Development And Characterization Of Pulsatile Release Tablet Of Nizatidine

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Abstract: The objectives of pulsatile release tablet of nizatidine are pulsatile, it is inhibit the peptic secretion. The core tablets containing Nizatidine (150 mg/ tablet), lactose, microcrystalline cellulose (Avicel® PH101), polyvinyl pyrrolidone (PVP K30) and superdisintegrant like crosspovidone, crosscarmellose sodium (Ac-Di-Sol®) sodium starch glycolate, were prepared by direct compression. Initially, the core tablet excipients were dry blended in polybags for 10min, followed by the addition of Talc, magnesium stearate and Aerosil® 200. The powder components were further blended for 5min. The core tablets (diameter, 9mm; biconvex; average tablet weight, 360mg) were compressed using a Eight station tablet machine (karnavati, Ahmadabad, India). Nizatidine was observed to be almost white buff crystalline powder, sulphur mercapton odour with metallic bitter test. The results are. The melting point was found to be 131-134°C. The solubility studies of Nizatidine were performed in various solvents. The Nizatidine was to be freely soluble in chloroform, in methanol soluble in water and buffered solution slightly soluble in ethyl acetate and isopropanol. The melting was observed at 131-134°C. The DSC curve of pure Nizatidine exhibited a single endothermic responses corresponding to the melting of drug. Onset of melting was obtained at 135°C. The superdisintegrant crosscarmellose sodium, crosspovidone, sodium starch glycolate shows broad endothermic fusion peaks at 96.11°C, 94.96°C and 84.48°C respectively which is due to glass transition state. The DSC spectra of physical mixture of Nizatidine and mixture of other excipients has also shown same endothermic peak like pure drug. These observations of DSC study indicate absence of significant interaction between drug and excipients used in tablets formulation.

Keywords: formulation of nizatidine, superdistigrant crosspovidone, crosscarmellose sodium, evaluation

1.0 INTRODUCTION:

1.1 Peptic ulcer

A peptic ulcer, also known as PUD or peptic ulcer disease, is the most common ulcer of an area of the gastrointestinal tract that is usually acidic and thus extremely painful. The lining of the stomach and small intestines is protected against the irritating acids produced in your stomach. If this protective lining stops working correctly and the lining breaks down, it results in inflammation (gastritis) or an ulcer. Most ulcers occur in the first layer of the inner lining. A hole that goes all the way through the stomach or duodenum is called a perforation.1

A major causative factor of gastric and duodenal ulcers is helicobacter pylori infection. This bacterium can cause a chronic active gastritis (type B gastritis), resulting in a defect in the regulation of gastrin production by that part of the stomach, and gastrin secretion can either be increased, or as in most cases, decreased, resulting in hypo or achlorhydria. Gastrin stimulates the production of gastric acid by parietal cells and, in H. pylori colonization responses that increase gastrin, the increase in gastric acid can contribute to the erosion of the mucosa and therefore ulcer formation. Another major causative factor of NSAIDs. The gastric mucosa protects itself from gastric acid with a layer of mucus, the secretion of which is stimulated by certain prostaglandins. NSAIDs block the function of cyclooxygenase-1 (cox-1), which is essential for the production of these prostaglandins. COX-2 selective anti-inflammatory preferentially inhibits cox-2, which is less essential in the gastric mucosa, and roughly halves the risk of NSAID-related gastric ulceration. As the prevalence of H. pylori-caused ulceration declines due to increased medical treatment, a greater proportion of ulcers will be due to increasing NSAID use among individuals with pain syndromes as well as the growthhasing populations that develop arthritis. A major causative factor of gastric and duodenal ulcers is smoking and ulcer formation.2 Others have been more specific in exploring the risks involved and have found that smoking by itself may not be a significant risk factor, unless associated with H. pylori infection.3,4 Similarly, while studies have found that alcohol consumption increases risk when associated with H. pylori infection, it does not seem to independently increase risk, and even when coupled with H. pylori infection.5

2. Types of ulcer based on location: (Duodenum) Duodenal ulcer, (Oesophagus) Esophageal ulcer, (Stomach) Gastric ulcer.

1.2 Medication treating peptic ulcer

Antiulcer drugs refer to the property of a substance or treatment that reduces the gastric acid secretions, duodenal ulcer chronic remitting and relapsing diseases. Goal of antiulcer therapy are

- Relief of pain,
- Ulcer healing,
- Prevention of complication,
- Prevention of relapse.

1.2.1 Classification of drugs for peptic ulcer

- Relief of pain,
- Ulcer healing,
- Prevention of complication,
- Prevention of relapse.
1. Gastric acid secretion inhibitor
   - H₂ antihistamines: Cimetidine, Ranitidine, Famotidine, 
     Roxatidine, Loxatidine, Nizatidine
   - Proton pump inhibitors (PPI): Omeprazole, Esomeprazole, Lansoprazole, Pantoprazole, Rabeprazole
   - Prostaglandin analogues (PA): Misoprostol
   - Anticholinergics: Pirenzepine, Propantheline, Oxyphenonium

2. Gastric acid neutralizers (Antacids)
   - Systemic antacids: Sodium bicarbonate, Sod. citrate
   - Nonsystemic antacids: Magnesium hydroxide, Mag. trisilicate, Aluminium hydroxide gel, Calcium carbonate, Magaldrate

3. Ulcer protective: Sucralfate, colloidal bismuth subcitrate (CBS)

4. Anti-H₂ pylori drugs: Amoxicillin, Clarithromycin, Metronidazole, Tetracycline.¹

H₂ antagonist
Peptic ulcer occur in that part of gastrointestinal tract which is exposed to gastric acid and pepsin i.e. stomach and duodenum. It is result probably due to an imbalance between aggressive (acid, pepsin, bile and H₂ pylori) and defensive factor (gastric mucous, bicarbonate secretion, prostaglandin, innate resistance of the mucosal cell) factor.² Normal gastric acid secretion follows circadian rhythm with a sudden surge of gastric acid when gastric pH level goes far below 4 for at least 1 hour in the midnight. This pathophysiological condition is termed as nocturnal acid breakthrough (NAB). But recently it is observed that up to 70% patients appears to be resistance to even high doses of proton pump inhibitor taken twice daily.

Mechanism of Action³⁰
The H₂-receptor antagonists inhibit acid production by reversibly competing with histamine for binding to H₂ receptors on the basolateral membrane of parietal cells. Four different H₂-receptor antagonists, who differ mainly in these drugs, are less potent than proton pump inhibitors but still suppress 24-hour gastric acid secretion by about 70%. The H₂-receptor antagonists predominantly inhibit basal acid secretion, which accounts for their efficacy in suppressing nocturnal acid secretion. Because the most important determinant of duodenal ulcer healing is the level of nocturnal acidity, evening dosing of H₂-receptor antagonists is adequate therapy in most instances.

Therapeutic Uses
The major therapeutic indications for H₂-receptor antagonists are to promote healing of gastric and duodenal ulcers, to treat uncomplicated GERD and to prevent recurrence of stress ulcers.

Pharmacological Action
H₂ block: H₂ antagonist block histamine induced gastric acid secretion, cardiac stimulation, uterine relaxation and bronchial relaxation, they attenuated fall in BP due to histamine, especially the late phase response seen with high doses they are highly selective, and have no effect on H₂ mediated responses or on the action on the other autacoids.

Gastric secretion: They only significant in vivo action of H₂ blockers inhibition of gastric secretion. All phases of secretion are suppressed dose dependently, but the basal nocturnal secretion suppressed more completely. Secretary responses to not only histamine but all other stimuli are attenuated. This reflects the permissive role of histamine in amplifying responses to other autacoids. The volume, pepsin content and intrinsic factor secretion are also reduced.

1.0 Introduction to Pulsatile Drug Delivery System
During the past several decades, conventional drug dosage forms have been widely used for treatment of various conditions. These drug dosage forms typically provide an immediate or rapid medication release, and supply a given concentration of drug to the body's systemic circulation system without any rate control. To maintain the effective plasma drug concentration, frequent administration is required. Due to poor drug efficacy, the incidence of side effects, frequency of administration and patient compliance of these conventional drug preparations, many traditional drug dosage forms are undergoing replacement by second-generation, modified drug-release dosage forms (Fig. 1). Treatments of numerous diseases using traditional drug products are often inconvenient and impractical if disease symptoms occur during the night or early morning. During the early 1990s, second-generation modified-release drug preparations achieved continuous and constant-rate drug delivery, in which constant or sustained drug output minimize drug concentration “peak and valley” levels in the blood, so promoting drug efficacy and reducing adverse effects. Modified-release drug preparations are expected to provide reduced dosing frequency and improved patient compliance compared to conventional release preparations. Second-generation modified release dosage forms include prolonged-release, delayed-release, and controlled release preparations.¹¹,¹²
Several controlled-release preparations present numerous problems such as resistance and drug tolerance, and activation of the physiological system due to long-term constant drug concentrations in the blood and tissues. Physiological tolerance may develop as an organism builds resistance to the effects of a drug substance after repeated exposures. This indicates strongly that it is not always desirable to maintain constant blood levels of a drug over long periods. Pulsatile drug delivery systems also reveal that the body's biological rhythm may affect normal physiological function, including gastrointestinal motility, gastric acid secretion, gastrointestinal blood flow, renal blood flow, hepatic blood flow, urinary pH, cardiac output, drug-protein binding, and biological functions such as heart rate, blood pressure, body temperature, blood plasma concentration, intraocular pressure, and platelet aggregation. Most organ functions vary with the time of the day, particularly when there are rhythmic and temporal patterns in the manifestation of a given disease state. Thesymptoms of many diseases, such as bronchial asthma, myocardial infarction, angina pectoris, hypertension, and rheumatic disease have followed the body's biological rhythm. Day-night variation in asthmatic dyspnea and variations in the incidence of myocardial infarction occur throughout the early morning hours. Controlled-release medications deliver continuous treatment, rather than providing relief of symptoms and protection from adverse events solely when necessary. The development of a third-generation of advanced drug delivery systems (DDSs) to optimize and create new innovative DDSs which provide defined dose, at a chosen rate, at a selected time, to a targeted site is now a growing challenge. A chronodelivery system, based on biological rhythms, is a state-of-the-art technology for drug delivery. Chronomodulated DDSs not only increase safety and efficacy levels, but also improve overall drug performance. Chronomodulated drug delivery systems such as pulsatile drug delivery systems. The oral controlled-release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time, thereby ensuring sustained therapeutic action. However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as pulsatile release. Recent studies have revealed that diseases have a predictable cyclic rhythm and that the timing of medication regimens can improve the outcome of a desired effect. This condition demands release of drug as a “pulse” after a time lag and such systems have to be designed in a way that complete and rapid drug release should follow the lag time. Such systems are known as pulsatile drug delivery systems (PDDS), time-controlled systems, or sigmoidal release systems (Fig. 2).

