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The term chrono basically refers to the observation that every metabolic event undergoes rhythmic changes in time (Sajan et al., 2009). Chronopharmaceutics consist of two words chronobiology and pharmaceutics (Belgamwar et al., 2008). Chronobiology is the study of biological rhythms and their mechanism (Gandhi et al., 2011), whereas pharmaceutics is the science of dosage form design (Aulton and Taylor, 2002). Chronopharmacology is the science concerned with variations in the pharmacological actions of various drugs in a day (Jha and Bapat, 2004). Physiological and biological conditions of the human body vary considerably in a day; leads to changes in both disease state and plasma drug concentrations. Human circadian rhythm is based on sleep-activity cycle, is influenced by genetic makeup and hence, affects the body’s functions day and night period. The dependence of bodily functions in certain disease states on circadian rhythm is well known. A number of hormones are released in the morning, while others are released during sleep. Accordingly, diseases such as hypertension, asthma, allergic rhinitis, peptic ulcer and arthritis follow the body's circadian rhythm (Sajan et al., 2009; Udupa and Gupta, 2009).

Chronotherapeutics is the discipline concerned with delivery of drugs in vivo to match rhythms of disease symptoms in order to optimize therapeutic outcomes and minimize side effects. As more is learned about chronotherapeutics, it is becoming increasingly more evident that the medication intake time may be even more considerable than was recognized in the past (Sajan et al., 2009; Jha and Bapat, 2004). The practice of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to maintain constant drug levels throughout a 24-hour period, may be altering as researchers report that some medications may work better if their administration is synchronized with day-night patterns and biological rhythms (Devdhawala and Seth, 2010). From these points of view, development of dosage forms, in which drug is released only at a required time and effective drug levels are maintained, has been desired for chronotherapy. Chronomodulated drug delivery system is mainly concerned with delivery of the drug to synchronize the plasma drug concentrations to biological rhythm in diseased condition. When constant drug plasma levels need to be avoided, as in chronotherapy, time-controlled or pulsed-release formulations are preferable, especially in the treatment of early morning symptoms (Sajan et al., 2009). By timing drug administration, plasma peak is obtained at an optimal time and the number of doses per day can be reduced. Saturable first-pass metabolism and tolerance development can also be avoided (Devdhawala and Seth, 2010).
The chronotherapy of a medication may be accomplished by the appropriate timing of conventionally formulated dosage form, and the special drug delivery system to synchronize drug concentrations to rhythms in disease state activity (Ohdo, 2010). Now a days chronotherapy is widely used in clinical medicine; these include special evening theophylline systems for chronic obstructive pulmonary disease (Cazzola et al., 1999), conventional evening H2-receptor antagonists for peptic ulcer disease (Devdhawala and Seth, 2010; Khasawneh and Affarah, 1992), conventional evening cholesterol medications for hyperlipidemia (Devdhawala and Seth, 2010; Henley et al., 2002), and special bedtime tablet and capsule blood pressure-lowering medication systems (Smolensky and Peppas, 2007).

3.1. Chronopharmacology and chronotherapeutics

Chronopharmacology is the study of the manner and the extent to which the kinetics and dynamics of medications are directly affected by endogenous biological rhythms (Devdhawala and Seth, 2010; Smolensky and Peppas, 2007). In recent days because of scientific advancement, new insights in the functioning of the body were gained by 24 h monitoring of heart beat, hormone levels, temperature etc. Many diseases are identified to be based on body rhythm such as cardiovascular diseases, arthritis, duodenal ulcers, asthma, cancers, diabetes, hypercholesteremia, some neurological conditions, psychiatric disorders and sleep disorders as discussed earlier (Smolensky and Peppas, 2007). Severe episodes of asthma occur mainly during the night and early mornings. The peak in serum cortisol, aldosterone, testosterone, adrenaline, platelet adhesiveness and blood viscosity was observed during the initial hours of diurnal activity. Whereas the peak, in the rhythms of basal gastric acid secretion, white blood cells, lymphocytes, prolactin, melatonin, eosinophils, ACTH, follicle stimulating hormone (FSH) and leutinizing hormone (LH) is manifested during specific times of sleep span. Insulin, cholesterol, triglycerides, platelet numbers and uric acid peak occur during the day and evening (Ohdo, 2007; Smolensky et al., 1999).

The administration of drugs as per circadian rhythms of diseases has to be taken into consideration while treating any disease. Chronotherapeutics may be achieved by optimizing the dosing schedules of 12 h medication systems, better timing of conventional once-a-day medication/delivery systems, or application of special tablet and capsule
formulations dosed at designated times to proportion medications over the 24 h in synchrony with rhythm-determined requirements (Smolensky and Peppas, 2007).

Chronotherapeutics is a branch of therapy that involves synchronizing the drug application in a manner that coincides with circadian rhythms in order to achieve an optimal therapeutic success (Khan et al., 2009; Landau et al., 1991). The knowledge of 24 h rhythm in the risk of disease plus evidence of rhythm dependencies of drug pharmacokinetics, effects, and safety constitutes the rationale for chronotherapy (Ohdo, 2010). Chronotherapeutics takes into account rhythm determinants in chronopathology, chronokinetcs, chronodynamics and chronotoxicology of medications, and circadian time structure to determine the drug-delivery pattern and administration time to optimize desired benefits and minimize adverse effects. Chronotherapeutics need not involve only new medicines but also the better application of established ones in a different and more biologically efficient manner (Smolensky and Peppas, 2007).

3.2. Circadian rhythms of asthma and allergic rhinitis (AR)

There are a number of conditions which show a circadian pattern and advantage could be taken by timing and adjusting the administration of drugs according to the circadian rhythm of the disease. Asthma is one of the most common diseases with the largest circadian variation (Jha and Bapat, 2004), is characterized by persistent airway inflammation, heightened airway hyper-reactivity to antigens and other environmental agents, and markedly reduced and abnormal airway caliber. The symptoms of BA include dyspnea (difficulty in breathing), wheezy chest, and croupy cough. All of these signs and symptoms are at least partially reversible with bronchodilator and anti-inflammatory medication and environmental control (Smolensky et al., 2007). The severity of BA varies between patients and even in the same individual over a period of time. The majority of patients experience that symptoms generally worsen during the night and early hours of the morning and pulmonary function often deteriorate at the same time. (Burioka et al., 2010; Douglas, 1985). It is well known that one of the main chronobiological features of asthma is the worsening of symptoms between midnight and early morning, which is referred to as the morning dip. Dethlefsen and Repges has followed up a total of 3129 asthma patients and recorded the times when they experienced dyspnea in their diaries, revealing that symptoms became worse during the early morning hours. Burioka et al. (2010) has presented the data of Dethlefsen and Repges in the form of graph as shown in Figure 3.1.
Figure 3.1. Early morning exacerbation of symptoms in asthma (Burioka et al., 2010)

