002).
Consequently polysaccharide drugs and diet can affect the colonic pH. Colonic pH is reduced in disease state (Evans et al., 1988). The strong acidic fluid of the stomach is one of the biggest obstacles to the delivery of intact acid labile prodrugs to the colon. These pH changes affect the degree of ionization of weak acidic and basic produgs and their chemical stability.

**Colonic micro flora**

The bacterial flora of animal GI tracts is a very complex ecosystem that contains various aerobic and anaerobic microorganisms. Approximately one third of fecal dry weight consists of bacteria, in which as many as 400 different bacteria species are found, which are predominantly anaerobic such as Bacteroids, Bifidobacterium, Eubacterium and Clostridium and a small number of fungi. The enzymes produced by these microorganisms can significantly metabolize endogenous and exogenous compounds. The carbohydrates and other dietary fiber is not digested in the stomach and small intestineare, but degraded by the action of polysaccharidase and glycosidase enzymes (Kumar et al., 2009).

**Pathological Factor**

The pathological states also have pronounced effect on Colonic absorption of drug molecules by affecting the Colonic transit. For example: diarrhoea will result in increase in the gastric motility and constipation results in decrease in colonic motility (Mrsny, 1992).

**Pharmaceutical factors**

The desired release profile of the active ingredient in the Colonic fluids affects the formulations for Colonic delivery. Generally, the dissolution and release rate from Colonic formulations is thought to be decreased in the Colon, which is attributed to the fact that less fluid is present in the Colon than in the small intestine. The poor dissolution and release rate may in turn lead to lower systemic availability of drugs. These issues could be more problematic when the drug candidate is poorly water-soluble and require higher doses for therapy. In general, delayed-release dosage forms which may be designed either to provide a ‘burst release’ or a sustained/prolonged release once they
reach the Colon. Physicochemical and biopharmaceutical properties of the drug such as solubility, stability, and permeability at the intended site of delivery affect the design of CDDS (Nirav et al., 2008).

2.5.3. METHODS OF TARGETING DRUG TO THE COLON

An oral colon targeted delivery system should retard drug release in the stomach and small intestine but allows complete release in the colon. The system designed for the delivery of drug in the colon, which is based on the core being coated with one or more successive layers of polymers. Two broad categories of biopolymers have been employed for formulating colonic systems are biodegradable and non biodegradable polymers. The mode of drug release from colon targeted biopolymer systems can include one or more of the following mechanisms (Chourasia and Jain, 2003):

- Diffusion
- Polymer erosion
- Microbial degradation
- Enzymatic degradation (mammalian and/or bacterial)

CDDS may be single or multiple unit dosage form. Single unit drug delivery systems may suffer from the disadvantage of unintentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology that may lead to drastically compromised systemic drug bioavailability or loss of local therapeutic action in the colon. Recently, much emphasis is being laid on the development of multiparticulate dosage forms because of the potential benefits like increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying (McNeill et al., 1993). Multiparticulate approaches tried for colonic delivery includes formulations in the form of pellets, granules, microparticles and nanoparticles. The multiparticulate systems enabled the drug to reach the colon quickly, because of their smaller particle size as compared to single unit dosage forms these systems are capable of passing through the GIT easily, leading to less inter and intra subject variability. Moreover, multiparticulate systems tend to be more uniformly dispersed in the GIT and also ensure more uniform drug absorption (Claudia and Leopold 1999). In general, four primary approaches for colon targeted delivery are:
pH dependent System

In the stomach, pH ranges between 1 and 2 during fasting but increases to 4 after eating. The pH is about 6.5 in the proximal small intestine and about 7.5 in the distal small intestine. From the ileum to the colon, pH declines significantly. It is about 6.4 in the cecum. The pH in the transverse colon is 6.6 and 7.0 in the descending colon. The pH-dependent systems take the advantage that pH of the human GIT. The most common and more practical method adopted by the pharmaceutical industry was the use of enteric coating, in which pH dependent system is developed by applying coating of pH sensitive polymer to core containing drug as shown in figure 11. The polymers described as pH dependent in colon specific drug delivery are insoluble and able to withstand at low pH levels but become increasingly soluble as pH rises and able to disintegrate at neutral or shortly alkaline pH of the terminal ileum and preferably at ileocecal junction. The discharge of the drug starts in the distal ileum and is completed in the ascending colon in either a slow release or a burst release manner.

The pH sensitive polymers like; Polyvinyl acetate phthalate (PVAP), Hydroxypropyl methylcellulose phthalate (HPMCP), Hydroxy propyl methylcellulose acetate succinate (HPMCAS), Eudragit L100-55, Cellulose acetate phthalate (CAP), Shellac, Eudragit S-100, and Cellulose acetate tri melitate (CAT), which will produce colon targeted delayed release system (Crison et al., 1995). These polymer coatings are insensitive to the acidic conditions of the stomach and dissolve only at the higher alkaline pH environment of the lower small intestine. Most commonly, copolymers of methacrylic acid and methyl methacrylate that dissolve at pH 6 (Eudragit L) and pH 7 (Eudragit S) have been investigated, the site specificity of these polymers can be poor. To overcome the problem of premature drug release, a copolymer of methacrylic acid, methyl methacrylate and ethyl acrylate which dissolves at a slower rate and at a higher threshold pH (7-7.5) has been developed. Colon targeted systems based on methacrylic resins have described for
insulin, prednisolone, quinolones, salsalazine, cyclosporine, beclomethasone dipropionate and naproxen (Brahma, 2007). Enteric coated colon targeted products available in market are listed in table 4.

![Schematic representation of enteric coated layered systems](image)

Figure 11: Schematic representation of enteric coated layered systems

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Name</th>
<th>Formulation</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesalamine</td>
<td>Asacol</td>
<td>Eudragit – S coated tablets</td>
<td>0.8-2.4 g/d</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>Salofac</td>
<td>Eudrigit – L coated tablets</td>
<td>1.0-4.0 g/d</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>Claversal</td>
<td>Eudrigit – L coated tablets</td>
<td>1.0-2.0 g/d</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Entocort</td>
<td>Eudrigit – L coated beads</td>
<td>9 mg/d</td>
</tr>
</tbody>
</table>

The site-specificity of pH dependent formulations can be poor. The shallow pH gradient between the small and large intestine, the pH change in disease state, decline in pH from the end of the small intestine to the colon, lengthy lag times at the ileo-cecal junction, rapid transit through the ascending colon and inter-subject variation in physiological parameters which can result in poor site-specificity of enteric-coated single-unit formulations.

**Time dependent systems**

One obvious alternative to the pH-dependent colonic carriers is the time-dependent drug release systems, in which hydrophilic, slow swelling polymers such as methylcellulose or hydroxypropylmethyl cellulose are used to delay drug unload after gastric emptying. Time controlled release system (TCRS) such as sustained or delayed release dosage forms are also very promising drug release systems. Time dependent delivery systems release their drug load after a preprogrammed time delay. To attain colonic release, the
lag time should equate to the time taken for the system to reach the colon. Colon targeting is achieved by prolonging the lag time of about 5 to 6 hours.

One of the earliest systems to utilize this principle was the Pulsincap® device. Pulsincap® was discussed earlier in the chapter 2, refer page no. 14 to 15 for more information. However, due to potentially large variations of gastric emptying time of dosage forms in humans, in these approaches, colon arrival time of dosage forms cannot be accurately predicted, resulting in poor colonical availability. Thus, time dependent systems are not ideal to deliver drugs to the colon specifically for the treatment of colon related diseases; because of the following disadvantages (Vandelli et al., 1996):

- Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake. Limitation of time dependent release systems is that they are not able to sense any variation in the upper GIT transit time.
- Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug.
- Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhea, and the ulcerative colitis.

Appropriate integration of pH sensitive and time release functions into a single dosage form may improve the site specificity of drug delivery to the colon. Enteric coated time-release press coated (ETP) tablets, are composed of three components, a drug containing core tablet (rapid release function), the press coated swellable hydrophobic polymer layer (Hydroxy Propyl cellulose layer (HPC), time release function) and an enteric coating layer (acid resistance function) as shown in figure 12. The tablet does not release the drug in the stomach due to the acid resistance of the outer enteric coating layer. After gastric emptying, the enteric coating layer rapidly dissolves and the intestinal fluid begins to slowly erode the press coated polymer (HPC) layer. When the erosion front reaches the core tablet, rapid drug release occurs since the erosion process takes a long time as there is no drug release period (lag phase) after gastric emptying. A nominal lag time of five hours is usually considered sufficient to achieve colon targeting. The duration of lag
phase is controlled either by the weight or composition of the polymer (HPC) layer. Mixture of Hydroxypropylmethyl cellulose (HPMC) and lactose powder compression coated on core tablets of 5-fluorouracil, for colon drug delivery that based on time-dependent approach.