Figure 1: Progress of pharmaceutical preparation

Several controlled-release preparations present numerous problems such as resistance and drug tolerance, and activation of the physiological system due to long-term constant drug concentrations in the blood and tissues. Physiological tolerance may develop as an organism builds resistance to the effects of a drug substance after repeated exposures. This indicates strongly that it is not always desirable to maintain constant blood levels of a drug over long periods. Pulsatile drug delivery systems also reveal that the body's biological rhythm may affect normal physiological function, including gastrointestinal motility, gastric acid secretion, gastrointestinal blood flow, renal blood flow, hepatic blood flow, urinary pH, cardiac output, drug-protein binding, and biological functions such as heart rate, blood pressure, body temperature, blood plasma concentration, intraocular pressure, and platelet aggregation. Most organ functions vary with the time of the day, particularly when there are rhythmic and temporal patterns in the manifestation of a given disease state. The symptoms of many diseases, such as bronchial asthma, myocardial infarction, angina pectoris, hypertension, and rheumatic disease have followed the body's biological rhythm. Day-night variation in asthmatic dyspnea and variations in the incidence of myocardial infarction occur throughout the early morning hours. Controlled-release medications deliver continuous treatment, rather than providing relief of symptoms and protection from adverse events solely when necessary, the development of a third-generation of advanced drug delivery systems (DDSs) to optimize and create new innovative DDSs which provide defined dose, at a chosen rate, at a selected time, to a targeted site is now a growing challenge. A chronodelivery system, based on biological rhythms, is a state-of-the-art technology for drug delivery. Chronomodulated DDSs not only increase safety and efficacy levels, but also improve overall drug performance. Chronomodulated drug delivery systems such as pulsatile drug delivery systems. The oral controlled-release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time, thereby ensuring sustained therapeutic action. However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as pulsatile release. Recent studies have revealed that diseases have a predictable cyclic rhythm and that the timing of medication regimens can improve the outcome of a desired effect. This condition demands release of drug as a “pulse” after a time lag and such systems have to be designed in a way that complete and rapid drug release should follow the lag time. Such systems are known as pulsatile drug delivery systems (PDDS), time-controlled systems, or sigmoidal release systems (Fig. 2).

Figure 2: Schematic representation of different drug delivery system

PDDS have been developed in close connection with emerging Chronotherapeutics views. In this respect, it is well established that the symptoms of many pathologies, as well as pharmacokinetic and pharmacodynamic profiles of most drugs, are subject to circadian variation patterns. As far as widespread chronic pathologies with nighttime or early morning symptoms are concerned, such as cardiovascular disease (CVD), bronchial asthma, and rheumatoid arthritis (RA), remarkable efficacy, tolerability, and compliance benefits could arise from modified release medicaments. After bedtime administration, would allow the onset of therapeutic drug concentration to coincide with the time at which disease manifestations are more likely to occur. Performance of pulsatile delivery fulfills such goals. In addition to being potentially suitable for chronotherapy...
py, pulsatile release is also exploited to target proximal as well as distal colonic regions via the oral route. Following are the reasons which force the inventors to think about the shift from conventional sustained release approach to the modern pulsatile delivery of drugs.

- **First pass metabolism:** Some drugs like betablockers, and salicylamide, undergo extensive first pass metabolism. To minimize the pre-systemic metabolism, these drugs require fast drug input to prevent saturation of metabolizing enzymes. Thus, a constant/sustained oral delivery would reduce the oral bioavailability.

- **Biological tolerance:** The pharmacotherapeutic effect of the drug declines with the continuous release of drug plasma profiles. For example, biological tolerance to trans-dermal nitro-glycerin.

- **Chrono-pharmacological needs:** According to circadian rhythms, it has been observed that symptoms and inception of disease occur during specific time periods of the 24 hours a day. For example, Asthma, rheumatoid arthritis and anginapectoris attacks are most frequently in the morning hours.

- **Local therapeutic need:** For the local disorders treatment of such as Crohn’s disease, Inflammatory Bowel Disease (IBD), ulcerative colitis and Inflammatory Bowel Syndrome (IBS). The absorption in the small intestine is highly advantageous to attain the therapeutic effect and to reduce side effects.

- **Instability of the drugs in GI fluid:** In case of such compounds, the uses of sustained release preparations are widely suggested and acceptable from the therapeutic point of view.

- **Different drug absorption behavior in GIT:** In common, drug absorption is somewhat slow in the stomach, rapid in the small intestine than stomach, and sharply minimizes in the large intestine to compensate the changes in absorption characteristics.

**Circadian rhythms and their implications:**

Circadian rhythms are self-sustaining, endogenous oscillation, exhibiting periodicities of about one day or 24 hours. Normally, circadian rhythms are synchronized according to the body’s pacemaker clock, located in the suprachiasmatic nucleus of the hypothalamus. The physiology and biochemistry of human beings are not constant during the 24 hours, but variable in a predictable manner as defined by the timing of the peak and trough of each of the body’s circadian processes and functions. The peak in the rhythms of basal gastric and secretion, white blood cells (WBC), lymphocytes, prolactin, melatonin, eosinophil, adrenal corticotrophin hormone (ACTH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH), is manifested at specific times during the nocturnal sleep span. The peak in serum cortisol, aldosterone, testosterone plus platelet adhesiveness and blood viscosity follows later during the initial hours of diurnal activity. Hematocrit is the greatest and airway caliber the best around the middle and afternoon hours, platelet numbers and uric acid peaks later during the day and evening. Hence, several physiological processes in the human vary in a rhythmic manner, in synchrony with the internal biological clock, as shown in fig. 3.

**Figure 3:** Human circadian time-structured dependent pulsatile hormone secretion.
Figure 4: The circadian pattern of diseases

Through a number of clinical trials and epidemiological studies, it has become evident that the levels of disease activity of a number of clinical disorders have patterns associated with the body’s inherent clock set according to circadian rhythms. Infect just as the time of day influences normal biological processes, so it affects the pathophysiology of disease and its treatment. Examples of some of the diseases are shown in Table 1.

Table 1: Circadian rhythm and manifestation of clinical diseases

<table>
<thead>
<tr>
<th>Disease/syndrome</th>
<th>Circadian rhythmicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic Rhinitis</td>
<td>Worse in the morning/upon rising</td>
</tr>
<tr>
<td>Asthma</td>
<td>Exacerbations more common during the sleep period</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Symptom more common during the sleep period</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>Symptom worse in the middle/later portion of the day</td>
</tr>
<tr>
<td>Angina Pectoris</td>
<td>Chest pain and ECG changes more common in the early morning</td>
</tr>
<tr>
<td>Myocardial Infraction</td>
<td>Incidence greatest in the early morning</td>
</tr>
<tr>
<td>Stroke</td>
<td>Incidence higher in the morning</td>
</tr>
<tr>
<td>Sudden Cardiac Death</td>
<td>Incidence higher in the morning after awakening</td>
</tr>
<tr>
<td>Peptic Ulcer Disease</td>
<td>Worse in the late evening and early morning hours</td>
</tr>
</tbody>
</table>

Chronopharmacotherapy

Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions. "Chronopharmaceutics" consist of two words: Chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms. There are three types of mechanical rhythms in our body. They are:

i. Circadian
ii. Ultradian
iii. Infradian

Circadian: This word comes from Latin word "circa" means about and "dies" means day. Ultradian Oscillation of shorter duration are termed as Ultradian (more than one cycle per 24 h). Infradian Oscillations that are longer than 24 h (less than one cycle per day).

1.3.2 Diseases with established circadian rhythms

The diseases recently targeted for pulsatile drug delivery are those which have enough scientific background to justify chronopharmaceutical drug delivery system.
compared to conventional drug administration. These include asthma, arthritis, duodenal ulcer, cancer, cardiovascular diseases, diabetes, hypercholesterolemia, neurological disorders, etc., which have good circadian rhythm.  

**Duodenal ulcer**

Generally, gastric acid secretion is highest in the evening in duodenal ulcer patients, and it decreases in the early morning.  