The most common symptoms of allergic rhinitis (AR) are sneezing, nasal rhinorhea, red itchy eyes, nasal pruritus and nasal congestion was found to occur most recurrently before breakfast in the morning and least frequently in the middle of the day (Mandal et al., 2010). The nasal congestion and obstruction at some point in the night can be so severe that it often disrupts sleep, resulting in daytime fatigue, poor work and school performance, irritability, and altered or depressed mood (Smolensky et al., 2007). There are two phases of occurrence of allergic rhinitis i.e. early phase (developing within minutes) and late phase (manifesting after 12-16 h). The early phase response in AR typically induces the symptoms of sneezing, nasal itch, and rhinorhea, due to release of certain preformed chemical mediators, such as histamine, prostaglandins, cytokines, TNF-α, chemotactic factors and protease enzymes from degranulating nasal mast cells. The late phase response induces the symptoms of nasal congestion and obstruction due to the exacerbation of inflammation of the nasal, sinus, and other tissue of the upper airway, mainly involves cellular events, i.e., the elaboration, adhesion, and infiltration of circulating leukocytes, T cells, and eosinophils (Smolensky et al., 2007; Storms, 2004).

Reinberg et al., (1988) has collected the data from study on a group of 765 patients (male and female) obeying to a routine of daytime activity alternating with nighttime sleep and assessments were made using visual analogue scales four equally spaced times during the waking span for 1 week. Sneezing, nasal congestion and rhinorhea were more of a problem than nasal pruritis. On average, the severity of all the symptoms was utmost in the morning, both in men and women. Smolensky et al., (2007) has presented the data in graphical form as shown in Figure 3.2.
3.3. Asthma and allergic rhinitis (AR) as comorbid conditions

It has been proved that high percentage of persons suffering from AR have concomitant asthma, and vice-versa. Using the Johns Hopkins Asthma and Allergy Center database, investigators found that the prevalence of rhinitis in atopic individuals with asthma ranged from 88.8% in adolescents to 94.3% in adults (Nayak, 2003). Lombardi and colleagues examined the prevalence of asthma alone, AR alone, and both diseases in a cohort of 99 subjects. Of these, AR was diagnosed in 44 subjects, asthma was diagnosed in 12 subjects, and asthma plus AR was diagnosed in the remaining 43 subjects. At 10-year follow-up, nearly one-third of the subjects with only AR had developed asthma at a mean onset time of 5 years. Of those with baseline asthma alone, one-half developed AR at a mean onset time of 7 years. No spontaneous remission of either asthma or AR was observed during the course of the study (Nayak, 2003; Lombardi et al., 2001). In another study, Brown College students were studied for 23 years. This study proved that AR and positive allergy skin test are significant risk factors for developing new asthma. Subjects with asthma were
approximately twice more likely to have a history of AR than subjects who did not have asthma (85.7% versus 40.7%). Also, asthma occurred over seven times more often in individuals with a history of AR than in participants without a history of AR (21.3% versus 3.0%). The Brown study also suggested that the course of asthma occurs in parallel to that of AR (Nayak, 2003; Greisner et al., 1998; Settipane et al., 1994).

In summary, epidemiological data support a linkage between asthma and AR. In addition, manifestations of disease in the upper and lower airway provide additional support for a connection between the two. This evidence, coupled with common risk factors, suggests the possibility of refining preventive measures for asthma and AR, as well as redefining optimal treatment approaches. An understanding of the role of such mediators as histamine and leukotrienes in asthma and AR allows disease management geared toward the pathophysiological mechanisms of both the diseases (Nayak, 2003).

3.4. Pathophysiology of asthma and AR
The contribution of several common inflammatory mediators in the upper and lower airway supports the concept of a unified airway. These mediators, including histamine, leukotrienes, thromboxane, prostaglandins, platelet-activating factor, chemotactic factors, adenosine, and bradykinin are synthesized by and/or released from a variety of inflammatory cells. The concurrence of these cells and mediators in both asthma and AR provides evidence of inflammatory processes in the upper and lower airway and a linkage between the two diseases. Histamine and leukotrienes are of special interest, as medications currently exist that effectively target them. Previously, research involving upper- or lower-airway disease focused on evaluating drugs that block nasal or bronchial provocation induced by histamine or methacholine. Recently, the role of the LTs, which are far more potent inflammatory mediators than histamine, has come to the forefront as researchers are able to detect these compounds in biological secretions and fluids and as drugs that interfere with the 5-lipoxygenase products of the arachidonic acid pathway have been developed (Nayak, 2002).

The cysteinyl leukotrienes (LTC\(_4\), LTD\(_4\), LTE\(_4\)), derivatives of the 5-lipoxygenase pathway of arachidonic acid metabolism, are the important mediators of airway allergic inflammatory disease. These eicosanoids are released from various activated inflammatory cells, including mast cells and eosinophils, and subsequently bind to CysLT1 receptors on target cells, provoking both local and systemic effects. Binding has been shown to correlate
with the underlying pathophysiology of allergic rhinitis and asthma as shown in Figure 3.3, and therapies that target these mediators represent important treatment options. Initial exposure to allergen leads to production of allergen-specific IgE by B-cells in response to T-cell cytokine secretion. The binding of IgE to receptors on mast cells or basophils results in cell activation and release of a variety of mediators, including leukotrienes. Subsequent effects on target organs and other inflammatory cells ultimately produces the characteristic symptoms and prolongation of the allergic response (William, 2007).

Figure 3.3. Overview of the pathophysiology of asthma and AR (William, 2007)

3.5. Role of leukotrienes (LTs) in asthma and AR
Cysteinyl LTs (cyst-LTs), the most potent pro-inflammatory mediators, recognized as playing an important role in the pathogenesis of lower-airway disease, have been shown to be elevated in nasal secretions after antigen challenge (Figure 3.4). These data, along with other data, have established LT inhibition as a possible treatment target in both asthma and AR. The LT receptor antagonists (LTRAs), which have a high affinity for the LTD4 receptor, have established efficacy and safety in adults and children with variable severity and types of asthma. Results from clinical studies also have documented the efficacy of LTRAs, alone or in combination with other agents, in the treatment of AR (Nayak, 2004; Nayak, 2002).
3.6. Chronotherapy of asthma and allergic rhinitis

Chronotherapeutics is medical treatment administered according to a schedule that corresponds to a person's biological clock to synchronize drug level with medical conditions, in order to maximize the health benefits and minimize adverse effects. It can sometimes be achieved by the prudent timing of conventional sustained release formulations, although confidence on modified release drug-delivery systems seems to establish a more reliable means of matching drug level to biologic need and tolerance (http://www.atsjournals.org; Smolensky, 1996).