**ETP tablets**

Figure 12: Design of enteric coated timed-release press coated tablet

**Microbially triggered colonic drug delivery system**

Apparently, a more expedient approach for site-specific drug delivery to the colon is by developing systems, which can sense arrival into the colon and release the drug upon activation. Such systems can be formulated utilizing some specific property of the colon in comparison to the other parts of the GIT. The gastrointestinal tract is inhabited by a variant microflora all along. A large number of anaerobic and aerobic bacteria are present the entire length of the human GI tract. The resident gastrointestinal bacteria provide a further means of effecting drug release in the colon. GI tract contains aerobic bacteria such as *E. Coli, Strepto cocci, Staphylo cocci, Lactobacilli, Fungi etc.*, and anaerobic bacteria such as *Bacteroids, Bifid bacteria* etc. These bacteria predominantly colonize the distal regions of the GIT, where the bacterial count in the colon is $10^{11}$ per gram, as compared with $10^4$ per gram in the upper small intestine. The flora becomes diverse and luxuriant in the colon. Moreover, 400 different species are present in colon. Colonic bacteria are predominately anaerobic in nature, survive by fermenting a wide range of substrates left undigested in the small intestine and produce enzymes like; β-glucuronidase, β-xylosidase, α-arabinosidase, β-galacto sidase, nitroreductase, azoreductase, deaminase, hydroxylase etc., that are capable of metabolizing endogenous and exogenous substrates, such as carbohydrates (e.g., oligosaccharides, polysaccharides,
mucopolysaccharides) and proteins that escape digestion in the upper GIT (VR sinha and Rachana, 2001). It appears today that cleavage of biodegradable polymers by the colonic bacterial flora is a more attractive mode of colon targeting. Many of the polysaccharide-based delivery systems shield the drug from the hostile environments of the upper GIT. When these delivery systems arrive into the colon, glycosidic linkages within the polysaccharides are hydrolysed releasing the drug candidate. The main saccharolytic species are *Bacteroides* and *Bifidobacterium*. So, hydrolysis of saccharide substrates is equally attractive for the design of targeting tools to the colon.

Polysaccharides, the polymer of monosaccharide retains their integrity because they are resistant to the digestive action of gastrointestinal enzymes. The matrices of polysaccharides are assumed to remain intact in the physiological environment of stomach and small intestine but once they reach in the colon, they are acted upon by the bacterial polysaccharidase enzyme and results in the degradation of the matrices. To obtain energy for cellular functions, the colonic bacterial flora ferments a variety of nonabsorbable di-, oligo and plant polysaccharides by secreting typical glycosidic enzymes such as amylase, pectinase, xylanase, β-D-xylosidase, β-D-galactosidase and β-D-glucosidase. This family of natural polymers used for the area of drug delivery as it is comprised of polymers with a large number of derivatizable groups, a wide range of molecular weights, varying chemical compositions, wide availability, inexpensive, nontoxic, biodegradable and high stability (Lagusundaram et al., 2009). A large number of polysaccharides have been investigated for their use in colon targeted drug delivery systems are listed in table 5. The most important fact in the development of polysaccharide derivatives for colon targeted drug delivery is the selection of a suitable biodegradable polysaccharide. As these polysaccharides are usually found to be too water soluble, are crosslinked or derivatized to made water insoluble by crosslinking to allow their passage in the small intestine. Very important is an optimal proportional of the hydrophobic and hydrophilic parts respectively and the number of free hydroxy groups in the polymeric molecule (Patel et al., 2007). Although offering more accurate homing tools, polysaccharide colonic delivery systems suffer from a premature release of their drug load to a certain extent in the upper segments of the GI tract. This early discharge is inherent and associated with the swelling of the carrier. So, most enzymatically
controlled colonic drug carriers cannot function optimally without the aid of a protective coat (primary carrier), whether pH-dependent or depending on the erosion of a physical barrier. Other option is polysaccharides are mixed with other synthetic film forming polymers to form mixed films, which overcome the poor film forming property of polysaccharides and resist drug release in the tracts of the upper GIT but retain the bacterial degradability.

**Table 5:** Various biodegradable polysaccharides for colon targeting

<table>
<thead>
<tr>
<th>Polysaccharide</th>
<th>General Properties</th>
<th>Drug used</th>
<th>Bacterial Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylose</td>
<td>Unbranched starch consisting of D-glucopyranose residues linked by α-(1→4) bond</td>
<td>Diclofenac sodium, Propranolol HCl</td>
<td>Bacteroids, Bifidobacterium</td>
</tr>
<tr>
<td>Chitosan</td>
<td>high molecular weight cationic polysaccharide, poly(N-glucosamine) derived from chitin in crab and shrimp shells by deacetylation</td>
<td>5-(6) carboxy fluorescein (CF), Sodium Diclofenac, Acetaminophen, Insulin</td>
<td>Bacteroids</td>
</tr>
<tr>
<td>Chondroitin</td>
<td>Mucosopolysaccharides consists of D-glucuronic acid linked to D-acetyl-D-galactosamide, which is sulphated at C-6</td>
<td>Indomethacin, Atenolol, 5-ASA</td>
<td>Bacteroids</td>
</tr>
<tr>
<td>Sulfate</td>
<td>Cyclic structure of 6, 7 or 8 glucose units linked through α-(1,4')-glucosidic bonds</td>
<td>Telmisartan, Lornoxicam</td>
<td>Bacteroids</td>
</tr>
<tr>
<td>Cyclodextrins</td>
<td>a linear polymer backbone with mainly 1,6-α-β-glucopyranosidic linkage</td>
<td>Naproxen, Hydrocortisone</td>
<td>Bacteroids</td>
</tr>
<tr>
<td>Dextran</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Guar gum
- naturally occurring galactomannan polysaccharide consisting of a linear chain of β-D-mannopyranose joined by β-(1–4) linkage with α-D-galactopyranosyl units attached by 1,6-links in the ratio of 1:2

### Pectin
- non-starch linear polysaccharides with mainly α-(1–4)-linked D-galacturonic acid residues interrupted by 1,2-linked L-rhamnose residues

### Inulin
- naturally occurring polysaccharide, chemically, it consists of β-2-1 linked D-fructose molecules, having a glucosyl unit at the reducing end

### Alginates
- A linear polymer consisting of D-mannuronic acid and L-guluronic acid residues arranged in blocks in polymer chain. Sodium salt of alginates used

### Xanthan gum
- Trisaccharide of β-D-mannose-β-D-guluronic

<table>
<thead>
<tr>
<th>Ph.D Thesis</th>
<th>Introduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guar gum</td>
<td>Methotrexate, 5-fluorouracil, Dexamethasone, Bacteroids, Ruminococcus</td>
</tr>
<tr>
<td></td>
<td>Budesonide, diltazem HCl</td>
</tr>
<tr>
<td>Pectin</td>
<td>Indomethacin, Carvedilol, Ropivacaine, Bacteriods, Bifidobacterium</td>
</tr>
<tr>
<td></td>
<td>Paracetamol, Theophylline Eubacterium</td>
</tr>
<tr>
<td>Inulin</td>
<td>Diclofenac sodium, metoprolol Bifidobacterium</td>
</tr>
<tr>
<td>Alginates</td>
<td>5-ASA, metoprolol tartrate Bacteriods, Bifidobacterium</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>Diltazem HCl, ibuprofen Bacteroids</td>
</tr>
</tbody>
</table>
acid-\(\alpha\)-D-mannose attached with alternate glucose residues of the main chain

**Prodrug Approach**

There is a steep gradient of enzyme activity along the GIT; these enzymes are derived from gut microflora. There are a no. of reducing enzymes such as nitroreductase, azoreductases, N-oxide reductase, sulphoxide reductase, hydrogenase and hydrolytic enzymes such as esterases, amidases, glycosidases, glucuronidase, sulfatase. Enzymes produced by the colonic bacterial are capable of catalyzing a number of metabolic reactions, which includes reduction (of double bonds, nitro groups, azo groups, aldehydes, sulphoxides, ketones, alcohols, N-oxides and arsenic acid), hydrolysis (of glycosides, sulphates, amides, esters, nitrates, and sulphonates), deamination, decarboxylation, dealkylation, acetylation, nitrosamine formation, heterolytic ring fission and esterification. The prodrugs, from which the release of drug is triggered by the action of colonic bacteria enzymes such as azo-reductase, glucosidases, and glucronidases in the colon have devised (Krishnaiah and Satyanarayana, 2001).