One group of authors studied incidence of ulcer perforation for daily (circadian), weekly (circaseptan) and yearly (circannual) time effects. A circadian perforation showed highest incidence in the afternoon, while gastric perforation showed a major peak around noon and a secondary peak near midnight. For duodenal ulcer perforation, the circannual pattern was characterized by a 6-month rhythm, with significantly higher incidences in May–June–July and in November–December in most subgroups.  

**Bronchial asthma**

It is characterized by airway inflammation resulting in hyperresponsiveness of lower respiratory tract and various environmental stimuli. Airway resistance increases progressively at night in asthmatic patients. This asthma known as nocturnal asthma, isan exacerbation of asthma with increased symptoms, airway responsiveness and lung function. Daytime mean age provokes the release of pro-inflammatory mediators from mast cells and eosinophils. These cells are the source of adhesion molecules, cytokines, and chemokines, which play a role in the late-phase reaction, resulting in bronchoconstriction and exacerbation of symptoms.  

**Allergic rhinitis**

Common symptoms of allergic rhinitis are sneezing, nasal rhinorrhea, red, itchy eyes, nasal pruritus, and nasal congestion. Each patient has symptoms, and the most frequent was found to occur most frequently before breakfast and in the morning and least frequently in the middle of the day. There are two phases of occurrence of allergic rhinitis: early (within 24 hours) and late (manifesting after 12–16 hours). The early phase is caused by the release of histamine, prostaglandins, cytokines, TNF-α, Chemotactic factors, etc., resulting in sneezing, nasal itching, and rhinorrhea. On the other hand, the late phase is caused by elaboration, adhesion, and infiltration of circulating leukocytes, T cells, and eosinophils, evoking nasal congestion, obstruction due to the exacerbation of inflammation, and sinus and other tissue ischemia.  

**Pain**

Pain control is one of the most important therapeutic priorities. Although numerous clinical practice guidelines for pain management have been published, inadequate pain relief remains a significant health care issue. It was reported that the highest threshold occurred at the end of the resting period, while the least threshold was seen at the end of the activity period. In arthritis, there is a circadian rhythm in the plasma concentration of C-reactive protein and interleukin-6 and patients with rheumatoid arthritis. Besides, different opioid peptides like 5-hydroxytryptamine, bradykinin, glutamate, NO, substance P, cytokines, and prostanoids are involved in the activation of receptors. Brain concentration of substance P in rat model is highest in the night with a circadian variation. It was reported that the levels of endogenous opioid peptides are higher at the starting point of the day and lower in the evening both in neonate and adult human volunteers. Patients with osteoarthritis tend to have less pain in the morning and more at night. While patients with rheumatoid arthritis have pain that is usually peak in the morning and decreases throughout the day.  

**Cardiovascular diseases**

In cardiovascular diseases, capillary resistance and vascular reactivity are higher in the morning and decrease after the middle of the day. Platelet reactivity increases and fibrinolytic activity decreases in the morning, leading to an increase in fibrinogen levels. This variation is affected by a variety of external factors, such as individual differences, age, gender, hemodynamic changes, and environmental variables. Increased heartrate, blood pressure, blood pressure variation, and fibrinolytic activity show a circadian variation in both men and women. The association between the circadian rhythm of fibrinogen and blood pressure is important. Atrial arrhythmias are present in the middle of the day, with higher frequency in the daytime and lower frequency in the night time with the abnormal foci under the same long-term autonomic regulation as normal pacemaker tissue. According to study, ventricular tachyarrhythmias show a higher frequency in the circadian rhythm of fibrinogen. Both pharmacokinetic and pharmacodynamics of some oral nitrates, calcium channel blockers, and β-adrenoceptor antagonists have been shown to be influenced by the circadian time of their administration.  

**Rheumatoid arthritis (RA)**

The chronobiology, chronopharmacology, and chronotherapeutics of pain have been extensively reviewed. For instance, the effect of circadian rhythm on the plasma concentration of C-reactive protein and interleukin-6 and patients with rheumatoid arthritis. Patients with osteoarthritis tend to have less pain in the morning and more at night, while those with rheumatoid arthritis have pain that is usually peak in the morning and decreases throughout the day. Chronotherapy for all forms of arthritising NSAIDs such as Ibuprofen should be timed to ensure that the highest blood levels of
Sleep disorder

Many biological signaling e.g. sleep disorder occurring in the central and autonomous nervous systems show complex time structure with rhythm and pulsatile variations in multiple frequencies. The time of sleep required by each person is usually constant, although there is a wide variation among individuals. Sleep consists of a rhythmic (circadian) combination of the changes in physiological, biochemical, and psychological processes. When the circadian rhythm is disturbed, or when the individual processes are abnormal during sleep, it may result in a variety of disorders. One such example is delayed sleep-phase syndrome which is characterized by severe sleep-onset insomnia normally, sleep is impossible until 3 a.m. or later until there is great difficulty in awakening in the morning. The ability to cope with circadian rhythm disturbances also differs from person to person. Identification of the individual variation would be of importance in dealing with certain sleep disorders.

1.3.3 Classification of PDDS depending on Target release.

From a technological standpoint, pulsatile drug delivery systems are further divided into single and multiple units system

a) Single units system

Capsular system:

Different single-unit capsular PDDS have been developed (Fig 5). A general design of such systems consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined time lag due to swelling, erosion, or dissolution. The Pulsincap® system is an example of such a system that is made up of a water-insoluble capsule body filled with drug formulation. The body is closed at the open end with a swellable hydrogel plug. Upon contact with the dissolution medium or gastrointestinal fluids, the plug swells, pushing itself out of the capsule after a time lag. This is followed by a spontaneous release of the drug (Fig 5).

Figure 5: Schematic diagram of capsular system

The time lag can be controlled by manipulating the dimension and the position of the plug. For water insoluble drugs, a spontaneous release can be ensured by inclusion of effervescent agents or disintegrants. The plug material consists of insoluble but permeable and swellable polymers (e.g., polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g., saturated polyglycolide, glyceryl monoleate, and enzymatically controlled erodible polymers, e.g., pectin). These formulations are well tolerated in animals and healthy volunteers, and there have been no reports of gastrointestinal irritation. However, there was a potential problem of variable gastric residence time, which was overcome by enteric coating the system to allow its dissolution only in the higher pH region of the small intestine.

b) Port systems

The Port System consists of a gelatin capsule coated with a semi-permeable membrane (e.g., cellulose acetate) housing an insoluble plug (e.g., lipidic) and a non-osmotically active agent along with the drug formulation. When it comes in contact with the aqueous medium, water diffuses across the semi-permeable membrane, resulting in increased inner pressure that ejects the plug after a lag time. The lag times are controlled by the thickness of the semi-permeable membrane. The system showed good correlation in lag times of *in-vitro* and *in-vivo* experiments in humans. In order to deliver drug in liquid form, an osmotically driven capsular system was developed. In this system, liquid drug is absorbed into highly porous particles, which release the drug through an orifice of a semi-permeable capsule supported by a non-expanding osmotic layer after the barrier layer is dissolved. The capsule system delivers drug by the capsule’s osmotic infusion of moisture from the body. The capsule wall is made up of an elastic material and possesses an orifice. As the osmosis proceeds, the pressure within the capsulercises, causing the wall to stretch. The orifice is then opened, and the drug is released when the elastic wall relaxes, the flow of the drug through the orifice coincide with peak pain.
essentially stops, but when the elastic wall is distended beyond a threshold value, the orifice expands sufficiently to allow drug release at a required rate. Elastomers, such as styrene-butadiene copolymers, have been suggested.\textsuperscript{36}

\textbf{Osmotichasedpump capsule}

Osmotic delivery capsules ("osmotic pumps") function by virtue of walls which selectively pass water into the capsule reservoir. Absorption of water by the capsule through these walls is driven by a water-attracting agent in the capsule interior which creates osmotic pressure across the capsule wall. The water-attracting agent may be the beneficial agent itself whose controlled release is sought, but in most cases, it is a separate agent specifically selected for its ability to draw water and this separate agent is being isolated from the beneficial agent at one end of the capsule. In either case, the structure of the capsule walls does not permit the capsule to expand, and as a result, the water uptake causes discharge of the beneficial agent through an orifice in the capsule at the same rate that water enters by osmosis.

Figure 6: Different types of osmotic pumps used for PDDS

Linkwitz and co-workers proposed a drug delivery capsule where drug delivery is driven by the osmotic infusion of moisture from a physiological environment. The capsule has a delivery orifice which opens intermittently to achieve pulsatile delivery effect. The wall in which the orifice is formed is constructed of an elastic material (Elastomers) which stretches under a pressure differential caused by the pressure rise inside the capsule as the osmotic infusion progresses. The orifice is small so that when the elastic wall is relaxed, the flow rate of drug through the orifice is substantially zero, but when the elastic wall is stretched due to the pressure differential across the wall exceeding a threshold, the orifice expands sufficiently to allow the release of the drug at a physiologically beneficial rate. The selection of the materials from which the device is constructed and the configuration of the device and its dimensions controls the length of time between pulses.\textsuperscript{37}

\textbf{Drug delivery system with eroding or soluble barrier coating}

In this system, the drug reservoir is surrounded by a soluble barrier layer that dissolves with time, and the drug releases at once after this lag time. Chronotropic system consists of a core containing drug reservoir coated by a hydrophilic polymer HPMC. An additional enteric coated layer controls variability in gastric emptying this layer to overcome intrasubject variability in gastric emptying rates. The lag time and the onset of action are controlled by the thickness and the viscosity grade of HPMC. The time clock system is a delivery device-based on solid dosage form that is coated by an aqueous dispersion.