Most of the drugs currently used for chronotherapy of asthma are administered once at night with the goal of preventing chronic airway inflammation or the onset of airflow limitation. A single dose at night contributes to improve patients' adherence and better self-management of asthma (Burioka et al., 2010). The most commonly prescribed medicines in the management of asthma are β2-agonist, theophylline and corticosteroids. β2-agonists are frequently prescribed in the management of bronchial asthma. Conventional, short-acting β2-agonist aerosol medications are trusted upon to relieve acute asthma crises; however, as a monotherapy they afford limited or no protection against nocturnal bronchial asthma. Postma et al. (1986) and Koeter et al. (1985) were the first to evaluate the chronotherapy of the terbutaline (β2-agonist) SR tablet (Bricanyl Depot®: AB Draco, Sweden) medication in a group of patients diagnosed with reversible airways disease. Another albuterol (β2-agonist) SR tablet (Volmax®: Glaxo, UK; Muro, USA) medication
was also assessed as a chronotherapy of NBA. Volmax® relies on an osmotic-based drug-delivery system to achieve the controlled and steady release of albuterol throughout 12 or even 24 h dosing intervals (Smolensky et al., 2007).

Theophylline has long been used in the management of NBA, and for many years sustained release delivery systems were considered the treatment of choice for this medical condition. A commonly used approach for treatment of nocturnal asthma has been the evening use of sustained release theophylline. The chronotherapy of theophylline entails the purposeful delivery of medication in unequal amounts during the 24 h so that an elevated concentration is achieved during the night-time, when the risk of BA is greatest, and a reduced concentration is achieved during the day-time, when the risk of BA is lowest (Smolensky et al., 2007). But, theophylline has been shown to adversely affect sleep quality. Corticosteroids have been used in a chronotherapeutic manner, with the finding that their long-term oral administration at 8:00 A.M. and 3:00 P.M. was more effective in controlling nocturnal asthma than the same doses given at 3:00 P.M. and 8:00 P.M. Not only oral steroids but inhaled corticosteroids can also be dosed chronotherapeutically for improved efficacy (http://www.atsjournals.org; Reinberg et al., 1983).

Leukotriene modifiers are an entirely new class of drugs for asthma treatment, which have entered clinical practice since 1996-97. One of the main advantages of leukotriene antagonists is that they are active orally, which avoids the problem of inhaled route compliance and their effect comes within 24 hours, while inhaled corticosteroid takes much longer time to achieve maximal response. They are the only class of drug in asthma which are having both bronchodilator and anti-inflammatory property (Samaria, 2000).

Salient effects of leukotriene antagonists (Samaria, 2000)

- Leukotriene antagonists are effective in blocking bronchoconstriction following exercise and cold air in asthmatic patients.
- They also block aspirin induced asthmatic episode.
- They are recommended as alternative to inhaled steroids in mild persistent asthma.
- Antileukotriene drugs have additive effect with inhaled corticosteroids; especially in patients with severe bronchial asthma.
- LTRAs help in reduction in doses of oral or inhaled β2 agonist drugs.
- LTRAs have the steroid sparing effect both for oral and inhaled steroids. It may lead to decrease in doses of the inhaled steroids by 400 to 600 µg.
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The chronotherapy of AR takes into consideration the 24 h pattern in the manifestation and intensity of symptoms and known circadian, i.e., ingestion-time, differences in the pharmacodynamics of individual therapies. Variety of medications, such as H1-receptor antagonists, decongestants, and anti-inflammatory (leukotriene-receptor antagonists and modifiers and aerosol glucocorticoid) ones, are used to manage and control the symptoms and underlying pathophysiology of AR. Even though a large segment of the population suffers from AR, so far only the chronopharmacology and chronotherapy of H1-receptor antagonist medications have been explored (Smolensky et al., 2007). As monotherapy for allergic rhinitis, leukotriene antagonists have reduced day time and night time symptoms of allergic rhinitis. A strategy combining the treatment of both upper and lower airway disease in terms of efficacy and safety appears to be optimal (ARIA guidelines 2001). In many ways, Leukotriene receptor antagonists represent a rational approach to such “one airway” disease management (Pawankar, 2003). As compared to glucocorticoids (GCS), which are currently the most effective treatment available for asthma and rhino sinusitis, leukotriene antagonists are specific in their mechanism of action and are thereby relatively free from serious side-effects. They will play an important role as single therapy in patients with co-existing asthma and rhinitis and are likely to have a unique place in the treatment (Lane, 1998). LTRA monotherapy or concurrent LTRA plus antihistamine therapy improves symptoms of asthma and AR and reduces inflammation. Both approaches have proven efficacy and safety, and the oral formulations offer patient convenience, which may translate into improved adherence to therapy and greater patient satisfaction (Lagos and Marshall, 2007). Montelukast is a selective orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene 1 (CysLT 1) receptor is considered as effective and safe in the treatment with asthma, allergic rhinitis or both diseases based on clinical evidence (Nayak, 2004).

3.7. Drug delivery systems for chronotherapeutics

Using the concept of circadian rhythms, chronotherapeutic disorders can be treated via specialized drug delivery systems (Hassan and Haefeli, 2010). In recent years, extensive emphasis has been placed on drug delivery systems that provide pulsatile drug release for the treatment of chronotherapeutic disorders. When treating chronotherapeutic disorders where pulsatile drug delivery is necessary, drug may be released after a lag-phase at a predetermined time intervals when they are most needed. Pulsatile drug delivery offers
advantages such as extended day-time or night-time activity, reduced side-effects, reduced
dosing frequency and dose size, improved patient compliance and lower treatment costs
(Khan et al., 2009; Sturis et al., 1995). Pulsatile release formulations include time
controlled release and site-specific dosage forms. When constant drug plasma levels need
to be avoided, as in chronotherapy, time-controlled or pulsed-release formulations are
preferable, especially in the treatment of early morning symptoms. By timing drug
administration, plasma peak is obtained at an optimal time, and the number of doses per
day can be reduced (Sajan et al., 2009; Anal, 2007).