A prodrug is a pharmacologically inactive derivative of a parent molecule that requires enzymatic transformation in the biological environment to release active drug at the target site. This approach involves covalent linkage between the drug and its carrier; so that upon oral administration, the moiety remains intact in the upper part of the GIT and after reached in the colon, enzymatic cleavage will regenerate the drug. The choice of carrier is largely determined by the functional group available on the drugs (Vyas and Khar, 2002). The problem of stability of certain drugs from the adverse environment of the upper GIT can be eliminated by Pro drugs formation, which is converted into parent drug molecule once it reaches to colon.

Back in 1942, Svartz discovered one of the first marketed azo prodrug, made by binding sulfapyridine to 5-ASA through the azo linkage, sulfasalazine was developed to deliver the sulfapyridine site-specifically to the colon for the treatment of intestinal infection
(figure 13), later drug was found to be effective in the treatment of inflammatory bowel
diseases/ulcerative colitis, its pharmacological activity is attributable to the 5-ASA moiety that is released after cleavage of the azo linkage. Other azo prodrugs of 5-amino salicylic acid are olsalazine, and balsalazine (Intestinol®), all of them containing two molecules linked by an azo bond as shown in figure 13. The prodrugs pass the stomach and the small intestine unchanged and on reaching the caecum, the azo linkages are cleaved to form a pair of amines by the action of azoreductases produced by anaerobic bacteria in the colon, the drug is released in a micro-fine physical state that promotes absorption and guarantees maximum topical and systemic activity (VR sinha and Rachana, 2001).

Figure 13: The examples of 5-amino salicylic acid prodrugs: sulfasalazine (I), olsalazine (II) and balsalazine (III)

A number of other linkages susceptible to bacterial hydrolysis specifically in the colon have been prepared where the drug is attached to hydrophilic moieties like amino acid, glucuronic acid, glucose, galactose, cellulose etc. There are a large number of plant glycosides such as flavonoids, amygdalins, and sennosides. Further, many exogenous and endogenous substances are metabolized to water-soluble glucuronides in mammals and are excreted as the conjugates. These glycosides and glucuronides are polar compounds
and are generally poorly absorbed from the GI tract. As a result, when these conjugates reach the lower portions of the GI tract, they are hydrolyzed to liberate the aglycones by the action of colonic bacteria, so, glucosides and glucuronides can work as colon-specific delivery prodrugs. The steroid glycoside prodrugs such as dexamethasone-β-d-glycoside, prednisolone-β-d-glycoside and budenoside-β-D-glucuronides; are evidently better targeted to the colon. They show a more favourable anti-inflammatory effect in the large intestine, a better bioavailability, and potentially reduced side effects, because the effective dose can be reduced (Krishnaiah and Satyanarayana, 2001). The narcotic prodrugs like; naloxone-β-d-glycoside and nalmefene-β-d-glycoside also pass the small intestine unabsorbed and are enzymatically cleaved by glycosidases of microflora, to liberate drug after reaching the caecum.

Amino acids such as alanine, methionine, tyrosine, and glutamic acid consisting of polar groups like -NH$_2$ and -COOH have been used as carriers for colon-targeted drug delivery. These prodrugs were designed to be bulky and hydrophilic to remain unabsorbed in the upper GIT. However, the intestinal microflora of the colon hydrolyzed the drug-amino acid conjugate and the drug was released free into the lumen of the colon. An example of such amino acid conjugates includes amide linkage formed between 5-ASA and glycine.

Drug-dextran conjugates are synthesized by direct attachment of a drug with a carboxylic group to dextran. Once they reach the caecum, dextranases of the colonic microflora cleave the ester bond, converting the prodrug to the effective drug. An instructive example is the prodrug naproxen-dextran (Bronsted et al., 1995). Cyclodextrins (CyDs) are cyclic oligosaccharides usually consisting of six to eight glucose units, which are called α-, β-, and γ-cyclodextrins, respectively. They are fermented by some colonic microflora into small saccharides and thus absorbed as maltose or glucose in the large intestine. Cyclodextrin prodrugs were prepared by conjugating 5-ASA, biphenylylacetic acid (BPAA), ketoprofen, a steroidal drug prednisolone, and anticancer agent 5-fluorouracil on to the hydroxyl groups of α-, β-, and γ-cyclodextrins through an ester linkage and investigated the release in colon.
2.5.4. NOVEL APPROACHES FOR COLONIC DRUG DELIVERY SYSTEMS

- Osmotic controlled drug delivery to colon (OROS – CT)
- CODESTM (A novel colon targeted delivery system)

**Osmotic Controlled Drug Delivery (OROS-CT)**

The OROS-CT (Alza Corporation) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable. The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 push-pull osmotic units of 4 mm in diameter encapsulated within a hard gelatin capsule as shown in figure 14. Push pull osmotic pump contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. This osmotic pump is enteric coated and an orifice is drilled through the membrane on the drug layer side (Watanabe, 1998). After swallowing of the OROS-CT, the gelatin capsule containing the push-pull units dissolves and all units liberated in gastric environment. Because of its enteric coating, each push-pull unit is prevented from absorbing water in the acidic environment of the stomach and hence no drug is release. As the unit enters the small intestine, the enteric coating dissolves in this higher pH environment (pH >7), water enters the unit, causing the osmotic push compartment to swell and swelling of the push compartment, forces drug from drug compartment to out of the orifice at a rate precisely controlled by the rate of water absorption through the semipermeable membrane. For treating ulcerative colitis, each push pull unit is designed with a 3-4 h delay release time to prevent drug release in the small intestine. Drug release starts only when the unit reaches the colon. OROS-CT units can maintain a constant release rate for up to 24 hours in the colon.

**Novel Colon Targeted Delivery System (CODESTM)**

CODESTM was designed to avoid the inherent problems associated with pH or time dependent CDDS systems. CODESTM is a combined approach of pH dependent and microbial triggered CDDS. It has been developed by utilizing a unique mechanism involving lactulose, which acts as a trigger for site specific drug release in the colon (Shown in figure 15). The system consists of a tablet core containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently over coated with an enteric material, Eudragit L (Jeong et al., 2002). Upon administration, the
enteric coating protects the tablet while it is located in the stomach and then dissolves quickly upon reaching into intestine. The acid soluble material coating then protects the preparation as it passes through the alkaline pH of the small intestine. As the tablet arrives in the colon, the bacteria enzymatically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH surrounding the tablet and initiates the dissolution of the acid soluble coating and subsequent drug release (Jain et al., 2007).

![Diagram](image)

**Figure 14:** Osmotic controlled colon targeted drug delivery system

**2.5.5. EVALUATION OF COLON TARGETED DRUG DELIVERY SYSTEM**

*In vitro* methods

The ability of the coats/ carriers to remain intact in the physiological environment of the stomach and the small intestine is generally assessed by conducting drug release studies. *In vitro* dissolution study of Colon delivery systems is performed using the USP dissolution apparatus in multimedia for different periods of time to stimulate the gastrointestinal tract pH and transit time that the colon specific delivery system might encounter *in vivo*. To stimulate the pH changes along the gastrointestinal tract, the dissolution study is carried out in media with pH 1.2, pH 6.8, and pH 7.2 sequentially. *In vitro* dissolution study is performed for 2 h in the pH 1.2 medium and then media is replaced with fresh pH 6.8 dissolution medium for 3 h. After 2 h, dissolution medium is replaced with pH 7.2 dissolution medium and study is performed until more than 80%
drug release. For colon targeted drug delivery, there should be no drug release in dissolution study at pH 1.2 and pH 6.8. The colonic pH is near to 7.2, so, there should be complete drug release in pH 7.2 dissolution media (Vandelli et al., 1996, Jain et al., 2007).

**Figure 15:** Schematics of the conceptual design of CODESTM

For microbially triggered colonic system, to study the effect of microbial degradation of polymers on drug release, the *in vitro* dissolution study by carried out in a pH 7.2 dissolution media containing rat/rabbit/guinea pig cecal contents under anaerobic conditions because cecal content is rich with the enzyme contents. For Enzyme induction, 2 ml of a 1 % w/v dispersion of a natural polymer in water is administered to the rat/rabbit/guinea pig daily for 7 days before the study. The abdomen is cut, ceci is isolated and ligated at both ends and discrete. About 8 gm of cecal content is weighed and transfer to phosphate buffer pH 7.2 and CO₂ continuously pass through solution to provide anaerobic condition (Kumar et al., 2009, Sarasija and Hota, 2000).
In vivo methods

In vivo studies are usually performed to evaluate the site specificity of drug release. Although animal models have obvious advantages in assessing Colon-specific drug delivery systems, human subjects are increasingly utilized for evaluation of this type of delivery systems with visualization techniques such as γ-scintigraphy imaging.