Figure 7: Schematic diagram of delivery system with erodible coating layer

This coating is a hydrophobic surfactant layer which a water-soluble polymer is added to improve adhesion to the core. Contact with the dissolution fluid, the dispersion rehydrates and disperses. The lag time could be controlled by the thickness of the film. After the lag time, i.e., the time required for hydration, the core immediately releases the drug. This system has shown reproducible results in vitro and in vivo. The effect of low calorie and high calorie meal on the lag time was studied using gamma scintigraphy. The mean lag time of drug releases was 345 and 333 min respectively. Midha et al developed palatal a pulsatile delivery system for d-threomethyl phenidate additional CNS stimulant in a dosage form comprising at least two individual drugs containing dosage limit housed in a closed capsule. The dosage units are designed in the form of compressed tablets.\textsuperscript{40}
The first drug release pulse occurs within 1-2h, followed by a lag period during which no release occurs. Second dose is released in 3-5h of ingestion. This is again followed by a second no-release interval. Release of third dose occurs within 7-9h of ingestion. To provide such delayed-release dosage units, coating is done with bioerodible gradually hydrolysable polymers. The release amount of coating material per dosage unit decides the time interval between interval and drug release. Dittigen et al. invented a multiple unit dosage form comprising of compressed compositions having different amounts of ingredients and combination.

Hormones, viz., progesterone, testosterone, dehydroepiandrosterone, their concentration in blood varies over 24h of the analogues and inhibitory substances for these hormones also follow a circadian rhythm. Examples of such classes include antihistamines, glucocorticoids, mineral corticoids and antihistamines. The formulation comprises of four compressed in a capsule. The first composition is formed to provide rapid release in a capsule in which at least 75% of the effective ingredients are delivered within 45 min. The second composition provides a uniformly maintained release profile in which 100% of the effective ingredients are released within 3 of ingestion. Third compressed combination delivers at least 75% of effective ingredients within 45 min of reaching duodenum and intestine at a pH of 6 to 7.5. Coating is given by gastric-resistant agents (PMMA or shellac). Fourth compressed combination releases 100% of the effective ingredient 3h after reaching pH of 6-7.

➢ Drug delivery system with rupturable layer:
A novel formulation for once daily administration (prior to sleeping) that provides an initial delay followed by controlled release of the drug. A method for preparing a timespecific delayed, controlled release formulation of a dosage form is also provided which includes coating a single pellet with at least one dosage layer, which is coated by at least one seal coat and at least one outer rate controlling layer of a water soluble polymers.

By that way, it is possible to maintain drug plasmatic concentrations in a desired, effective range in a circadian fashion while simplifying the administration of the drug to only once daily.

Figure 8: Schematic diagram of delivery system with rupturable coating layer

b) Multiple Units

➢ Systems Based on Change in Membrane Permeability
Numerous pharmaceutical forms are available. As already mentioned, the delayed release for oral administration is the release of the drug must be controlled according to therapeutically purpose and the pharmacological properties of the active ingredient. In consequence, it is not always desirable the blood levels to be constant. On the contrary, in order to avoid any habituation and in order to avoid the therapeutic plasma concentration levels reached only at the desired moment, i.e. during sleep or at the moment of awakening. Dosage form for pulsatile release proposed by Chen containing a plurality of different pellets composed with a core and several coating layers. The pellets are composed of a core containing the drug and a swelling agent which expands in volume when exposed to water. The core is enclosed within a membrane or coating which is permeable to water. The membrane is composed of a water insoluble and permeable film forming polymer, a watersoluble film forming polymer and a permeability reducing agent. When the unit dose releases the pellets into the digestive tract, water diffuses through the coating and into the core. As water is taken up by the swelling agent, the core expands, exerting force on the coating until it bursts, releasing the drug. The permeability reducing agent reduces the rate at which water reaches the swelling agent, thereby delaying release time.
The watersolublepolymerdissolves, weakening the coating so that it bursts sooner. By varying the proportions of the three coating ingredients and/or coating thickness from one pelletpopulation to another, the release timing of the pellets can be very effectively controlled.43

1.3.4 Approaches of Pulsatile Drug Delivery Depending on Target Release

- **Timecontrolled delivery system:**
  The principle of time-controlled drug delivery systems is that the release of the drug happens according to a predetermined rate so to achieve maximum therapeutic and minimum toxic effect. Systems having a lag phase (delayed release systems) and systems where the release is following a biological circadian rhythm are the most commonly used controlled release systems. As already mentioned, the delayed drug release for meeting chronotherapeutical needs provides optimum drug delivery for a number of widespread chronic pathologies. Most delayed release delivery systems are reservoir devices covered with a barrier coating, which dissolves, erodes or ruptures after a lag phase. Well known coating techniques are applied to pellets and tablets to delay drug’s release. Conventional coatings dissolve slowly to release drugs into the intestine. Another well-known coating technique employs a water-permeable but insoluble film which encloses the active ingredient and an osmotic agent. As water from the gut slowly diffuses through the film into the core, the core swells until the film bursts, releasing the drug. The film coating may be adjusted for selecting suitable rates of water permeation, and thereby, release time. Alternatively, the tablet coating may be impermeable, and water enters through a controlled aperture in the coating until the core bursts. When the tablet bursts, the content is released immediately or over a longer period of time. These and other techniques may be employed to formulate tablets or capsules with the requisite time interval before drug release.

Ting described a presscoated, pulsatile drug delivery system suitable for oral administration, having an immediate-release compartment, made by a compressed blend of an active agent and one or more polymers, enveloped by an extended-release compartment, made by a compressed blend of the active agent and hydrophilic and hydrophobic polymers, able to provide a first order delivery of the active agent, interrupted by a timed, pulsed delivery of an increased amount of the active agent. When the extended release compartment is enveloped by an optional instantaneous release compartment, can provide a dose sufficient to exceed the liver’s metabolic capacity and to maintain therapeutic levels, preferably throughout a 24-hour period.44

- **pHsensitive 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. In case of pH-dependent system, advantage has been taken of the fact that there exists different pH environments at different parts of the gastrointestinal tract. By selecting the pH-dependent polymers drug release at specific location can be obtained. Examples of pH...
dependent polymers include cellulose acetate phthalate, polyacrylates, and sodium carboxymethyl cellulose. These polymers are used as enteric coating materials so as to provide the release of drug in the small intestine.

- **Enzymes Present in the Intestinal Tract**

  Several prodrugs rely on colonic bacteria for release. In these systems, colonic bacteria are utilized to degrade the substrate. The bacterial amount has been estimated about 10^11 per gram in the colon. The bacterial species in the colon have been estimated to be around 400 (anaerobic in nature). In the past, polymers cross linked with azo-aromatic groups have been used to achieve colonic drug delivery. The first compound that came out in the market was sulfasalazine, a prodrug consisting by 5 aminosalycilic acid linked by an azo bond to sulphapyridine. When the chemical entity was reaching the site of action (colon) a reduction reaction was taking place and the 5 aminosalycilic acid was becoming available. However, due to potential carcinogenic activity, azo-aromatic compounds have now replaced with natural polysaccharides. Natural polysaccharides such as amylose, chitosan, dextran, guar gum, and pectin are currently investigated for colonic delivery. To overcome the problem of premature release due to their hydrophilic nature they are usually mixed with water insoluble polymers. Nevertheless, no granted patents on enzymatic drug delivery have been found.

- **Inflammation-induced pulsatile release**

  On receiving any physical or chemical stress, such as injury, fracture etc., inflammation takes place at the injured sites. During inflammation, hydroxyl radicals are reproduced from the inflammation-responsive cells. Yui and co-workers focused on the inflammatory induced hydroxyl radicals and designed drug delivery systems which responded to the hydroxyl radicals and degraded in a limited manner. They used hyaluronic acid (HA) which is specifically degraded by the hyaluronidase or free radicals. Degradation of HA via the hyaluronidase is very low in a normal state of health. Degradation via hydroxyl radical is however, usually dominant and rapid when HA is injected at inflammatory sites. 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.

- **Glucose-responsive insulin releasing devices**

  In case of diabetes mellitus, there is a rhythmic increase in the level of glucose in the body requiring injection of insulin at propertime. Several systems have been developed which are able to respond to changes in glucose concentration. One such 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.

- **Externally regulated systems**

  For releasing the drug in a pulsatile manner, another way can be the externally regulated systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. Magnetically regulated systems contain magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads.

### 1.3 Drug and Excipients Profile

#### 1.4.1 Drug profile

**Name:** NIZATIDINE

**Structural Formula:**

![Nizatidine Structure](image)

**Molecular Formula:** C_{12}H_{21}N_{5}O_{2}S_{2}

**Molecular Weight (M_r):** 331

**CAS Number:** 76963-41-2


**Melting Range:** 131ºC to 134ºC
IR spectra: Figure 12: IR spectra of Nizatidine

Nizatidine occurs as almost white or slightly brownish, crystalline powder.

**Solubility:** Nizatidine is freely soluble in chloroform, soluble in methanol, soluble in water and buffered solutions, slightly soluble in methylacetate and dosopropranolol.

Nizatidine is essentially insoluble in benzene, diethyl ether and octanol.

λ_max: 314 nm.

**Half Life:** The elimination half-life is 1 to 2 hours.

**Volume of Distribution:** The volume of distribution is 0.8 to 1.5 L/kg.

**Protein Binding:** 35%

**Bioavailability:** 70-80%

The recommended oral dosage for adults is 300 mg once daily at bedtime. An alternative dosage regimen is 150 mg twice daily.