Various technologies to develop chronotherapeutic drug delivery systems have been
extensively studied in recent decades. Chronotherapeutic delivery systems may be a single
unit or multiple unit systems, mainly include tablet, capsule, advanced osmotic devices and
multiparticulate delivery system. These units have the capability of delivering therapeutic
agents into the body in a time or position controlled pulsatile release fashion. Some of the
FDA approved chronotherapeutic delivery system present in the market for treatment of
asthma are listed in Table 3.1.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Category</th>
<th>Proprietary name and dosage form</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terbutaline</td>
<td>β2 agonist</td>
<td>Bricanyl Depot®, SR tablet</td>
<td>AB Draco, Sweden</td>
</tr>
<tr>
<td>Albuterol</td>
<td>β2 agonist</td>
<td>Proventil Repetabs®, Multilayered SR tablet</td>
<td>Schering, USA</td>
</tr>
<tr>
<td>Bambuterol</td>
<td>β2 agonist</td>
<td>Bambec® Astra</td>
<td>Draco, Sweden</td>
</tr>
<tr>
<td>Formoterol</td>
<td>β2 agonist</td>
<td>Sustained effect aerosol</td>
<td>Ciba Geigy, Europe</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>β2 agonist</td>
<td>Sustained effect aerosol</td>
<td>Glaxo UK and USA</td>
</tr>
<tr>
<td>Theophylline</td>
<td>bronchodilator</td>
<td>Euphylong®, SR tablets</td>
<td>Byk Gulden, Germany</td>
</tr>
<tr>
<td>Theophylline</td>
<td>bronchodilator</td>
<td>Uniphyll®/Uniphyllin®, SR tablets</td>
<td>Purdue Frederick, USA</td>
</tr>
<tr>
<td>Theophylline</td>
<td>bronchodilator</td>
<td>Theodur®, SR tablets</td>
<td>Schering USA</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>Glucocorticoids</td>
<td>Alvesco® metered dose inhaler</td>
<td>Teijin Pharma Ltd. Japan</td>
</tr>
<tr>
<td>Methyl prednisolone sodium</td>
<td>Corticosteroid</td>
<td>Medrol®</td>
<td>Upjohn, USA</td>
</tr>
<tr>
<td>Nedocromil sodium</td>
<td>Mast cell stabilizer</td>
<td>Tilade®</td>
<td>Fiscons, UK</td>
</tr>
</tbody>
</table>
3.7.1. System with rupturable polymeric coating
These types of devices are consisting with a core surrounded by rupturable polymeric layer. As the water/media ingress through the polymeric coating membrane, a positive pressure builds up inside the system which results in rupture of outer polymeric layer. The core having active component contains swelling polymer/agents, osmogens or gas-producing effervescent excipients. The major factors that affect the lag time are the rate of water permeation through outer membrane and mechanical resistance of the surrounding layer. Ueda et al., (1994) reported a time controlled explosion system (TES), where drug was released neither by diffusion control nor by dissolution control but a quite novel mechanism i.e. explosion of the outer membrane (Roy and Shahiwala, 2009).

3.7.2. System with soluble or eroding polymeric coating
These are a class of reservoir type pulsatile drug delivery system (PDDS) based on soluble/erodible polymeric layers surrounding the drug containing core. It may be of a single unit or multiparticulate. The surrounding outer layer dissolves or erodes after a definite period of time followed by burst release of active pharmaceuticals from the reservoir core. The onset of release and lag time can be controlled by the thickness of the outer barrier membrane.

3.7.3. System with change in membrane permeability
A change in membrane permeability depends mainly on the physicochemical characteristics of the drug and its interaction with the surrounding rate controlling layer. A minute quantity of sodium acetate, citric acid, succinic acid etc. in the core has also momentous effect on the drug permeability of the eudragit film. As these acids in the core solubilizes, the permeability of the polymeric membrane increases. That leads to the release of complete dose within a few hours after initial lag time (Mandal et al., 2010).

3.7.4. Compression coated tablet
These are composed of an inner drug containing core surrounded by an outer layer that gradually erodes/dissolves to make a lag time of drug release. This compression coating technique eliminates the complicated and time-consuming coating processes and also protects the drug from moisture to make it stable. Factors affecting the drug release are mainly percentage weight ratio of the coating polymers, type of polymer coatings and component of excipients in the core tablets. The polymers in the coat of the tablet
formulation to control drug release could include non-saccharidic swelling polymers viz., hydrophilic cellulose derivatives, alginic acid, carrageenans, guar gum (Gug), xanthan gum (XG) and locust bean gums, polyvinyl alcohol (PVA) and polyethylene oxide (PEO); hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC) and calcium or sodium carboxymethylcellulose (CMC), as well as hydrophobic polymers, ethylcellulose (Gazzaniga et al., 2008).

3.7.5. Capsule type delivery system
Several systems have been designed based on capsular drug delivery for pulsatile release. These systems mainly consist of an insoluble capsule body, filled with drug and then sealed with a swellable hydrogel plug. The lag time is controlled by a plug which either erodes or pushes itself outside the insoluble capsule body allowing the drug to release rapidly. Polymers used for developing these hydrogel plugs are various viscosity grades of different swellable polymer like hydroxypropyl methylcellulose (HPMC), polymethyl methacrylates, PVA, PEO, sodium alginate, guar gum, xanthan gum etc. Gohel and Sumitra developed a system wherein weighed quantity of dicalcium phosphate (DCP) was filled into the capsule body followed by the drug (diltiazem HCl). Weighed amount of the hydrophilic swellable polymers such as HPMC/guar gum was placed on top and compressed lightly using a rod to form a compact plug (Gohel and Sumitra, 2002). Nayak et al. (2009) designed a capsule-based drug delivery system for delayed delivery of valsartan for early morning surge of blood pressure. The hydrogel plug has been replaced by an erodible tablet, which has a tight fit in the capsule to prevent entry of fluid. Assembly of the pulsed release capsule device consisted of (i) swellable polymer weighed into the precoated capsule body; (ii) a drug tablet placed onto the compacted swellable polymer layer; (iii) an erodible tablet made up of hydrophilic polymers inserted into the mouth of the capsule. During the release process, it erodes away from the mouth of the capsule. The erosion rate of tablet plug controls the lag time of release. The capsule body is closed with water soluble cap.

3.7.6. Osmotic drug delivery system
Osmotic based delivery systems are most promising strategy-based devices for controlled drug delivery. Osmosis can be defined as the net transport of water across a semi-permeable membrane driven by difference in osmotic pressure due to solute concentrations across the membrane. Osmosis is exploited for development of ideal controlled drug delivery system.
Osmotic pressure created by osmogen is used as driving force for these systems to release the drug in controlled manner. These osmotic based systems suitable for oral administration usually consist of a core containing drug, osmotic agent and a water swellable polymer which is further coated with a semipermeable polymeric membrane having one or more delivery ports/orifice. As the core absorbs water, it expands in volume, which delivers the drug solution or suspension out through delivery orifice. The rate of absorption of water by core mainly depends on the difference in osmotic pressure cross the semi-permeable membrane. The major advantages of osmotic based systems are that they are applicable to drugs with wide range of aqueous solubility and release the drug at a rate that is independent of the pH and hydrodynamics of the external dissolution medium (Thombre et al., 2004).