Animal studies

Different animals such as rats, pigs and dogs have been used to evaluate the performance of CSDD (Hata et al., 1994). To closely simulate the human physiological environment of the Colon; the selection of an appropriate animal model for evaluating a Colon-specific delivery system depends on its triggering mechanism and system design. For example, guinea pigs have comparable glycosidase and glucuronidase activities in the Colon and similar digestive anatomy and physiology to that of human, so they are more suitable in evaluating glucoside and glucuronate conjugated prodrugs intended for Colon delivery. Rats are also used to evaluate Colon-specific drug delivery systems based on azo-polymers or prodrugs containing azo bonds because the distribution of azoreductase activity in GI tract is similar between rats and human subjects. The in vivo study of CODESTM was evaluated in beagle dogs using acetaminophen as a model drug and lactulose as the matrix-forming excipient in the core tablet. The ability of intestinal PCDCs to obtain Colon-specific delivery was also investigated in beagle dogs (Shibata et al., 2001).

Human studies

A variety of techniques like (I) endoscopy (II) roentgenography (III) gamma scintigraphy are used for monitoring the in vivo behavior of the oral dosage forms.

Endoscopy

It is an optical technique in which a fibre is used to directly monitor the behavior of the dosage form after administration. This method requires administration of a mild sedative to facilitate the swallowing of the endoscope tube (Van et al., 1995).

Roentgenography

The inclusion of radio-opaque material into the solid dosage form enables it to be
visualized by the use of X-rays. By incorporating Barium sulfate into the pharmaceutical dosage forms, it is possible to follow the movement, location and the integrity of the dosage form after oral administration by placing the subject under a fluoroscope and taking a series of X-rays at various time points (Van et al., 1995).

**Gamma scintigraphy**

The most useful technique, to date, to evaluate the in vivo behavior of dosage forms in animals and humans is external γ-scintigraphy. It requires the presence of γ-emitting radioactive isotope in the dosage form that can be detected in vivo by an external gamma camera. The dosage form can be radio-labelled using conventional labeling or neutron activation methods (Van et al., 1995).

2.6. **SOLVENTLESS COATING TECHNIQUE**

To overcome the disadvantages of film coating, Solventless coating technology has come up with the use of solvents like solvent exposure, solvent disposal, and residual solvent in product in pharmaceutical coating. It reduces the cost by eliminating the tedious and expensive processes of solvent disposal/treatment. Solventless coating techniques are being actively investigated that are used to coat pharmaceutical tablets and capsules.

- Compression coating
- Electrostatic Powder coating
- Magnetically Assisted Impaction Coating (MAIC)
- Hot Melt Coating

2.6.1. **ELECTROSTATIC POWDER COATING**

The method of electrostatic powder coating is very useful in paint technology, food technology, metal coatings, and finishing industry. It is also useful in the coating of tablets as well as capsules (Aline et al., 2009). The principle of electrostatic powder coating involves spraying of a mixture of finely grounded particles and polymers onto a substrate surface without using any solvent and then heating the substrate for curing on oven until the powder mixture is fused into film. According to the charging mechanism, steps in the deposition of charged particles onto the substrate are (Cerea et al., 2004):
a) Charged particles are uniformly sprayed onto the substrate in virtue of mechanical forces and electrostatic attraction,

b) Particles accumulate on the substrate before the repulsion force of the deposited particles against the coming particles increase and exceed the electrostatic attraction,

c) Finally once the said repulsion becomes equivalent to the said attraction, particles cannot adhere to the substrate any more, and the coating thickness does not increase any more.

Properties of powder such as particle size distribution, chemical composition, electrical resistivity, hygroscopicity, fluidity and shape distribution play significant role on the performance of powder coating such as transfer efficiency, film thickness, adhesion and appearance (Mazumder et al., 1997). Also deposition temperature, nozzle-to-substrate distance, and nozzle geometry plays an important role in the electrostatic coating process (Leeuwenburgh et al., 2006). The uniformity of the powder coating by moving the powder sample is measured by the infrared light transmission through it.

2.6.2. MAGNETICALLY ASSISTED IMPACTION COATING (MAIC)

Conventional coating methods that can attach the guest (coating material) particles onto the host (material to be coat) particles causes degradation of particle size, shape and composition caused by the building up of heat. Many pharmaceutical ingredients, being organic and relatively soft, are very sensitive to heat and can quite easily be deformed by severe mechanical forces. The magnetically assisted impaction coating (MAIC) devices can coat guest particles on the soft organic host without causing major changes in the material shape and size. The rise in temperature is negligible; this is an added advantage when dealing with temperature sensitive powders such as pharmaceuticals (Ramlakhan et al., 2000).

Apparatus for MAIC consists of processing vessel surrounded by the series of electromagnets connected to the alternating current. The measured mass of the magnetic particles, host and guest materials are placed in the vessel. When a magnetic field is applied, the magnetic particles are agitated and move furiously inside the vessel,
producing a fluidized bed system. These agitated magnetic particles impart energy to the host and guest particles, causing collisions and allowing coating to be achieved by means of impaction or peening of the guest particles onto the host particles. The magnetic particle motion studies suggest that the primary motion due to the magnetic field is promoting de-agglomeration of the guest particles, allows impaction of one particle onto another, causes spreading and shearing of the guest particles onto the surface of the host particles. Thus, it is promoting coating and formation of coated products. The parameters have to be affected are magnetic particle size, mass ratio of magnetic particles to powder host and guest particles, guest particle size, processing time, current or voltage, and frequency (Singh et al., 2001).

2.6.3. HOT MELT COATING

In hot melt coating method, the coating material is applied in its molten state on the substrate then solidified by cooling. Hence, the necessity of the application of any solvent is fully eliminated in coating of pharmaceutical formulation like tablets and pellets. Lipid, waxes, fatty bases and hydrogenated vegetable oils are the most suitable coating material in hot melt coating. As the lipid based coatings are less expensive, less weight gain and processing time is short, hot melt coating is also cost effective (Padsalgi et al., 2008). The various technologies of hot melt coatings are:

a) Fluidized bed coating (top spray and bottom spray),
b) Spray congealing/coating,
c) Pan coating (pan spray and pan pour).

Fluidized bed coating method proved capable of coating tablets up to 1 g (John and Paul, 1996). Spray coating/congealing, is a process whereby slurry of molten matrix material and substrate is sprayed through into a cooling chamber, where the droplets solidify rapidly. In pan coating, conventional pan coater can be used for the hot melt coating. Only the difference is that the coating agent is in molten state instead of solution state. Pan spray coating technique is the best technique to control the release due to uniform film formation, while pan pour technique shows variation in the release of drug from the same batch due to non uniform coating and very low coating efficiency.
Various key factors should be considered during the hot melt coating like molecular weight, thermal behavior, and rheology of excipients in molten state because they affect the strength, flexibility, rheological and drug release pattern of the coat. A difficulty in hot melt coating is maintaining adequate operational safety, as high temperatures, close to 200°C, are employed. The choice of coating excipients depends primarily on its “functional” (such as retardation drug release rate, prevention of environmental degradation, and masking of unpleasant taste) in the dosage form (Achanta et al., 1997). For sustain release applications, as a coating excipients such as as natural and synthetic waxes, hydrogenated vegetable waxes, polyglycolysed glycerides are used. Examples of some marketed hot melt coating excipients are Gelucires, Precirol, Stearines, Myvaplex, Compritol 888ATO (Barthelemya et al., 1999).

2.6.4. COMPRESSION COATING TECHNIQUE

Although less popular, it gained increased interest in the recent years for creating modified release products. It involves the compaction of coating materials around a preformed tablet core using specially designed tablet compression equipment. So, it is known as press coating. This technique does not require use of any special solvent for coating purpose. So, compression coating also known as solventless coating technique or dry coating technique (Hardik et al., 2011). Compression coated tablet has two parts, internal core and surrounding coat.

![Compression coated tablet](image)

**Figure 16:** Compression coated tablet

**Advantages of compression coating over solvent coating process**

A dry-coated tablet was recently renewed as a novel system to deliver a drug in a pulsatile way, at predetermined times following oral administration. This novel system is
not only rate controlled but is also time controlled. Press coating gained wide interest claiming some advantages over regular and pan coating, such as:

- The dry-coated tablets were prepared by a direct compression method. This compression method eliminates the time-consuming and complicated coating or granulation processes and also improves the stability of the drug by protecting it from moisture.
- This technique has many advantages because no special coating solvent or coating equipment are needed for coating of tablet and manufacturing speed is faster (Swati et al., 2010).
- It reduces the cost by eliminating the tedious and expensive processes of solvent disposal/treatment. Moreover, the technology can significantly reduce the processing time because there is no drying and evaporation step and the entire process is done without any heat in most cases and thus can provide an alternative technology to coat temperature-sensitive drugs (Cole et al., 1995).
- Development of press coating technique, hydro-alcoholic film-coating was ceased on account of the growing awareness of environmental and safety issues connected with the use of organic solvents (Zhu and Zhang, 2005).
- Low labor and energy requirements.
- Validation of this process is easy because parameters that require great control are less.
- To protect hygroscopic, light-sensitive or oxygen-labile drugs from environmental-atmospheric ill effects (Janugade et al., 2009).
- Compression coating often used to prevent decomposition of acid-labile drugs by gastric fluids by coating enteric polymer over the core tablet containing drug, so that; it will not release the drug in stomach.
- Often, compression coating also used to separate two incompatible materials (one in the core and the other in the coat), for example: Artesunate and Amodiaquine compression coated tablet.
- This technique also applied for drugs that require modification of drug release (such as repeat-type tablets). For a repeat action tablet, as the outer layer provides the initial dose while the inner core release the drug later on (Janugade et al., 2009).
➢ To mask bitter taste of drug and for protection of volatile substances (Swati et al., 2010).