**Pharmacokinetics:** The absolute oral bioavailability of Nizatidine exceeds 70%. Peak plasma concentrations occur from 0.5 to 3 hours following the dose. Plasmas levels are less than 10 mcg/L. The elimination half-life is 1 to 2 hours. The clearance is 40 to 60 L/h, and the volume of distribution is 0.8 to 1.5 L/kg. Nizatidine exhibits dose proportionality over the recommended dose range.

**Mechanism of Action:** Nizatidine (H2 receptor antagonists) inhibit acid production by reversibly competing with histamine for binding to the H2 receptors on the basolateral membrane of parietal cells. These drugs are less potent than proton pump inhibitors but still suppress 24-hour gastric acid secretion by about 70%. Nizatidine is predominantly inhibiting basal acid secretion, which accounts for its efficacy in suppressing nocturnal acid secretion. Because the most important determinant of duodenal ulcer healing is the level of nocturnal acidicity, evening dosing of Nizatidine is adequate therapy in most instances. Nizatidine also may stimulate GI motility.

**Indication:** The major therapeutic indications for Nizatidine (H2 receptor antagonists) are to promote healing of gastric and duodenal ulcers, to treat gastroesophageal reflux disease, and to treat non-steroidal anti-inflammatory drug (NSAID)-associated ulceration.
uncomplicated GERD, and to prevent the occurrence of stress ulcers.

**Contraindications:** Nizatidine is contraindicated in patients with known hypersensitivity to the drug. Because cross-sensitivity in this class of compounds has been observed, H₂-receptor antagonists, including Nizatidine, should not be administered to patients with a history of hypersensitivity to other H₂-receptor antagonists.

Headache, dizziness, drowsiness, constipation, diarrhea, stomach pain, runny nose, sneezing, coughing, sweating

Nizatidine should be used with caution in patients with kidney or liver problems, women who are pregnant or breastfeeding, and care should be taken in those whose symptoms change and who are middle-aged or older as this drug can mask the symptoms of gastric cancer.

**DosageForm:** Tablet, capsule, solution.

Store in a tightly closed container at room temperature between 59-86 degrees F (15-30 degrees C) away from moisture and light.

1.4.2 Name: CROSCARMELLOSE SODIUM

**Synonyms:** Ac-di-sol, Modified cellulose gum

**CASRegistryNumber:** 74811-65-7

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

**IRspectra:**

![Figure 13: IR spectra of croscarmellose sodium](image)

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules. In tablet formulations, croscarmellosesodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellosesodium should be added in both the wet and dry stages of the process (intra- and extra granularly) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by wet-granulation process. Croscarmellosesodium is used in oral pharmaceutical formulations as a disintegrant for capsules, and granules. Disintegrant in tablets in 0.5-5.0% concentration, disintegrant in capsules in 10-25% concentration.

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

**Solubility:** Insoluble in water, although croscarmellose sodium rapidly swells to 4-8 times its original volume on contact with water. Practically insoluble in acetone, ethanol, and toluene.

**Stability and Storage:** Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellosesodium as disintegrant, showed no significant difference in drug dissolution after storage at 30°C for 14 months. Croscarmellosesodium should be stored in a well-closed container in acool, dry place.

**Incompatibilities:** The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contains hygroscopic excipients such as sorbitol. Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metal such as aluminum, mercury, and zinc.

1.4.3 Name: LACTOSE

Lactochem. Lactose monohydrate, MonohydratePharmatose.

**Molecular Weight:** 360.31

**CASRegistryNumber:** 64044-51-5
Structure:

![Structure of lactose](image)

Empirical Formula: \( C_{12}H_{22}O_{11} \cdot H_2O \)

IR spectra:

![IR spectra of lactose](image)

Functional Category:
- Binding agent
- Diluents for dry-powder inhalers, tabletbinder, tableland capsules diluents.

Lactose is widely used as filler or diluents in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas. Lactose is also used as a diluent in dry-powder inhalation. Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics. This permits the selection of the most suitable material for a particular application; for example, the particle size range selected for capsules is often dependent on the type of encapsulating machine used. Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size permits better mixing with other formulation ingredients and utilizes the binder more efficiently.

In the solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e., \( \alpha \)-lactose monohydrate, \( \beta \)-lactose anhydrous, and \( \gamma \)-lactose anhydrous. The stable crystalline forms of lactose are \( \alpha \)-lactose monohydrate, \( \beta \)-lactose anhydrous, and stable \( \gamma \)-lactose anhydrous. Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; \( \alpha \)-lactose is approximately 20% as sweet as sucrose, while \( \beta \)-lactose is 40% as sweet.

Stability and Storage:

- Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions. The purities of different lactose can vary, and color evaluation may be important, particularly if white tablets are being formulated. The color stabilities of various lactose grades differ. Solutions show a mottle after storage; lactose should be stored in well-closed containers in a cool, dry place.

Incompatibilities:

- A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products. Lactose is also incompatible with amino acids, aminophylline, amphetamines, and lisinopril.

Related Substances:

- Lactose anhydrous
1.4.4 Name  CROSSPOVIDONE
Synonym: Crospovidonum, Crospophar.
CASRegistryNumber: 9003-39-8
EmpiricalFormula: (C6H9NO)n
FunctionalCategory: Tablet disintegrant.
IRSpectra: 

![Figure16:IRspectraofcrosspovidone](image)

Applications: Crosspovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct compression or wet-and-dry granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crosspovidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles. Crosspovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crosspovidone can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crosspovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

Description: Crosspovidone is a white-to-cream white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

Stability and Storage: Crosspovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatibilities: Crosspovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crosspovidone may form molecular adducts with some materials.

1.4.5 Name  SODIUMSTARCHGLYCOLATE
Synonym: Carboxymethyl starch.
Structure: 

![Figure17:structureofsodiumstarchglycolate](image)

CASRegistryNumber: 9063-38-1
Description: Sodium starch glycolate is a white-to-off-white, odorless, tasteless, free-flowing powder.
Functional Category: Tablet and capsule disintegrant.

IRSpectra:

![Figure 18: IR spectra of sodium starch glycolate](image)

Applications: Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant antcapsuleandtabletformulations. 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. Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired.

Stability and Storage: Sodium starch glycolate is stable and should be stored in a well-closed container in order to protect it from wide variation of humidity and temperature, which may cause caking. The physical properties of sodium starch glycolate remain unchanged for up to 3–5 years if it is stored at moderate temperatures and humidity.

Incompatibilities: Sodium starch glycolate is incompatible with ascorbic acid.

1.4.6 Name MICROCRYSTALLINE CELLULOSE

Synonyms: Avicel PH, Cellets, Celex, Celphere, crystalline cellulose, Emcocel.

Chemical Name: Cellulose

Structure:
Figure 19: Structure of Microcrystalline Cellulose

**CAS Registry Number:** 9004-34-6

**Empirical Formula:** \((C_6H_{10}O_5)_n\)

**Functional Category:** Adsorbent; suspending agent; tablet and capsule diluents; tablet disintegrant.

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

**IR Spectra:**

![IR Spectra of Microcrystalline Cellulose](image)

**Applications:** Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluents 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/diluents, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tabletting.

**Solubility:** Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

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

**Incompatibilities:** Microcrystalline cellulose is incompatible with strong oxidizing agents.

1.4.7 Name: MAGNESIUM STEARATE

**Synonyms:** Dibasic magnesium stearate; magnesium distearate.

**CAS Registry Number:** 557-04-0

**Empirical Formula:** \(C_{36}H_{70}O_4\) \(\text{MgO}_4\)

**Molecular Weight:** 591.34

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

**Application:** Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations primarily used as a lubricant in capsule and tablet formulation where it is used in concentrations between 0.25% - 5.0% w/w.

**Description:** Magnesium stearate is a very fine, light white, precipitated or milled impalpable powder of low bulk density having a faint order of stearic acid and characteristic taste.
Stability and Storage: Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

Incompatibility: Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alka-loid salts.

Related Substances: Calcium stearate; magnesium aluminum silicate; stearic acid; zinc stearate

1.4.8 Name: COLLOIDAL SILICON DIOXIDE
Synonyms: Aerosil, colloidal silica; fumed silica, fumed silicon dioxide.
CAS Registry Number: 7631-86-9
Empirical Formula: SiO2
Molecular Weight: 60.08
Functional Category: Adsorbent, Anticaking agent, Emulsion stabilizer; glidant, suspending agent, tablet disintegrant, thermal stabilizer, viscosity-increasing agent.

Applications: Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products. Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting and capsule filling. Colloidal silicon dioxide is used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations. With other ingredients, it can be used to increase the viscosity of a system. Viscosity is largely independent of temperature. However, changes to the pH of a system may affect the viscosity.

Description: Colloidal silicon dioxide is a submicron, fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white, odorless, tasteless, amorphous powder.

Stability and Storage: Colloidal silicon dioxide is hygroscopic but absorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0–7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system. However, at a pH greater than 7.5, the viscosity-increasing properties of colloidal silicon dioxide are reduced; and at a pH greater than 10.7, this ability is lost entirely since the silicon dioxide dissolves to form silicates. Colloidal silicon dioxide should be stored in a well-closed container.

Incompatibilities: Incompatible with diethylstilbestrol preparations.

1.4.9 Name: TALC
Synonyms: Hydrous magnesium calcium silicate, hydrous magnesium silicate, purified French chalk, Pur talc, soapstone, steatite.
CAS Registry Number: 14807-96-6
Molecular Weight: Mg₆(Si₂O₅)(OH)₄
Functional Category: Anticaking agent, glidant, tablet and capsule diluents, tablet and capsule lubricant.