3.7.8. Multiparticulate delivery system

Various techniques are available for the pulsatile delivery, broadly classified as, Single-unit and Multiple-unit systems. In recent pharmaceutical applications involving pulsatile delivery, multiparticulate dosage forms are gaining much favor over single-unit dosage forms. The potential benefits include increased bioavailability; predictable, reproducible and generally short gastric residence time; no risk of dose dumping; reduced risk of local irritation; and the flexibility to blend pellets with different compositions or release patterns. Because of their smaller particle size these systems are capable of passing through the GI tract easily, leading to less inter- and intra-subject variability. The major mechanism by which the drug is released from pellets depends on the type of coating; insoluble coating under all physiological conditions, pH-dependent coating whose solubility changes dramatically at some point in GI tract and slowly erodible coating (Roy and Shahiwala, 2009).

Ueda et al. (1994) developed a time-controlled explosion systems (TES), where drug is released by a quite innovative mechanism i.e. by sudden explosion of the outer membrane. It is especially useful with low solubility drugs in which drug release is delayed due to slow diffusion of the drug through a permeable coating. Pulsatil release pellets containing diclofenac sodium were prepared by extrusion-spheronization technology further coated with two layers, inner swelling layer and outer controlled layer. The lag time and rate of drug release were influenced by the swelling material, the coating level of the inner swelling layer and the outer controlled layer. (Roy and Shahiwala, 2009).
Narisawa et al. (1993 and 1996) have developed a delivery system capable of pulse release depending on the change in diffusion properties of eudragit RS. They found significant increase in release pattern from a core of theophylline coated with eudragit RS in presence of organic acid solution containing succinic, acetic, glutaric, tartaric, malic, or citric acid. When succinic acid was incorporated into the core of eudragit RS-coated theophylline beads, the drug release profile showed a typical sigmoidal pattern. This was due to the interaction of quaternary ammonium groups present in eudragit RS with acids which leads to greater hydration of film (Roy and Shahiwala, 2009).

Tekade and Gattani, (2010) prepared dual cross-linked pulsatile release beads containing theophylline (TPH) as a model drug and employing a simple technique (ionotropic gelation) using sodium alginate and delonix regia gum (DRG). The purpose of combining sodium alginate and DRG for formulation of dual cross-linked bead is to get the advantage of increased swelling of both these natural polymers in higher pH followed by burst release after a pre-determined lag time. The prepared beads were further coated with eudragit polymers having pH-dependent solubility in order to increase the lag time prior to rapid and complete drug release. It has been reported that eudragit L 100 and S 100 in a ratio of 1:2 w/w showed maximum solubility in pH 6.8 buffer solution. Thus, this combination of these two polymers was selected for coating of dual cross-linked beads. Khan et al., (2010) has developed pH dependent microbeads of alginate and chitosan beads exploiting pH sensitive property for colon targeted delivery of theophylline. Alginate and chitosan beads were prepared by ionotropic gelation method followed by enteric coating with Eudragit S100. The formulated beads can be used effectively for the delivery of drug to colon.

Low density floating multiparticulate PDDS reside specifically in the stomach and are not affected by variability of pH, local environment, or the gastric emptying rate. A blend of floating and pulsatile principles of drug delivery system would have the advantage that a drug can be released in the upper GI tract after a definite time period of no drug release. Sharma and Pawar, (2006) developed a low density floating beads of sodium alginate containing porous calcium silicate (Florite RE), for time and site specific drug release of meloxicam for chronotherapy of rheumatoid arthritis. The floating time for this system was controlled by density of beads and hydrophobic character of drug. Badve et al., (2007) developed hollow calcium pectinate beads for floating-pulsatile release of diclofenac sodium intended for chronopharmacotherapy of rheumatoid arthritis.
3.8. Marketed chronopharmaceutical technologies
Various systems have been developed and marketed taking chronopharmaceutics in consideration. One of the first commercially available oral products to employ the use of chronotherapy is the long acting bronchodilator Uniphyl® (Purdue Frederick Co., Norwalk, Connecticut, USA). Chronopharmaceutical technologies currently available include: OROS® (DURECT Corporation, Cupertino, California, USA), CODAS® (Elan Corporation, Gainesville, Florida, USA), CEFORM® (Biovail Corporation, Mississauga, Ontario, Canada), CONTIN® (Purdue Pharma, Pickering, Ontario, Canada), TIMERx® (Penwest Pharmaceutical Company, Danbury, Connecticut, USA), Diffucaps® (Eurand Pharmaceuticals, Yardley, Pennsylvania, USA) and Pulsincaps® (Catalent Pharma Solutions, Somerset, New Jersey, USA).

**OROS®**
OROS® delivery system patented by the DURECT Corporation (Cupertino, California, USA) utilizes an osmotic mechanism to provide pre-programmed, controlled drug delivery in a time or site specific manner to the gastrointestinal tract (Mandal et al., 2010). The drug delivery technology comprises a drug-loaded compartment, a push compartment and a semi permeable membrane laser drilled to link the drug layer with exterior of the drug delivery system. Drug release occurs due to the influx of fluid across the semi-permeable membrane into the push compartment. The increase in osmotic pressure forces drug to diffuse through the microscopic orifice (Khan et al., 2009). Covera-HS® (verapamil), an antihypertensive was formulated using L-OROS® technology by Alza Corporation for delayed overnight drug release to prevent the surge in blood pressure that occurs in patients during the early morning (Gauniya, 2007).

**CODAS®**
Chronotherapeutic Oral Drug Absorption System (CODAS®) manufactured by Elan Corporation (Florida, USA) is a multiparticulate system designed for bedtime dosing that provides a delayed onset of drug release. The technology comprises a drug loaded core and a release controlling membrane surrounding the core. Here, release controlling layer contains a mixture of both water-soluble and water-insoluble polymers. When these dosage forms are exposed to GI fluid or water, the water-soluble polymer dissolves and drug diffuses through the pores present in the coating. The water-insoluble polymer acts as a barrier and maintains the release of the drug (Khan et al., 2009). The CODAS® technology
has been applied to the chronopharmaceutical, Verelan® PM (verapamil) and introduced into the US market (Schwarz Pharma, USA). This formulation is designed to release verapamil, 4-5 h after ingestion. Bed-time administration of this formulation, the maximum plasma concentration is achieved in the early hours of the morning (Yui et al., 1992).

**CEFORM®**
The CEFORM® technology (Biovail Corporation, Mississauga, Ontario, Canada) allows the production of uniformly shaped and sized microspheres, having a diameter of 150-180 µm. The microspheres can be used in a wide variety of dosage forms including tablets, capsules, suspensions, effervescent tablets and sachets (Khan et al., 2009; Youan, 2009; Youan, 2004). The microspheres can be coated for controlled release either with an enteric coating or combined into a fast/slow release combination (Mandal et al., 2010). The technology was developed for chronotherapeutic drug delivery of Cardizem® LA which is a once-daily diltiazem formulation (Khan et al., 2009). Graded-release diltiazem HCl extended release formulation (GRD) administered once daily at bedtime significantly reduces blood pressure and heart rate over the 24 h interval. Greater reduction is obtained between 6 a.m. and 12 p.m., when circadian BP is highest, compared to morning administration of the same dose (Nayak et al., 2009; Youan, 2004).