➢ It provides alternative approach to the multilayer tablet, to achieve quick/slow or slow/quick release pattern. Example: A quick/slow release pattern is achieved by compression coating of quick release ibuprofen components over the slow release ibuprofen tablet core. Quick release coating components contains ibuprofen with crosscarmellose sodium, while, slow releasing tablet core is polymeric matrix of HPMC K100M and ethylcellulose, into which ibuprofen is dispersed.

➢ To protect the gastric mucosa from irritation by certain drugs by using enteric coating material in the outer press-coating granules.

However, common drawbacks of the press-coating technique are:

➢ The multistep processes involved.

➢ Reproducible central positioning of the core tablet within press-coated tablet (PCT) is a major challenge for large scale industrial manufacturing.

➢ Difficulties in achieving good friability values after press coating of immediate release powder onto controlled release tablet core due to poor adhesion of powder to the coating.

The only requirement for producing the compression-coated tablet dosage form is that the core material should possess the ability to flow into a die during production.

Methods of compression coating

The conventional compression coating method

This type of tablet (compression coated tablet) has two parts, internal core and surrounding coat. The core tablet is small porous tablet and prepared on one turret. For preparing compression coating of core tablet, another turret with a bigger die cavity is used. The conventional compression coating method is as follows: 1) first the coat material is filled inside of the die to half, 2) core tablet is mechanically transferred on the powder for the outer layer, 3) surround the core tablet with the remaining coat material, 4) compress the powder, which has the core tablet inside. Major disadvantage of this method is to achieve a reproducible central positioning of the core tablet within press-
coated tablet (PCT). It require to perform two steps separately; formation of tablet core and compression coating of coating components on to tablet core as shown in figure 17.

![Diagram of conventional compression coating method]

**Figure 17**: Steps involved in conventional compression coating method

**One step dry coating method**

Now a day, a novel One Step Dry Coated Tablets (OSDRC) manufacturing method has been invented. The manufacturing method for OSDRC is different from conventional methods in that dry-coated tablets can be made with only one process. One of the major
advantages of OSDRC is that we can expect to produce dry coated tablets, which always contain the core tablet exactly in the center of the whole tablet. The schematic sequence of the OSDRC manufacturing method is shown in figure 18. This OSDRC manufacturing method is developed by a rotary type tableting machine using a single set of punches and die. Every upper and lower punch in the OSDRC system has a double structure as shown in figure 18. Each punch consists of a center punch (diameter: 6 mm) and an outer punch (diameter: 7, 8 and 10 mm).

The OSDRC system employs three compression processes. The first compression forms lower outer layer (indicated as the first-outer layer), the second compression to builds up the first-outer layer/core complex and the third compression shapes the whole tablet, including both the upper-outer and side-outer layers (indicated as the second-outer layer).

In the first step to form the first-outer layer, the lower-center punch is slid down to fill up the space made by the lower-center punch with the powder for the first-outer layer (Polymer). Then, the powder is pre-compressed by the upper-center punch. While the upper-center punch is pushing down the pre-compressed first-outer layer to downward, the lower-center punch slid down at the same time. After pre-compression, the upper-center punch is pull up to create a space, which was to be filled up with the drug powder for the core. Drug powder is then subjected to pre-compression by the upper-center punch, this form complex of first outer layer with core powder. While the upper-center punch is pre-compression, the lower-outer punch is sliding down, that create the space over the pre-compressed complex of the first-outer/core, and which is fill up with the remaining powder (Polymer) to build up the second-outer layer. At the last compression, the remaining powder is compress by the upper and lower punches with the pre-compressed complex. The final compression employs simultaneous movement of the center and outer punches at a fixed speed of 1mm/min under constant pressures. The tips of the center and outer punches were adjusted to create a flat face like a normal punch. The quantity of powder for the second-outer layer was adjusted to create the same thickness as that of the 1st-outer layer (Yuichi et al., 2004).
Figure 18: Steps of OSDRC manufacturing method.
2.7. DRUG PROFILE

ATENOLOL

Atenolol is classified as a β₁-selective (or 'cardioselective') drug, one that exerts greater blocking activity on myocardial β₁-receptors than on β₂ receptors in the lung. Atenolol is a selective β₁ receptor antagonist, a class of drugs used primarily in cardiovascular diseases. It is used as first-line treatment of hypertension. Atenolol works by blocking the action of certain natural chemicals in your body, such as epinephrine, on the heart and blood vessels. This effect lowers the heart rate, blood pressure, and strain on the heart.

Atenolol exerts greater blocking activity on myocardial β₁-receptors than on β₂ receptors in the lung. The β₂ receptors are responsible for keeping the bronchial system open. If these receptors are blocked, bronchospasm with serious lack of oxygen in the body can result. However, due to its cardioselective properties, the risk of bronchospastic reactions if using atenolol is reduced compared to nonselective drugs as propranolol. Unlike propranolol, atenolol does not pass through the blood–brain barrier thus avoiding various central nervous system side effects (Gurpreet et al., 2009).

![Chemical structure of atenolol](image)

**Figure 19:** Chemical structure of atenolol

**Synonyms:** 1-p-Carbamoylmethylphenoxy-3-isopropylamino-2-propanol, 4-(2-Hydroxy-3-((1-methylethyl)amino)propoxy)benzeneacetamide (BP’ 2007)

**Category:** Antihypertensive agents, Adrenergic beta-1 receptor antagonists, Sympatholytics, Anti-arrhythmia agents

**Molecular weight:** 266.3361 g/mol

**Chemical structure:** C₁₄H₂₂N₂O₃ (IP’ 2007)
IUPAC name: 2-(4-{2-hydroxy-3-[(propan-2-yl)amino]propoxy}phenyl)acetamide

Melting point: 154 to 156°C

Water solubility: 1.33*10^4 mg/L (at 25 °C), 4.29*10^-1 g/l (Maryadele et al., 2006)

logP: 0.57

pKa: 9.6

CAS number: 29122-68-7

ATC code: C07AB03

Route of administration: Oral or IV

Absorption: Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces.

Protein binding: Plasma protein binding is 6-16%.

Toxicity: LD_{50}=2000-3000 mg/kg (orally in mice) (USP’ 2007).

Dosage forms: Oral Tablet: 25 mg, 50 mg, 100 mg, Intravenous Injection: 0.5 mg/ml

Pharmacokinetic data (http://www.drugbank.ca/drugs/DB00335)

- \( t_{max} = 2 \) to 4 hours after oral dosing (time elapsed before maximal concentration in the blood plasma is reached)

- **Half life**: The mean elimination half-life is 6-7 hours. However, the action of the usual oral dose of 25 to 100 mg lasts over a period of 24 hours.

- **Metabolism**: Atenolol undergoes little or no metabolism by the liver (<10%). A compromised liver function does not lead to higher peak-activity and/or a longer half-life with possible accumulation. This makes it attractive for use in individuals with end-stage liver disease.

- **Excretion**: In oral route, unabsorbed drug is excreted unchanged in the feces and the absorbed portion is eliminated primarily by renal excretion. Atenolol is excreted almost exclusively by the kidneys and is well removable by dialysis.

Medical uses

Atenolol is used with or without other medications to treat high blood pressure (hypertension) and in long-term management of patients with angina pectoris. Atenolol is used for a number of conditions includes: hypertension, angina, long cough, acute myocardial infarction, supra ventricular tachycardia, ventricular tachycardia, and the symptoms of alcohol withdrawal. Lowering high blood pressure helps prevent strokes,
heart attacks, and kidney problems. This medication is also used to treat chest pain (angina) and to improve survival after a heart attack. This medication may also be used to treat irregular heartbeat, heart failure, alcohol withdrawal symptoms, and to prevent migraine headaches (Lindholm, 2005, http://www.drugbank.ca/drugs,DB00335).

**Mechanism of action**

Atenolol competes with sympathomimetic neurotransmitters such as catecholamines for binding at β1-adrenergic receptors in the heart and vascular smooth muscle, inhibiting sympathetic stimulation. This results in a reduction in resting heart rate, cardiac output, systolic and diastolic blood pressure, and reflex orthostatic hypotension (Brown et al., 1976, http://www.drugbank.ca/drugs,DB00335).