Applications: Talc is widely used in oral solid dosage formulations to retardant in the development of controlled-release products. Talc is used as a powder coating for extended-release pellets; and as an adsorbent. In topical preparations, talc is used as an adjuvant for powder, although it should not be used for medicinal purposes; talc is a natural material; it may therefore contain microorganisms that should be sterilized when used as a dusting powder. Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

Description: Talc is a very fine, white to grayish-white, palpable, smooth, crystalline powder. It adheres readily to the skin and is soft to the touch, free from grittiness. Talc is not commonly used for clarification, but is also used in cosmetics and food products, mainly for its lubricant properties.

Solubility: Practically insoluble in water.

Stability and Storage: Talc should be stored in a well-closed container.
Incompatibilities: Closed container in a cool, dryplace.

Safety: Incompatible with quaternary ammonium compounds.

Talcis not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material. However, inhaled or intravenous abuse of products containing it can cause granulomas in body tissues, particularly the lungs. Although talc has been extensively investigated for its carcinogenic potential, it has not been suggested that there is an increased risk of ovarian cancer in women using talc. There evidences is inconclusive. However, talc contaminated with asbestos has been proved to be carcinogenic in humans, and asbestos-free grades should therefore be used in pharmaceutical products. Also, long-term toxic effects of talc contaminated with large quantities of hexachlorophene caused serious irreversible neurotoxicity in infants accidentally exposed to the substance.

1.4.10 Name POLYMETHACRYLATES
Synonyms: Methacrylic acid, Eudragit
Description: White powders with a faint characteristic odor
Molecular Weight: Average approx. 135,000.
Structural Formula: EUDRAGIT® is anionic copolymers based on Methacrylic acid and methyl methacrylate

![Polymethacrylates](image)

Figure 21: Structure of polymethacrylates

Functional Category: Film former, tablet binder.

Solubility: 1g of EUDRAGIT® dissolves in 7g methanol, ethanol, in aqueous isopropyl alcohol and acetone (containing approx. 3% water), as well as in 1N sodium hydroxide to give nearly clear to slightly cloudy solutions. EUDRAGIT® is practically insoluble in methyl acetate, methylene chloride, petroleum ether and water.

Stability: Minimum stability dates are given on the product labels and batch-related Certificates of Analysis. Storage Stability data are available upon request.

Storage: Store at controlled room temperatures (USP, General Notices). Protect against moisture. Any storage between 8°C and 25°C fulfills this requirement.

Incompatibilities: Incompatibilities occur with acid and/or alkaline conditions depending on which polymers are being used.

Application: Eudragit L, S types are used as enteric coating agents because they are resistant to gastric fluid. Different types are available that are soluble at different pH values: e.g. Eudragit L is soluble at pH > 6; Eudragit S is soluble at pH > 7. While Eudragit RS is used to form water-insoluble film coats for sustained-release products. Binder – Eudragit E (concentration between 5 to 20%). Film former – Eudragit L form acid-insoluble film coats for enteric purpose.

1.4.11 Name HYDROXYPROPYL METHYLCELLULOSE
Synonyms: Hydroxypropyl methyl cellulose, HPMC, Methocel, methyl hydroxypropyl cellulose
CAS Registry Number: 9004-65-3
Functional Category: Coating agent; film former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-
increasing agent.

**Applications:** Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, it 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.

**Description:** Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

**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 hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

**Stability and Storage:** Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. It undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gel point is 50–90°C, depending upon the grade and concentration of material. This powder should be stored in a well-closed container, in a cool, dry place.

**Incompatibilities:** Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, it will not complex with metallic salts or ionic organic salts to form insoluble precipitates.

**Safety:** Hypromellose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products. It is generally regarded as non-toxic and non-irritant material, although excessive oral consumption may have a laxative effect. The WHO has not specified an acceptable daily intake for hypromellosesince the levels consumed were not considered to represent a hazard to health.

1.4.12 Name **POLYVINYL PYRROLIDONE K30**

**Synonyms:** Kollidon, Plasdone, Poly[1-(2-oxo-1-pyrrolidinyl)ethylene], Polyvidone, PVP, 1-vinyl-2-pyrrolidinone polymer.

**Nonproprietary names:** BP-povidone, JP-Povidone, PHEur-povidonum, USP-povidone.

**Chemical name:** 1-Ethenyl-2-pyrrolidone homopolymer.

**Category:** Disintegrant, dissolution aid, suspending agent, tablet binder.

**Structure**

![Structure of vinylpolyvinylpyrrolidone K30](image)

Figure 22: Structure of vinylpolyvinylpyrrolidone K30
Molecular weight: 50,000

**FTIR-spectra**

![Figure 23: FTIR-spectra of PVPK-30](image)

**Description:**
It occurs as a fine, whitetocreamy white colored, odorless, hygroscopic powder.

**Solubility:**
Freely soluble in acids, chloroform, ethanol, ketones, methanol and water. Practically insoluble in ether, hydrocarbons and mineral oil.

**Viscosity:**
5.5 to 8.5 m Pas (aqueous solution)

**Stability:**
Darkens to some extent on heating at 150 °C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110-130 °C.

**Storage Condition:**
It should be stored in an airtight container in a cool, dry place.

**Safety:**
Generally regarded as non-toxic, non-irritant but adverse reactions may take place if taken intramuscularly or subcutaneously.

**Incompatibility:**
It is incompatible with sulfathiazole, sodium salicylate, salicylic acid, Phenobarbital, tamin.

### 1.4 Review of Literature

**Akhter, et al. 2011.**
A time controlled two pulse dosage form of Amoxicillin was developed. The compression coating inlay tablet approach was used to deliver the drug in two pulses to different parts of the GIT after a well-defined lag time between the two releases. This was made possible by formulating a core containing one of the two drug fractions, which was spray coated with a suspension of ethyl cellulose and a hydrophilic but water insoluble agent as a pore former (microcrystalline cellulose). Coating of up to 5% (m/m) was applied over the core tablet, giving a corresponding lag time of 3, 5, 7 and 12 h.

**Bauskar, et al. 2011.**
A tablet system consisting of cores coated with two layers of swelling and erodible coatings was prepared and evaluated as pulsatile drug delivery system. Cores containing Doxorubicin were prepared by direct compression of lactose, microcrystalline cellulose and containing a superdisintegrant (croscarmellose sodium, crospovidone) and an outer erodible layer of Hydroxypropyl methylcellulose (Methocel E 50). The effect of core composition and magnesium stearate in erodible layer was investigated. Erodible and dissolution tests were performed using the paddle method at 50 rpm in Simulated Gastric Fluid and Simulated Intestinal Fluid. The lag time of the pulsatile release tablets decreased with increasing amount of microcrystalline cellulose in the cores and increased with increasing level of erodible Hydroxypropyl methylcellulose (Methocel E 50) coating. Increasing level of the Hydroxypropyl methylcellulose (Methocel E 50) coating retarded the water uptake and thus prolonged the lag time.

**Gami, et al. 2011.**
Prepare pulsatile drug delivery system of Metoprolol succinate. In this work pulsatile drug delivery system was prepared by using swellable and erodible polymer. The polymers like Ac-di-sol and crospovidone were selected as swellable polymer and ethyl cellulose was selected as erodible polymer. The present work, core tablet (150 mg) containing 100 mg Metoprolol succinate was prepared by wet granulation technique. This prepared core tablet was coated by using 2.5% ethyl cellulose containing triethyl citrate plasticizer. This coating solution was sprayed to core tablet to achieve different percentage of weight.
gain into the core tablet. The prepared film-coated tablet was evaluated for in vitro drug dissolution study to obtain desirable immediate release of drug after lag time offdrug.

**Naik and Zine, 2011.** Chronopharmacutics is a branch of pharmacutics devoted to the design and evaluation of drug delivery systems that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy. A major objective of chronotherapy in the treatment of several diseases is to deliver the drug in high concentrations during the time of greatest need according to the circadian rhythm of diseases or symptoms. The main objective of the present study was to develop single-unit floating-pulsatile drug delivery system for obtaining no drug release during floating and in the proximal small intestine followed by pulsed drug release in distal small intestine to achieve Chronotherapeutic release of Aceclofenac for treatment of rheumatoid arthritis, osteoarthritis, spondylitis and to improve the patient compliance.

**Shirsagar and etal, 2012.** Developed pulpulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. To overcome the limitations of various approaches for imparting buoyancy, hollow porous beads were prepared by simple process of acid-base reaction during ionotropic cross linking by low viscosity sodium alginate and calcium chloride as a cross linking agent. In this study, investigation of the functionality of the sodium alginate to predict lag time.

**Latha and etal, 2011.** Todevlop optimised film-coated tablets of losartan potassium using nanomixture of hydrophilic polymer, Hydroxypropyl methylcellulose (HPMC) and microcrystalline cellulose (MCC) in order to achieve a predetermined lag time for chronotherapy. The press-coated tablets (PCT) containing losartan potassium in the outer core were prepared by compression-coating with HPMC 100 KM alone and admixed with MCC as the outer layer indifferent ratios. The effect of the outer layer on the lag time of drug release was investigated.

**Reddy and etal, 2011.** The purpose of this research study was to develop and optimize a controlled-release floating tablet of highly watersoluble drug Nizatidine in an effort to increase its gastric retention time in the stomach. The tablets were prepared by direct compression method with Hydroxypropyl methylcellulose (HPMC) of different viscosity grades. Carboxymethyl cellulose sodium (NaCMC) were incorporated as retarding polymers. Sodium bicarbonate was incorporated as effervescent agent. Formulations were evaluated for weight variation, thickness, hardness, percentage swelling, friability, and in vitro drug release, and floating lag time, total duration of floating, dissolution efficiency and in vivo Mean Residence Time (MRT) in the stomach.