**CONTIN®**
CONTIN® technology developed by Purdue Pharma (Ontario, Canada), involves combining a drug and hydrophilic polymer followed by selective hydration with a polar solvent and fixation through a higher aliphatic alcohol (Khan et al., 2009; Leslie, 1986). Here, cellulose polymer and a nonpolar solid aliphatic alcohol constitute molecular coordination complexes between them having utility as a matrix in controlled release formulations since it has a uniform porosity which may be varied. This technology is employed in the long-acting bronchodilator Uniphyl® (Arkinstall, 1988).

**TIMERx®**
TIMERx® technology was developed by Penwest Pharmaceuticals (Danbury, Connecticut, USA). This technology enables the drug to be delivered after a predetermined lag-phase that coincides with the circadian rhythm or allows the drug to be delivered to various sites within the gastrointestinal tract. This system is based on a hydrophilic matrix combining a hetero-dispersed mixture composed primarily of two polysaccharides, xanthan gum and
locust bean gum, in the presence of dextrose. The drug release is controlled by the rate of water penetration into the TIMERx® gum matrix, which expands to form a gel and subsequently releases the active drug substance. The rate of water permeation can be controlled precisely by varying the proportion of the gums, together with the tablet coating (Troy et al., 2003).

**Diffucaps®**

Diffucaps® technology developed by Eurand Pharmaceuticals (Pennsylvania, USA) capable of delivering drug to the body according to circadian rhythms (Khan et al., 2009). It is a capsule based system containing one or more drug-containing particles (e.g. beads, pellets, granules etc.). Each bead shows pre-programmed rapid or sustained release profile with or without lag time (Bisht, 2011; Devdhawala and Seth, 2010). The drug is layered onto an inert particle such as sugar spheres. The drug loaded core is then coated with a plasticized enteric coating and thereafter with a mixture of water insoluble and enteric polymers. The technology provides the versatility of combining two or more drugs in order to increase patient compliance and has been used to produce a chronopharmaceutical product known as InnoPran® XL (Sunil et al., 2011; Sajan et al., 2009).

**Pulsincaps®**

Pulsincap® system was developed by Catalent Pharma Solutions (Somerset, New Jersey, USA) (Khan et al., 2009). It consists of an insoluble capsule body enclosing the drug reservoir sealed with swellable hydrogel plugs and closed with soluble cap. Hydrogel plugs are made up of polymers like hydroxypropyl methyl cellulose, poly methyl methacrylates, poly vinyl acetate, polyvinyl alcohol, poly ethylene oxide, saturated polyglycolate d-glycerides, glyceryl monooleate, pectin etc. (Mandal et al., 2010; Gazzaniga et al., 2008). On oral administration the water soluble capsule cap dissolves in the gastric juices and the hydrogel plug swells. At a controlled and predetermined time point after the ingestion, the swollen plug is ejected from the Pulsincap® dosage form after which the encapsulated dosage formulation is released into the small intestinal fluid (Gohel and Sumitra, 2002). The variation in dimensions of the plug and its point/depth of insertion into the capsule determines the lag time produced prior to drug release (Mandal et al., 2010; Gazzaniga et al., 2008). Pulsincaps® technology has the versatility of allowing one or more mini-tablets, coated tablets, multiparticulates or granules to be loaded within the capsule for delivery of drug in a chronotherapeutic manner (Mandal et al., 2010).
EGALET® technology
Egalet® technologies offer controlled release profiles ranging from zero order release to delayed release (Youan, 2009). The delayed release form consists of impermeable shell with two lag plugs, enclosing a plug of active drug in the middle of the unit. The impermeable shells are made of ethylcellulose and plasticizers (such as cetostearyl alcohol) while the matrix of the plug is a blend of pharmaceutical excipients including polymers like polyethylene oxide (PEO). Time taken to erode the inert plug determines the lag time as drug releases after erosion of inert plug (Mandal et al., 2010; Youan, 2009).

3.9. Design of experiments (DOE)
All pharmaceutical products are formulated to specific dosage forms for drugs to be effectively delivered to patients. Different dosage forms require different pharmaceutical technologies and usually present different technical challenges for formulation development. Because of the complex technical challenges scientists encounter during formulation development, it is important to use an effective methodology. Design of experiments (DOE) and statistical analysis have been applied widely to formulation development, and are useful in product and process optimization. The major advantage of using DOE is that it allows all potential factors to be evaluated simultaneously, systematically, and quickly. Using DOE, one can evaluate the effect of each formulation factor on each response (and possibly the interaction effects between factors) and identify the critical factors based on statistical analysis. Once the critical factors have been identified, the optimal formulation can be defined by using proper DOE to optimize the levels of all critical factors. The manufacturing process also can be developed and optimized in the same fashion. When the formulation and manufacturing process of a pharmaceutical product are optimized by a systematic approach using DOE, scale-up and process validation can be very efficient because of the robustness of the formulation and manufacturing process (http://www.pharmtech.com).

Response surface methodology is a rapid technique used to empirically derive a functional relationship between an experimental response and a set of input variables in the development and optimization of pharmaceutical product. RSM trim down the number of experimental runs that are necessary to establish a mathematical trend in the experimental design region allow to determine the optimum level of experimental factors required for a given response (Singh et al., 2012).
3.10. Drug profile: Montelukast sodium (William, 2007)

Chemical formula: $C_{35}H_{35}ClNNaO_{3}S$

Category: Anti-asthmatic Agents, Anti allergic agent, Leukotriene Antagonists


Chemical structure:

[Chemical structure image]

BCS classification: Class II or IV compound

Physicochemical properties:

Montelukast sodium is a hygroscopic, optically active, and white to off-white crystalline/amorphous powder. It is freely soluble in ethanol, methanol, and water and practically insoluble in acetonitrile.

Description:

Montelukast sodium is a leukotriene receptor antagonist (LTRA) used for the maintenance treatment of asthma and to relieve symptoms of seasonal allergies. It blocks the action of leukotriene D4 on the CysLT1 in the lungs and bronchial tubes by binding to it. This reduces the bronchoconstriction otherwise caused by the leukotriene, and results in less inflammation. It is not useful for the treatment of acute asthma attacks. Because of its very specific locus of operation, it does not interact with other allergy medications such as theophylline. Montelukast is marketed in United States and many other countries by Merck & Co. with the brand name Singulair. It is available as oral tablets, chewable tablets, and oral granules. In India, it is also marketed under the brand name Montair® (Cipla, India) and Montek 10 mg (Sun Pharmaceutical Industries Ltd.).