**Contraindications** (http://en.wikipedia.org/wiki/Atenolol)

- Bradycardia (pulse less than 60 bpm)
- Cardiogenic shock
- Asthma (may cause broncho-constriction).
- Symptomatic hypotension (blood pressure of less than 90/60 mm Hg with dizziness, vertigo etc.)
- Metabolic acidosis (a severe condition with a more acidic blood than normal)
- Atrioventricular blockage of second and third degree (a particular form of arrhythmia)
- Acutely decompensated congestive heart failure (symptoms may be fluid retention with peripheral edema and/or abdominal fluid retention (ascites), and/or lung edema)
- Hypersensitivity and/or allergy to atenolol
- Pheochromocytoma (a rare type of tumor of the adrenal glands)
- Atenolol should not be taken by patients with preexisting bronchial asthma.
- The drug crosses the placenta barrier freely. In the milk of breastfeeding mothers, approximately 3 times the plasma concentrations are measured. Atenolol may retard fetal growth and possibly cause other abnormalities, and is classified by FDA in pregnancy category D. It should be used during pregnancy only if absolutely necessary.
Side effects

Atenolol causes significantly fewer central nervous system side effects (depression, nightmares). Other side effects have been known to include the following (Carlberg et al., 2004, http://en.wikipedia.org/wiki/Atenolol):

- Indigestion, constipation
- Dry mouth
- Dizziness or faintness (especially cases of orthostatic hypotension)
- Cold extremities
- Rhinitis
- Depression
- Confusion
- Insomnia, nightmares
- Fatigue, weakness or lack of energy
- Edema
- Unexplained/sudden weight gain

The following more-serious side effects have also been observed and/or reported:

- Hallucinations
- Low blood pressure (hypotension)
- Skin reactions, e.g. rash, hives, flaking of skin, worsening of psoriasis
- Sensation of 'pins and needles' hands or feet
- Irritated eyes, visual disturbances
- Difficulty hearing
- Difficulty speaking
- Unsteadiness when walking

**Overdose** (http://www.japi.org/special_issue_2009/article_03.pdf)

Symptoms of overdose are due to excessive pharmacodynamic actions on $\beta_1$ and also $\beta_2$-receptors include; bradycardia, severe dizziness, severe weakness, severe hypotension with shock, acute heart failure, hypoglycemia and trouble breathing (bronchospastic reactions). Treatment is largely symptomatic. Hospitalization and intensive monitoring is indicated. In early cases emesis can be induced. Activated
charcoal is useful to absorb the drug. Atropine will counteract bradycardia, glucagon helps with hypoglycemia, dobutamine can be given against hypotension and the inhalation of a $\beta_2$-mimetic as hexoprenalin or salbutamol will terminate bronchospasms. Blood or plasma atenolol concentrations may be measured to confirm a diagnosis of poisoning in hospitalized patients or to assist in a medicolegal death investigation. Plasma levels are usually less than 3 mg/L during therapeutic administration, but can range from 3–30 mg/L in overdose victims.

**Drug interactions**

Following medicines contain ingredients that could increase your heart rate/blood pressure or worsen heart failure. So, the uses of these medicines are prevented with atenolol (http://www.japi.org/special_issue_2009/article_03.pdf).

- Allergy treatments (or if you are undergoing allergy skin-testing);
- NSAIDs such as ibuprofen, naproxen
- Amiodarone (Cordarone, Pacerone), Clonidine (Catapres), Digoxin (digitalis, Lanoxin)
- Disopyramide (Norpace), Guanabenz (Wytensin)
- MAO inhibitors such as isocarboxazid (Marplan), tranylcypromine (Parnate), phenelzine (Nardil), or selegiline (Eldepryl, Emsam)
- Diabetes medication such as insulin, glyburide (Diabeta, Micronase, Glynase), glipizide (Glucotrol), chlorpropamide (Diabinese), or metformin (Glucophage)
- Heart medication such as nifedipine (Procardia, Adalat), reserpine (Serpasil), verapamil (Calan, Verelan, Isoptin), diltiazem (Cartia, Cardizem)
- Medicine for asthma or other breathing disorders such as albuterol (Ventolin, Proventil), bitolterol (Tornalate), metaproterenol (Alupent), pirbuterol (Maxair), terbutaline (Brethaire, Brethine, Bricanyl) and theophylline (Theo-Dur, Theolair)

**Precautions**

Atenolol can cause side effects that may impair your thinking or reactions. Be careful if you drive or do anything that requires you to be awake and alert. Avoid drinking alcohol, which could increase drowsiness and dizziness while you are taking atenolol.
Storage
Store it at room temperature away from light and moisture. Keep all medications away from children and pets.

2.8. EXCIPIENTS PROFILE
2.8.1. ETHYL CELLULOSE

Non proprietary name
- BP and USPNF: Ethylcellulose,
- PhEur: Ethylcellulosum

Synonyms: Aquacoat EDC; Aqualon; Ethocel; Surelease

Chemical name: Cellulose ethyl ether

Empirical formula: \( C_{12}H_{23}O_6(C_{12}H_{22}O_5)nC_{12}H_{23}O_5 \)

CAS Number: 9004-57-3

Description: Ethyl cellulose is a tasteless, free flowing, white coloured powder.

Physical properties
- **Density**: 0.4g/cm\(^3\)
- **Ethoxy content**: 47 – 48%
- **Glass transition temperature**: 129-133\(^0\)C
- **Solubility**: Practically insoluble in glycerin, propylene glycol and water. EC that contains less than 46.5% ethoxyl groups is freely soluble in chloroform, methyl acetate, tetrahydrofuran. EC that contains more than 46.5% ethoxyl groups is freely soluble in ethanol, ethyl acetate, methanol and toluene (Kibbe, 2000).
- **Specific gravity**: 1.12-1.15g/ cm\(^3\)
- **Moisture content**: Ethyl cellulose absorbs very little water from humid air or during immersion and that small amount evaporates readily.

Functional category: Coating agent; sustained release polymer, timely release polymer, encapsulating agent, flavoring fixative; tablet filler; (Lin et al., 2004, Durig et al., 2002).

Different grades of ethyl cellulose
Table 7 list out the different viscosity grade of ethyl cellulose is available in different particle size (Kibbe, 2000).
**Table 6:** Concentration of ethyl cellulose used

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microencapsulation</td>
<td>10-20</td>
</tr>
<tr>
<td>Sustained release tablet coating</td>
<td>2-20</td>
</tr>
<tr>
<td>Tablet coating</td>
<td>1-3</td>
</tr>
<tr>
<td>Tablet granulation</td>
<td>1-3</td>
</tr>
</tbody>
</table>

**Figure 20:** Structure of ethyl cellulose

**Table 7:** Different grades of ethyl cellulose

<table>
<thead>
<tr>
<th>Grade</th>
<th>Viscosity (mPa s)</th>
<th>Mean particle size (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethocel Std 4 Premium</td>
<td>3-5.5</td>
<td>204</td>
</tr>
<tr>
<td>N-7</td>
<td>5.6-8</td>
<td>160</td>
</tr>
<tr>
<td>Ethocel Std 7FP Premium</td>
<td>6-8</td>
<td>9</td>
</tr>
<tr>
<td>Ethocel Std 7 Premium</td>
<td>6-8</td>
<td>210</td>
</tr>
<tr>
<td>N-10</td>
<td>8-11</td>
<td>225</td>
</tr>
<tr>
<td>Ethocel Std 10F Premium</td>
<td>9-11</td>
<td>5</td>
</tr>
<tr>
<td>Ethocel Std 10P Premium</td>
<td>9-11</td>
<td>5</td>
</tr>
<tr>
<td>Ethocel Std 20P Premium</td>
<td>18-22</td>
<td>35</td>
</tr>
<tr>
<td>N-14</td>
<td>12-16</td>
<td>212</td>
</tr>
<tr>
<td>Ethocel Std 45P Premium</td>
<td>41-49</td>
<td>-</td>
</tr>
<tr>
<td>Ethocel Std 100FP Premium</td>
<td>90-110</td>
<td>194</td>
</tr>
<tr>
<td>Ethocel Std 100P Premium</td>
<td>90-110</td>
<td>40</td>
</tr>
</tbody>
</table>
Applications in Pharmaceutical Formulation or Technology

Ethyl cellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethyl cellulose to inhibit oxidation. Modified-release tablet formulations may also be produced using ethyl cellulose as a matrix former (Ozturk et al., 1990). Drug release through ethyl cellulose coated dosage forms can be controlled by diffusion through the film coating. High-viscosity grades of ethyl cellulose are used in drug microencapsulation (Narisawa et al., 1994).