**Pannala and Rathnanand, 2011.** Prepare and evaluate (invitro) Nizatidine immediate release tablets. The developed drug delivery system delivers programmed dose of drug intended for excessively secreted gastric acid and for promoting healing of duodenal ulcers thereby spontaneously delivering the drug when exposed into GIT for producing an anti-ulcer effect. Accordingly, immediate release drug-containing core tablets of Nizatidine were prepared by wet granulation method.

**Patil and etal, 2011.** Prepaid and evaluated press-coated pulsatile drug delivery system intended for treatment of early morning stiffness and symptomatic relief from pain with rheumatoid arthritis. The formulation involved press coating of arwtapurtable core around a rapidly disintegrating core tablet of Aceclofenac. A three-factor, two-level, full factorial design was used to investigate the influence of amount of glyceryl behenate, amount of sodium chloride in the coating, and the coating level on the responses, ie, lag time to release and amount of Aceclofenac released in 450 minutes. Glyceryl behenate and the coating level had a significant influence on lag time, while sodium chloride helped in the rupture of the coating layer.

**Jagdale and et al. 2010.** A tablet system consisting of cores coated with two layers of swelling and rupturable coatings was prepared and evaluated as pulsatile drug delivery system. Cores containing Atenolol as model drug were prepared by direct compression of different ratios of lactose and microcrystalline cellulose and were then coated sequentially with inner swelling layer containing superdisintegrant KYRON T 314 and an outer rupturable layer of ethyl cellulose. The effect of level of swelling layer and rupturable coating was investigated. Rupture and dissolution tests were performed using the USP Type II paddle method at 50 rpm in 0.1N HCl. The lag time of the pulsatile release tablets decreased with increasing amount of microcrystalline cellulose in the cores and increased with increasing levels of both swelling layer and rupturable ethylcellulose coating. Increasing levels of ethylcellulose coating retarded the water uptakeand thus prolonged the lag time.

**Shah and et al. 2010.** Advancement in drug delivery systems have contributed to innovative improvement in drug delivery system. Because of the frequency and eficacy of administration, sustained release dosage forms offer convenience and ambulatory patient compliance. Developed formula is multipleunit coated pulsatile delivery of Salbutamol Sulphate which can offer a solution for chronic bronchial disease. The prepared formulation was investigated for its in vivo efficacy against asthma and in vivo Mean Residence Time (MRT) of the drug in the stomach.

**Roy and Shahlwala, 2009.** Present work conceptualizes a specific technology based on combining floating and pulsatile principles to develop drug delivery system intended for chronotherapy in nocturnal acid breakthrough. This approach will be achieved by using a programmed delivery of ranitidine hydrochloride from a floating tablet with time-lagged coating. In this study, investigation of the functionality of the outer polymer coating to predict lag time and drug release was statistically analyzed using the response surface methodology (RSM).

**Zou and et al. 2008.** The objective of this work was to develop and evaluate a floating pulsatile drug delivery system intended for chronopharmacotherapy. Floating pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. To overcome limitations of various approaches for imparting buoyancy, we generated the system which consisted of three different parts: core tablet, containing the active agent, an erodible outer shell and a top cover buoyant layer. The dry coated tablet consists in a drug-containing core, coated by hydrophilic erodible polymer which is responsible for a lag phase in the onset of pulsatile release. The buoyant layer, prepared with Methocel® K4M, Carbopol® 934P and sodium bicarbonate, provides buoyancy to increase the retention of the...
oral dosage from the stomach. The effect of the hydrophilic rodible polymer characteristics on the lag time and drug release was investigated.

Shajandi and Patole, 2007. Preparation of multifunctional floating pulsatile drug delivery systems for obtaining nodrug release during floating and the proximal small intestine followed by pulsed, rapid drug release in the distal small intestine to achieve chronic therapeutic release of indomethacin. The system developed consists of drug-containing core pellets prepared by extrusion spheronization process, which were coated with an inner pH-dependent layer of Eudragit S100 and a second layer of sodium bicarbonate and HPMC K100M. Pellets showed instantaneous floating with no drug release in an acidic medium followed by pulsed drug release in a basic medium. Concentration of HPMC K100M and layering of Eudragit S100 significantly affected performance of pellets. The system showed excellent lag phase followed by rapid release in the distal small intestine which gives site and time specific delivery of indomethacin in peptic ulcer therapy of rheumatoid arthritis.

Gothoskar et al., 2008. Review of Disease like Bronchial asthma, Myocardial infarction, angina pectoris, Rheumatic disease, Ulcer, & Hypertension display time dependent effect. In Asthmatic disease reported sharp increase in asthmatic attack during early morning hours. Such a condition demands consideration of diurnal progress of disease rather than maintaining constant plasma drug level, a drug delivery system administrated at bedtime, but releasing drug well after the time of administration, would be ideal in this case.

Lin et al., 2004. An oral press-coated tablet was developed by means of direct compression to achieve the time-controlled disintegrating or rupturing function with a distinct predetermined lag function. This press-coated tablet containing sodium diclofenac sodium in the inner core was formulated with an outer shell by different weight ratios of hydrophobic polymer of micronized ethyl cellulose (EC) powder and hydrophilic excipients such as spray-dried lactose (SDL) or hydroxypropylmethylcellulose (HPMC). The effect of the formulation of an outer shell comprising both hydrophobic polymer and hydrophilic excipients on the time lag of drug release was investigated.

Sunthongjeen et al., 2008. A tablet system consisting of cores coated with two layers of swelling and drug release coating was prepared and evaluated as a pulsatile drug delivery system. Cores containing bufomedil HCI as model drug were prepared by a direct compression of different ratios of spray-dried lactose and microcrystalline cellulose and were then coated sequentially with an inner swelling layer containing cross-linked chitosan and an outer rupturable layer of ethylcellulose. The effect of core composition, level of swelling, and mechanical properties of ethylcellulose films was studied. The wet state was characterized by apuncture test. Rupture and dissolution tests were performed.

Bodmeier et al., 2003. Investigating the swelling characteristics of various swellable polymers in swelling layers that induce the rupturing of an outer polymer coating of the dissolved drug delivery systems. An apparatus was designed to measure simultaneously the swelling energy/force and water uptake of discs. The swelling energy of several excipients decreased in the following order: cross-linked chitosan > sodium carboxymethyl cellulose > silicone oil. Cross-linked hydroxypropyl methylcellulose. A linear correlation existed between the swelling energy and the water uptake.

Fan et al., 2001. To develop new pulsatile release tablets, which can suppress drug release in stomach and release the drug rapidly after a predetermined lag time of about 3 h in intestine, the release of tablets with ethylcellulose/Eudragit L as the coating film and cross-linked polyvinylpyrrolidone in the core tablets was investigated. The release of diltiazem hydrochloride from model drug in the core tablets was investigated in vitro.

Fukui et al., 2001. In this study, the dissolution profiles of diltiazem hydrochloride contained in core tablets compressed with a hydrophilic rodible polymer were evaluated. The effect of the rodible polymer characteristic on the lag time and drug release was investigated.

Ping et al., 1999. Non-cross linked and cross linked chitosan microspheres were prepared by spray drying method. The microspheres were pregelatinized and then coated with an acrylate-coated polymer. They were positively charged. The particle size ranged from 2 to 10 µm. The size and seta potential of the particles were influenced by the cross linking level. With decreasing amount of crosslinking agent (either glutaraldehyde or formaldehyde), both particle size and zeta potential were increased.

PREPARATION ENVISAGED

Oral drug delivery has been known for decades. The most widely utilized route of administration among all the routes that have been explored for the systemic delivery of different dosage form. Pulsatile drug delivery systems are gaining a lot of interest among the pharmaceutical community. These systems have a particular mechanism of delivering the drug rapidly and completely after a "lag time," i.e., in the absence of drug release. Though most drug systems are designed for the constant drug release over a prolonged period of time, pulsatile delivery systems are characterized by programmed drug release, as constant blood levels of a drug may not always be desirable. 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. Therefore, pulsatile drug delivery systems have been developed to overcome the problems associated with constant blood levels of a drug. Because pH of the gastric juice decreases in the stomach and increases in the duodenum, the delivery of H2 antagonist through PDDS is very effective, but because of the high pH in the stomach, the H2 antagonist should be released rapidly to give an early effect. It is demonstrated that adding a bed-time dose of H2 antagonist to an evening dose of proton pump inhibitor provides nocturnal...
recovery of gastric acid secretion. Hence the present study, the pulsatile drug delivery system of tablets will be adapted to achieve time-controlled drug delivery system using selective anti-ulcer drug (Nizatidine) with suitable polymer. Nizatidine is a potent histamine H2 receptor antagonist, has been a market leader for symptoms like erosive esophagitis and active gastric ulcers; until when proton pump inhibitors came to replace it. However, the recent failure of PPIs to prevent night-time gastric acid surge (which is associated with high nocturnal histamine concentration) brings open a new door for delivery of Nizatidine at specific times in relation to onset of symptoms.

Nizatidine is a potent histamine H2 receptor antagonist, has been a market leader for symptoms like erosive esophagitis and active gastric ulcers; until when proton pump inhibitors came to replace it. However, the recent failure of PPIs to prevent night-time gastric acid surge (which is associated with high nocturnal histamine concentration) brings open a new door for delivery of Nizatidine at specific times in relation to onset of symptoms.