Pharmacokinetics: Montelukast is available in several oral formulations: film-coated 10-mg tablets, chewable 4-mg and 5-mg tablets, and 4-mg oral granules. It is rapidly absorbed
following oral administration regardless of formulation. It is around 99% bound to plasma proteins and has elimination half-life of 2.7-5.5 h (mean 4.1 h). Studies in healthy human adult subjects have shown a mean oral bioavailability of 64% for the 10-mg tablet and 73% for the 5-mg chewable tablet. The mean oral bioavailability and $C_{\text{max}}$ were not influenced by a standard meal.

3.11. Excipient Profile (Rowe et al., 2009)

3.11.1. Calcium chloride dihydrate

Chemical Name: Calcium chloride dihydrate

Description: Calcium chloride occurs as a white or colourless crystalline powder, granules, or crystalline mass, and is hygroscopic (deliquescent).

Applications in pharmaceutical formulation or technology:
The main applications of calcium chloride as an excipient relate to its dehydrating properties and, therefore, it has been used as an antimicrobial preservative, as a desiccant (dehydrate), and as an astringent in eye lotions. It can be used as cross-linker in case of certain polymers.

3.11.2. Chitosan

Synonyms: 2-Amino-2-deoxy-(1,4)-β-d-glucopyranan; deacetylated chitin; β-1,4-poly-d-glucosamine; poly-d-glucosamine; poly-(1,4-β-d-glucopyranosamine) (Rowe et al., 2006).

Description: Chitosan occurs as odourless, white or creamy-white powder or flakes. Fiber formation is quite common during precipitation and the chitosan may look ‘cottonlike’.

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

Applications in pharmaceutical formulation or technology:
The suitability and performance of chitosan as a component of pharmaceutical formulations for drug delivery applications has been investigated in numerous studies. These include controlled drug delivery applications, use as a component of mucoadhesive dosage forms, rapid release dosage forms, improved peptide delivery, colonic drug delivery systems, and use for gene delivery. Chitosan has been processed into several pharmaceutical forms including gels, films, beads, microspheres, tablets, and coatings for liposomes.
Furthermore, chitosan may be processed into drug delivery systems using several techniques including spray-drying, coacervation, direct compression, and conventional granulation processes.

### 3.11.3. Croscarmellose sodium

**Synonyms:** Ac-Di-Sol, cross linked sodium carboxymethylcellulose

**Empirical Formula:** Croscarmellose sodium is a crosslinked polymer of carboxymethylcellulose sodium.

**Functional Category:** Tablet and capsule disintegrant.

**Description:** Croscarmellose sodium occurs as an odorless, white or grayish white powder.

**Applications in pharmaceutical formulation or technology:**
Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules. At concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

### 3.11.4. Dibutyl phthalate

**Synonyms:** Araldite 502, benzenedicarboxylic acid, benzene-o-dicarboxylic acid di-n-butyl ester, butyl phthalate, DBP

**Chemical name:** Dibutyl benzene-1, 2-dicarboxylate

**Functional Category:** Film-forming agent; plasticizer; solvent.

**Description:** Dibutyl phthalate occurs as an odourless, oily, colourless, or very slightly yellow-coloured, viscous liquid.

**Applications in pharmaceutical formulation or technology:**
Dibutyl phthalate is used in pharmaceutical formulations as a plasticizer in film-coatings. It has been evaluated as a pore-forming agent in novel delivery systems. It is also used extensively as a solvent, particularly in cosmetic formulations such as antiperspirants, hair shampoos, and hair sprays. In addition to a number of industrial applications, dibutyl phthalate is used as an insect repellent, although it is not as effective as dimethyl phthalate.

### 3.11.5. Ethylcellulose

**Synonyms:** Aquacoat ECD; Aqualon; E462; Ethocel; Surelease
Chemical name: Cellulose ethyl ether

Empirical Formula: Ethylcellulose is partially ethoxylated. Ethylcellulose with complete ethoxyl substitution (DS = 3) is $\text{C}_{12}\text{H}_{23}\text{O}_6 (\text{C}_{12}\text{H}_{22}\text{O}_5)\text{n}\text{C}_{12}\text{H}_{23}\text{O}_5$ where n can vary to provide a wide variety of molecular weights. Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of β-anhydroglucose units joined together by acetal linkages.

Functional Category: Coating agent; tablet binder; tablet filler; viscosity increasing agent.

Physicochemical properties: It is a tasteless, free-flowing, white to light tan colour powder and is practically insoluble in glycerine, propylene glycol, and water. It is stable, slightly hygroscopic material, resistant to alkalis, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters.

Applications in pharmaceutical formulation or technology:
Ethylcellulose is widely used in oral as hydrophobic coating agent for tablets and granules and topical pharmaceutical formulations as a thickening agent in creams, lotions, or gels, provided an appropriate solvent is used. In tablet formulations, ethylcellulose may additionally be employed as a binder. It is categorised as coating agent, flavouring fixative, tablet binder, tablet filler and viscosity-increasing agent.

3.11.6. Eudragit L100

Chemical/IUPAC name: Poly (methacrylic acid-co-methyl methacrylate) 1:1

Monographs:
- Ph. Eur.: Methacrylic Acid - Methyl Methacrylate Copolymer (1:1)
- USP/NF: Methacrylic Acid Copolymer, Type A - NF
- JPE: Methacrylic Acid Copolymer L

Eudragit L 100 are anionic copolymers based on methacrylic acid and methyl methacrylate.

Properties: It is a solid substance in form of a white powder with a faint characteristic odour.

Characteristics:
- Effective and stable enteric coatings with a fast dissolution in the upper bowel
- Granulation of drug substances in powder form for controlled release
- Site specific drug delivery in intestine by combination with eudragit S grades
3.11.7. Eudragit RSPO (http://eudragit.evonik.com)

Chemical/IUPAC name: Poly (ethyl acrylate-co-methyl methacrylate-co-trimethyl ammonioethyl methacrylate chloride) 1:2:0.1

Monographs:
- Ph. Eur.: Ammonio Methacrylate Copolymer, Type B
- USP/NF: Ammonio Methacrylate Copolymer, Type B - NF
- JPE: Aminoalkyl Methacrylate Copolymer RS

Eudragit RSPO is a copolymer of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups.

Properties: Insoluble, low permeability, pH independent swelling

Characteristics: Suitable for matrix structures and customized release profile by combination of RL and RS grades in different ratios.

3.11.8. Eudragit RLPO (http://eudragit.evonik.com)

Chemical/IUPAC name: Poly (ethyl acrylate-co-methyl methacrylate-co-trimethyl ammonioethyl methacrylate chloride) 1:2:0.2

Monographs:
- Ph. Eur.: Ammonio Methacrylate Copolymer, Type A
- USP/NF: Ammonio Methacrylate Copolymer, Type A - NF
- JPE: Aminoalkyl Methacrylate Copolymer RS

Eudragit RLPO is a copolymer of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups. The ammonium groups are present as salts and make the polymers permeable.