Stability and storage conditions

Ethyl cellulose is stable, slightly hygroscopic material. It is chemically resistant to alkalis both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic material than are cellulose esters. EC is subject to oxidation degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by the use of antioxidant and chemical additives that absorb light in the 230-340 nm range and storing at a temperature not exceeding 32°C in a dry area away from all sources of heat.

Safety

It is widely used in food products, oral and topical pharmaceutical formulations. It is not metabolized following oral consumption and is therefore a noncalorific substance. Because ethyl cellulose is not metabolized it is not recommended or parentral products; parentral use may be harmful to the kidney. It is generally regarded as a nontoxic, nonallergic and nonirritating material. As ethyl cellulose is not considered to be health hazard, the WHO has not specified an acceptable daily intake (Hardman et al., 2009).

- LD50 (Raddit, skin): > 5g/kg
- LD50 (Rat, oral): > 5g/kg

Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules, suspensions and tablets; topical emulsions and vaginal preparations). Included in nonparenteral medicines licensed in Europe. Included in the Canadian List of Acceptable Non-medicinal Ingredients.
2.8.2. HYDROXYPROPYLMETHYLCELLULOSE

Chemical Name: Cellulose hydroxypropyl methyl ether

Synonyms: Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.

Nonproprietary Names
- BP and USPNF: Hypromellose
- PhEur: Hypromellosum

CAS Number: 9004-65-3

Molecular weight: approximately 10 000–1 500 000.

Description: HPMC is an odorless and tasteless, white or creamy-white powder.

Melting point: 190-00°C

pH: 5.5-8.0 for a 1% w/w aqueous solution

Solubility: Soluble in cold water, forming a viscous colloidal solution; practically insoluble in 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. Different type viscosity grade of HPMC polymers are classified according to their relative methoxy-group and hydroxypropoxy-group contents (Kibbe, 2000).

Structural formula

![Structural formula of HPMC](image_url)

Where R is H, CH₃, or CH₃CH(OH)CH₂

Figure 21: Structure of Hydroxypropylmethylcellulose
**Functional category:** Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent (Sako K et al., 2002).

**Viscosity grade:** A wide range of viscosity types is commercially available (Kibbe, 2000). Typical viscosity values for 2% w/v aqueous solutions of HPMC, viscosities measured at 20°C were given in table 8.

**Table 8: Viscosity grade of HPMC**

<table>
<thead>
<tr>
<th>HPMC grade</th>
<th>Nominal</th>
<th>Viscosity (mPas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methocel K100LVP</td>
<td>100</td>
<td>80-120</td>
</tr>
<tr>
<td>Methocel K4M</td>
<td>4000</td>
<td>3000-5600</td>
</tr>
<tr>
<td>Methocel K15M</td>
<td>15000</td>
<td>12,000-21,000</td>
</tr>
<tr>
<td>Methocel K100M</td>
<td>1,00,000</td>
<td>80,000-1,20,000</td>
</tr>
<tr>
<td>Methocel E4M</td>
<td>4000</td>
<td>3500-5600</td>
</tr>
<tr>
<td>Methocel E3PREM LV</td>
<td>--</td>
<td>2.4-3.6</td>
</tr>
<tr>
<td>Methocel E5PREM LV</td>
<td>--</td>
<td>4-6</td>
</tr>
<tr>
<td>Methocel E15PREM LV</td>
<td>--</td>
<td>12-18</td>
</tr>
<tr>
<td>Metolose 60SH</td>
<td>--</td>
<td>50, 4000, 10 000</td>
</tr>
<tr>
<td>Metolose 65SH</td>
<td>--</td>
<td>50, 400, 1500, 4000</td>
</tr>
<tr>
<td>Metolose 90SH</td>
<td>--</td>
<td>100, 400, 4000, 15 000</td>
</tr>
</tbody>
</table>

**Applications in Pharmaceutical Formulation or Technology**

Hydroxypropyl methylcellulose (HPMC) is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, HPMC is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended-release tablet formulations (Chowhan, 1980, Rowe, 1984). 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. Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film forming solutions to film-coat tablets (Sebert P et al., 1993). Different type viscosity grade of HPMC polymers are classified according to their relative methoxy-group and hydroxypropoxy-group contents. Lower-viscosity grades are used in aqueous film-
coating solutions, while higher-viscosity grades are used with organic solvents. Examples of film coating materials that are commercially available include AnyCoat C, Spectracel, and Pharmacoat. HPMC is also used as a emulsifier, suspending and thickening agent at concentrations between 0.45–1.0% w/w in topical formulations, for eye drops and artificial tear solutions. In addition, HPMC is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products (Raymond et al., 2006).

Safety

HPMC is widely used as an excipient in pharmaceutical formulations, cosmetics and food products. HPMC is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may have a laxative effect. The WHO has not specified an acceptable daily intake for hypromellose since the levels consumed were not considered to represent a hazard to health.

- LD50 (mouse, IP): 5 g/kg
- LD50 (rat, IP): 5.2 g/kg

Regulatory Status: GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (ophthalmic preparations; oral capsules, suspensions, syrups, and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients (Raymond et al., 2006).

2.8.3. EUDRAGIT

Nonproprietary Names

- BP: Methacrylic acid–ethyl acrylate copolymer (1 : 1)
- PhEur: Acidum methacrylicum et ethylis acrylas polymerisatum (1 : 1)
- USPNF: Ammonio methacrylate copolymer

Synonyms: Methacrylic acid, Kollicoat MAE 30 D; Kollicoat MAE 30 DP; polymeric methacrylates

Chemical name and CAS number

- Eudragit S 100: Poly(methacrylic acid, ethyl acrylate) 1 : 1 (25086-15-1)
Eudragit S 100: Poly(methacrylic acid, methyl methacrylate) 1 : 2 (25212-88-8)

**Description:** Eudragit polymers are anionic copolymerisation product of methacrylic acid and methacrylate. Eudragit S100 is a white, free flowing powder with at least 95% of dry polymers. Eudragit L 100 is a solvent free powder contains ≥ 98% of the dried weight (Shridhar, 2007).

**Solubility:** Eudragit S100 is soluble in neutral to weakly alkaline conditions. Eudragit RL 100 is soluble in isopropanol and ethanol in combination with acetone or methylene chloride; also in methanol, chloroform, trichloroethylene, ethyl acetate (Raymond et al., 2006).

**Molecular weight range:** ≥100 000

**pH:** Eudragit L 1000 : ≥ 6.0, Eudragit S100: 7.5 – 8.5

**Viscosity:** 5-15 cps

Where, for Eudragit L and Eudragit S: R1, R3 = CH3, R2 = H and R4 = CH3

**Figure 22:** Structure of Eudragit

**Application in pharmaceutical formulation or technology**

Eudragit S type used as a enteric coating agent since they are resistant to gastric fluid. Eudragit polymers are used as film former to regulate drug liberation from transdermal systems on the membrane principle. Films formed by Eudragit are very flexible and elastic (Khan et al., 1999). Release rate is controlled via layer thickness and polymer/active substance ratio. Eudragit L 100 form water insoluble film coats for delayed release products. Permeability is dependent upon pH. Eudragit RL 100 film coats
are more permeable than those of Eudragit S 100 (Heller et al., 1987, Shendge et al., 2013).

**Health and safety:** Acute toxicity studies have been performed in rats, rabbits and dogs. No toxic effects were observed with type RL 100 at doses of dry lacquer substance ranging from 6-28 g/kg of body weight over a two-week period. No significant changes were found in the animal organs (Kibbe, 2000).

**Stability and storage conditions:** Dry powder forms appear to be stable at room temperature. Dispersions are stable for about one year after manufacturing if at room temperature stored in tight containers. The dispersions are sensitive to extreme temperatures (Lehmann, 1976).

**Regulatory Status:** Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

### 2.8.4. HYDROXYPROPYLCELLULOSE

**Nonproprietary Names**
- BP, JP and USPNI: Hydroxypropylcellulose
- PhEur: Hydroxypropylcellulosum

**Synonyms:** Cellulose, hydroxypropyl ether, E463, hyprolose, Klucel, Methocel, Nisso HPC, oxypropylated cellulose.

**Chemical Name:** 2-hydroxypropyl ether cellulose

**CAS Number:** 9004-64-2

**Molecular Weight:** 50 000–1 250 000

**Description:** HPC is a white to slightly yellow-colored, odorless and tasteless powder.

**pH:** 5.0–8.5 for a 1% w/v aqueous solution.

**Density:** 0.5 g/cm$^3$

**Melting point:** softens at 130$^\circ$C and chars at 260–275$^\circ$C.

**Solubility:** HPC is freely soluble in water below 38$^\circ$C, forming a smooth, clear, colloidal solution. In hot water, it is insoluble and is precipitated as a highly swollen floc at a temperature between 40 and 45$^\circ$C. Soluble 1 in 10 parts dichloromethane; 1 in 2.5 parts ethanol (95%); 1 in 2 parts methanol; 1 in 5 parts propan-2-ol; 1 in 5 parts propylene
glycol; and 1 in 2 parts water. Practically insoluble in aliphatic hydrocarbons; aromatic hydrocarbons and oils (Alderman, 1987).