Properties: Insoluble, high permeability, pH independent swelling

Characteristics:
- Customized release profile by combination of RL and RS grades in different ratios
- Suitable for matrix structures

3.11.9. Hydroxypropyl cellulose, low-substituted

Synonyms: Hyprolose, low-substituted; L-HPC

Chemical name: Cellulose, 2-hydroxypropyl ether (low-substituted)
Empirical formula and molecular weight: The USP32–NF27 describes low-substituted hydroxypropyl cellulose as a low-substituted hydroxypropyl ether of cellulose. Low-substituted hydroxypropyl cellulose is commercially available in a number of different grades that have different particle sizes and substitution levels.

Functional Category: Tablet and capsule disintegrant; tablet binder.

Description: Low-substituted hydroxypropyl cellulose occurs as a white to yellowish white powder or granules. It is odourless or has a slight, characteristic odour, and it is tasteless.

Applications in pharmaceutical formulation or technology:
It is primarily used as a disintegrant, and as a binder for tablets and granules in wet or dry granulation. It has been used in the preparation of rapidly disintegrating tablets produced by direct compression methods. There are a number of grades that have different particle sizes and substitution levels. LH-11 has the longest fibrous particles, and is typically used as an anti-capping agent and disintegrant for direct compression. LH-21 is less fibrous and is used as a binder and disintegrant for tablets through the wet-granulation process. LH-31 is a small-particle grade used especially for extrusion to produce granules, as it has a small particle size that is better for passing a screen. LH-B1 is the non-fibrous, high-density grade designed for fluid-bed granulation, and can be used for direct compression and/or formulations with a high low-substituted hydroxypropyl cellulose loading. Lower substitution grades LH-22 and LH-32 can be used for better disintegration capability, depending on the characteristics of the active ingredients.

3.11.10. Hydroxypropyl methylcellulose (Hypromellose)

Synonyms: HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur

Chemical name: Cellulose hydroxypropyl methyl ether;

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

Description: Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.
Applications in pharmaceutical formulation or technology:
In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0%.
Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. Hypromellose is also used as a suspending and thickening agent in topical formulations. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. It is also used commercially in liquid nasal formulations at a concentration of 0.1%. Hypromellose is used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.

3.11.11. Lactose, anhydrous
Synonyms: Anhydrous Lactose NF 60M; Anhydrous Lactose NF Direct Tableting; Lactopress Anhydrous; lactosum; lattioso; milk sugar; Pharmatose DCL 21; Pharmatose DCL 22; saccharum lactis; Super-Tab Anhydrous
Chemical name: O-β-D-galactopyranosyl-(1-4)-β-D-glucopyranose;
Functional Category: Directly compressible tablet excipient; dry powder inhaler carrier; lyophilization aid; tablet and capsule diluent; tablet and capsule filler.
Description: Anhydrous lactose occurs as white to off-white crystalline particles or powder. Several different brands of anhydrous lactose are commercially available which contain anhydrous β-lactose and anhydrous α-lactose. Anhydrous lactose typically contains 70–80% anhydrous β-lactose and 20–30% anhydrous α-lactose.
Applications in pharmaceutical formulation or technology:
Anhydrous lactose is widely used in direct compression tableting applications, and as a tablet and capsule filler and binder. It can be used with moisture-sensitive drugs due to its low moisture content.
3.11.12. Magnesium stearate

Synonyms: Magnesium octadecanoate; octadecanoic acid

Chemical Name: Octadecanoic acid magnesium salt

Functional Category: Tablet and capsule lubricant.

Description: Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Applications in pharmaceutical formulation or technology:
Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w.

3.11.13. Microcrystalline cellulose

Synonyms: Avicel PH; Celex; cellulose gel; pharmacel

Functional Category: Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant

Description: Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Applications in pharmaceutical formulation or technology:
Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. It is also used in cosmetics and food products. It is categorised as tablet disintegrant (5-15%), adsorbent (20-90%) and as diluents.

3.11.14. Polyethylene oxide

Synonyms: Polyox; polyoxirane; polyoxyethylene

Description: White to off-white, free-flowing powder, slight ammoniacal odour.
Functional Category: Mucoadhesive, coating agent, tablet binder, thickening agent.

Applications in pharmaceutical formulation or technology:
Polyethylene oxide can be used as a tablet binder at concentrations of 5–85%. The higher molecular weight grades provide delayed drug release via the hydrophilic matrix approach. It has also been shown to facilitate coarse extrusion for tableting as well as being an aid in hot-melt extrusion. The relationship between swelling capacity and molecular weight is a good guide when selecting products for use in immediate- or sustained-release matrix formulations. It is most commonly used now a days in osmotic based drug delivery systems.

3.11.15. Sodium alginate

Synonyms: Algin, alginic acid, sodium salt, sodium polymannuronate

Chemical name: Sodium alginate

Functional Category: Stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity increasing agent.

Description: Odourless and tasteless, white to pale yellowish-brown coloured powder.

Applications in pharmaceutical formulation or technology:
Sodium alginate is used as binder and disintegrant in tablet formulations, diluent in capsule formulations, thickening and suspending agent in pastes, creams and gels and as stabilizing agent for oil-in-water emulsions. It is categorized as stabilizing agent, suspending agent, tablet and capsule disintegrant, tablet binder, and viscosity-increasing agent. Recently, sodium alginate has been used for the aqueous microencapsulation of drugs, in contrast with the more conventional microencapsulation techniques which use organic solvent systems. It has also been used in the formation of nanoparticles.

3.11.16. Talc

Synonyms: Hydrous magnesium calcium silicate, soapstone; steatite

Functional Category: Anticaking agent, glidant, tablet and capsule lubricant

Description: White to greyish-white, odourless, impalpable, unctuous, crystalline powder.

Applications in pharmaceutical formulation or technology:
Talc was once widely used in oral solid dosage formulations as a lubricant and diluent, although today it is less commonly used. However, it is widely used as a dissolution
retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbent. In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves. Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder.

3.11.17. Triethyl citrate

Synonyms: Citric acid, ethyl ester; Citroflex 2; Citrofol AL; E1505; Hydagen CAT; TEC

Chemical name: 2-Hydroxy-1, 2, 3-propanetricarboxylic acid, triethyl ester;

Functional category: Plasticizer; solvent.

Description: It is a clear, viscous, odorless, and practically colorless, hygroscopic liquid.

Applications in pharmaceutical formulation or technology:
Triethyl citrate and the related esters acetyltriethyl citrate, tributyl citrate, and acetyltributyl citrate are used to plasticize polymers in formulated pharmaceutical coatings. The coating applications include capsules, tablets, beads, and granules for taste masking, immediate release, sustained-release, and enteric formulations. Triethyl citrate is also used as a direct food additive for flavoring, for solvency, and as a surface active agent.