**Structural Formula**

![Structural Formula](image)

\[ R \text{ is H or } [\text{CH}_2\text{CH(CH}_3\text{O}]_n\text{H} \]

**Figure 23:** Structure of hydroxypropylcellulose

**Functional Category:** Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent (Raymond et al., 2006).

**Applications in Pharmaceutical Formulation or Technology**

HPC is widely used in binder, film coating, and extended release matrix former in oral and topical pharmaceutical formulations. Concentrations of HPC of 2–6% w/w may be used as a binder. Concentrations of 15–35% w/w of HPC may be used to produce tablets with an extended drug release. The release rate of a drug increases with decreasing viscosity of HPC. Typically, a 5% w/w solution of HPC may be used to film-coat tablets (Banker et al., 1981). A low-substituted HPC is used as a tablet disintegrant. HPC is also used in microencapsulation processes and as a thickening agent. In topical formulations, HPC is used in transdermal patches and ophthalmic preparations. HPC is also used in cosmetics and in food products as an emulsifier and stabilizer (Ashok and Mahesh, 2006).

**Stability and Storage Conditions**

HPC powder is a stable material, although it is hygroscopic after drying. Aqueous solutions of hydroxypropyl cellulose are stable at pH 6.0–8.0, with the viscosity of
solutions being relatively unaffected. UV light will also degrade HPC and aqueous solutions may therefore decrease slightly in viscosity if exposed to light for several months. HPC powder should be stored in a well closed container in a cool, dry place (Raymond et al., 2006).

**Safety:** HPC is widely used as an excipient in pharmaceutical formulations, cosmetics and food products. HPC is generally regarded as an essentially nontoxic and nonirritant material. The WHO has not specified an acceptable daily intake for HPC since the levels consumed were not considered to represent a hazard to health.

- **LD50 (rat, IV):** 0.25 g/kg (23)
- **LD50 (rat, oral):** 10.2 g/kg

**Regulatory Status:** GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets; topical and transdermal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients (Raymond et al., 2006).

### 2.8.5. OKRA GUM

Okra gum is obtained from the fruits of Hibiscus esculentus (Lady Finger, family: Malvaceae) as shown in figure 24. Fruit of Hibiscus esculentus is a pentagonal, narrow, cylindrical capsule, from 2 to 12 inches long, tapering at the base, and about 1 inch in diameter. It is often curved, and is covered with hairs, especially along the ridges. The pods contain several roundish or kidney-shaped smooth seeds in each of the several cells. The fruits are rich in mucilage and protein (18-26%). It also contain abundant some fat (4%), water (80.7%) and ash (1.41%). Okara gum is a polysaccharide consisting of D-galactose, L-rhamnose and L-galacturonic acid (Girase et al., 2003). The gum is naturally available, inexpensive, consistent in quality and reliable in supply. Okra mucilage is water soluble, 1.7 million molecular weight glycoprotein which produces viscous, shear thinning and viscoelastic solutions in water. The viscosity of the borohydride soluble fraction is maximum at a pH range of 4-6. pH of 1% w/v aqueous solution of okara gum is 7.32. Specific gravity of 0.01% w/v aqueous solution of okara gum is 0.999.
Applications in Pharmaceutical Formulation or Technology

Okra gum having a pharmacological action like hepatoprotective and antidiabetic activities, Okra mucilage binds cholesterol and bile acid carrying toxins dumped into it by filtering liver, thus might act as a hepatoprotective agent. It also has antioxidant activity, free radical scavenging activity, inhibition of adhesion of Helicobacter pylori to human gastric mucosa. It is also useful in combating the onset of cancer, coronary disease, inflammation, arthritis, immune system decline, brain dysfunction and cataracts and diabetes. These attributes of okra gum are sufficient to justify a detailed assessment of the material as hydrophilic matrix in controlled-release delivery system. Okra gum has been investigated as a binding agent in tablet dosage forms, and has been shown to produce tablets with good hardness, friability and drug release profiles (Tavakoli et al., 2004). Okra gum matrices were found to be useful in the formulation of sustained release paracetamol tablets for up to 6 hr, and the appropriate combination of okra gum and HPMC was used to provide a time-independent release for longer periods (Talukdar et al., 1996). Okara gum in combination of Carbopol 941 used to prepare bioadhesives tablet of indomethacin and results indicate that tablets with equal ratio of C-941 and okra gum (1:1) gave the highest bioadhesive strength and percentage of drug release ranged from 53-90% in 0.1 N HCL after 8 hrs (Attama et al., 2003). VD Kalu prepared and evaluated sustained release tablet from okra gum and compared with sodium carboxymethylcellulose (NaCMC) using aspirin as the model drug to provide near zero-order release of aspirin from the matrix tablets (Kalu et al., 2007). Okra mucilages have emulsifying potential and they are used in preparation of typical o/w emulsions. Okra
gum having emulsion stabilizing properties, flocculant property, gives highest bioadhesive strength.

2.8.6. SODIUM STARCH GLYCOLATE

Nonproprietary Names

- **BP and USPNF**: Sodium starch glycolate
- **PhEur**: Carboxymethylamylum natricum

**Synonyms**: Carboxymethyl starch, sodium salt; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, Vivastar P.

**Chemical Name**: Sodium carboxymethyl starch

**CAS Number**: 9063-38-1

**Molecular weight**: $5 \times 10^5$ – $1 \times 10^6$

**Description**: SSG is a white to off-white, odorless, tasteless, free-flowing powder.

**Melting point**: does not melt, but chars at approximately 200°C

**Solubility**: sparingly soluble in ethanol (95%); practically insoluble in water. At a concentration of 2% w/v sodium starch glycolate disperses in cold water and settles in the form of a highly hydrated layer (Raymond et al., 2006).

**Swelling capacity**: in water, SSG swells to up to 300 times its volume.

**Viscosity (dynamic)**: Viscosity is 4.26 mPa s for a 2% w/v aqueous dispersion.

**Structural Formula**

![Structure of sodium starch glycolate](image)

**Figure 25**: Structure of sodium starch glycolate

**Functional Category**: Tablet and capsule disintegrant (Gebre et al., 1996).
Applications in Pharmaceutical Formulation or Technology

Sodium starch glycolate (SSG) is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling. SSG has also been investigated for use as a suspending vehicle (Caramella et al., 1978).

Safety: SSG is widely used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may be harmful.

Regulatory Acceptance: Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Nonmedicinal Ingredients (Raymond et al., 2006).

2.8.7. POLYVINYLPYRROLIDONE

Synonyms: E1201, Kollidon, Plasdone, poly[1-(2-oxo-1 pyrrolidinyl)ethylene], polyvidone, PVP, 1-vinyl-2-pyrrolidinone polymer, Povidone.

Chemical Name: 1-Ethenyl-2-pyrrolidinone homopolymer

Empirical Formula: (C₆H₉NO)n

Molecular Weight: 2500–30,000,000

CAS Number: 9003-39-8

Description: Povidone is a fine, white to creamy white colored and odorless powder.

Density: 1.17-1.18 g/ml

Glass transition temperature: 60°C

Solubility: Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil (Kibbe, 2000).

Grade: Povidone polymers are available in two grades; K and C. C grade products are pyrogen free and designed specifically for parenteral and ophthalmic use. The K-value is calculated from the kinematic viscosity of a 15 aqueous solution and hence is related to the average molecular weight of the polymer (Fikentscher and Herrle, 1945).

Functional Category: Disintegrant; dissolution aid; suspending agent; tablet binder.

Structural Formula

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Ph.D Thesis

Rajesh A. Keraliya
Applications in Pharmaceutical Formulation or Technology

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes (Becker et al., 1997). Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. Povidone solutions may also be used as coating agents. Povidone is additionally used as a suspending, stabilizing, or viscosity increasing agent in a number of topical and oral suspensions and solutions (Iwata and Ueda, 1996).

Safety

Povidone is widely used as an excipient, particularly in oral tablets and solutions. When consumed orally, povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes. Povidone additionally has no irritant effect on the skin and causes no sensitization (Fikentscher and Herrle, 1945).

Regulatory Status: Included in the FDA Inactive Ingredients Guide (IM and IV injections; ophthalmic preparations; oral capsules, drops, granules, suspensions, and tablets; sublingual tablets; topical and vaginal preparations). Included in the Canadian List of Acceptable Nonmedicinal Ingredients.