The oral absolute bioavailability of Nizatidine more than 70% peak plasma concentration occurs from 0.5 to 3 hours. Elimination half life is 1 to 2 hours and volume of distribution is 0.8 to 1.5L/kg. The aim of this study was to design a pulsatile release Nizatidine tablets, intended for chronotherapy in nocturnal acid breakthrough. This approach will be achieved by using a programmed delivery of Nizatidine from a core tablet with time-lagged coating. The prepared tablet will not give release of drug for the desired period after its administration after meal and then will release the drug when the acid secretion is higher in midnights after the lag time of three to four hours improving the efficacy of drug and hence improved patient compliance.

PLAN OF WORK

- Literature Survey
- Selection of Drug and Excipients
- Characterization of Drug
- Preformulation Studies
- Selection of UVS Spectroscopic Method for Estimation of Nizatidine and Preparation of Calibration Curve
- Formulation of Core Tablets of Nizatidine
  - Preparation of Powder Blend
  - Evaluation of Powder Blend
- Evaluation of Core Tablets of Nizatidine
  - Thickness
  - Hardness
  - Weight Variation
  - Friability
  - Drug Content
  - Disintegration Time
  - Dissolution Study
- Formulation of Pulsatile Release Tablet
- Evaluation of Pulsatile Release Tablet
  - Thickness
  - Hardness
  - Weight Variation
  - Lag Time.
  - Drug Content
  - Dissolution Study
- Kinetic Modelling
- Stability Testing

2.1. Preformulation Studies

Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing safe and stable dosage forms.

The preformulation studies performed include the study of organoleptic properties, melting point, solubility, etc. It also includes the UV spectroscopy, IR characterization, DSC, Construction of Beer-Lambert’s plot and drug-excipients interaction.

2.1.1. Analysis of Nizatidine

The obtained drug sample was used without further purification. Characterization of drug was done by physicochemical methods. The details are given below.

2.1.1.1. Organoleptic Properties and Description

The sample of Nizatidine was studied for organoleptic characters and it was found to be,

<table>
<thead>
<tr>
<th>Test</th>
<th>Specification</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colour</td>
<td>Yellowish</td>
<td>Yellowish</td>
</tr>
<tr>
<td>Taste</td>
<td>Bitter</td>
<td>Bitter</td>
</tr>
<tr>
<td>Odour</td>
<td>Sulphur-mercaptan</td>
<td>Sulphur-mercaptan</td>
</tr>
</tbody>
</table>
2.1.1.2. Melting Point determination\textsuperscript{51}

It is one of the parameters to judge the purity of drugs. In case of pure chemicals or photochemical, melting points are very sharp and constant. Since the drugs contain the mixed chemicals, they are described with a certain range of melting point. Melting point was determined using capillary method; it is essential parameter for the identification of drug. It is a temperature at which substance from solid to liquid. The melting point was determined by open capillary method and the uncorrected melting point found in the range of 131\textdegree{}C to 134\textdegree{}C.

2.1.1.3. Solubility Analysis\textsuperscript{51}

The solubility of Nizatidine was determined by adding excess amount of drug in the solvent (supersaturated) at 37 \textdegree{}C and kept for 24 hrs for equilibrium with occasional shaking. Equilibrium solubility was determined by taking supernatant and analyzing it on Shimadzu UV-1700 double beam spectrophotometer. Nizatidine is freely soluble in chloroform; soluble in methanol; soluble in water and buffered solution slightly soluble in ethylacetate and osopropranolol. Nizatidine is essentially insoluble in benzene, diethyl ether and octanol.

<table>
<thead>
<tr>
<th>Table 3: Solubility of Nizatidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent</td>
</tr>
<tr>
<td>Water</td>
</tr>
<tr>
<td>0.1N HCl</td>
</tr>
<tr>
<td>pH 6.8 phosphate buffer</td>
</tr>
<tr>
<td>pH 7.4 phosphate buffer</td>
</tr>
</tbody>
</table>

2.1.1.4. UV Spectroscopy\textsuperscript{51}

Determination of Wavelength ($\lambda_{\text{max}}$)

a. A stock solution of Nizatidine 100 \mu g/ml was prepared in 0.1N HCl. Recorded the UV spectrum was recorded over the wavelength range of 200-400 nm by Shimadzu -1700 as shown in Figure 24. The wavelength of maximum absorption ($\lambda_{\text{max}}$) was found to be 314 nm.

b. A stock solution of Nizatidine 100 \mu g/ml was prepared in pH 6.8 phosphate buffer. Recorded the UV spectrum was recorded over the wavelength range of 200-400 nm by Shimadzu -1700 as shown in Figure 25. The wavelength of maximum absorption ($\lambda_{\text{max}}$) was found to be 314 nm.

c. A stock solution of Nizatidine 100 \mu g/ml was prepared in pH 6.8 phosphate buffer. Recorded the UV spectrum was recorded over the wavelength range of 200-400 nm by Shimadzu -1700 as shown in Figure 26. The wavelength of maximum absorption ($\lambda_{\text{max}}$) was found to be 314 nm.

<table>
<thead>
<tr>
<th>Table 4: $\lambda_{\text{max}}$ of Nizatidine at different pH conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent</td>
</tr>
<tr>
<td>0.1N HCl</td>
</tr>
<tr>
<td>pH 6.8 phosphate buffer</td>
</tr>
<tr>
<td>pH 7.4 phosphate buffer</td>
</tr>
</tbody>
</table>
2.1.1.5. FTIRSpectrophotometricCharacterization: To identified drug Nizatidine IR spectrometric analysis was carried out by using[Affinity01shimadzu]FTIRSpectroscopyandspectrumwasrecordedintheregionof 4000-400cm⁻¹. The procedure
consists of dispersing a sample in potassium bromide powder [1:100] and placed into sample holder in the light path and the spectrum was obtained.

![Figure 27: IRSpectra of Nizatidine](image)

**Table 5: IR Peaks of Nizatidine**

<table>
<thead>
<tr>
<th>IR signals (cm⁻¹)</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>3280, 3210</td>
<td>NH stretch,</td>
</tr>
<tr>
<td>3107</td>
<td>CH stretch in NO₂-CH</td>
</tr>
<tr>
<td>3094</td>
<td>CH stretch in thiazolering</td>
</tr>
<tr>
<td>2945, 2860</td>
<td>CH stretch in NCH₃, CH₂CH₂</td>
</tr>
<tr>
<td>1521</td>
<td>Thiazolering</td>
</tr>
<tr>
<td>1435, 1422</td>
<td>CH deformation in NCH₃, CH₂CN stretch</td>
</tr>
<tr>
<td>1377, 1359</td>
<td>Thiazole ring for one frequency is sym NO₂, H-bonded, conjugated</td>
</tr>
</tbody>
</table>

2.1.1.1. Construction of Beer-Lambert’s Plot

**Linearity in 0.1 N HCl:**

Nizatidine (10 mg) was dissolved in 100 ml of 0.1 N HCl to obtain a working standard of 100 µg/ml. A series of solutions of Nizatidine in HCl buffer (pH 1.2) concentration of 2, 4, 6, 8, 10, 12 µg/ml was prepared. The absorbance of all solutions was measured using 0.1 N HCl as a blank at 314 nm using a spectrophotometer (Shimadzu 1700). A standard plot of absorbance vs concentration of drug was plotted. Correlation coefficient and regression equation were obtained from the calibration curve.

**Table 6: Beer-Lambert’s Plot in pH 1.2 buffer for Nizatidine.**

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Concentration (µg/ml)</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>0.171</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>0.294</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>0.491</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>0.594</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>0.745</td>
</tr>
</tbody>
</table>
Nizatidine (10mg) was dissolved in 100 ml of phosphate buffer (pH 6.8) to obtained working standard of 100µg/ml. A series of solution of Nizatidine in phosphate buffer (pH 6.8) concentration of 2, 4, 6, 8, 10, 12µg/ml was prepared. The absorbance of all the solution was measuring using phosphate buffer 6.8 as blank at 314 nm using UV spectrophotometer (Shimadzu 1700). A standard plot of absorbance v/s concentration of drug was plotted. Correlation coefficient and regression equation were obtained from the calibration curve.

Table 7: Beer-Lambert plot in pH 6.8 phosphate buffer for Nizatidine.

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Concentration (µg/ml)</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>0.14</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>0.213</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>0.331</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>0.439</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>0.534</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>0.631</td>
</tr>
</tbody>
</table>
**Linearity in Phosphate Buffer 7.4**

Nizatidine (10 mg) was dissolved in 100 ml of phosphate buffer (pH 7.4) to obtain a working standard of 100 µg/ml. A series of solutions of Nizatidine in phosphate buffer (pH 7.4) concentration of 2, 4, 6, 8, 10, 12 µg/ml was prepared. The absorbance of all the solution was measured using phosphate buffer 7.4 blank at 314 nm using UV spectrophotometer (Shimadzu 1700). A standard plot of absorbance vs concentration of drug was plotted. Correlation coefficient and regression equation were obtained from the calibration curve.

![Figure 30: Beer-Lambert's plot of Nizatidine in pH 7.4 phosphate buffer](image)

**Table 8: Beer-Lambert's plot in pH 7.4 phosphate buffer for Nizatidine.**

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Concentration (µg/ml)</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>0.117</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>0.215</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>0.284</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>0.391</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>0.472</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>0.582</td>
</tr>
</tbody>
</table>

**2.1.1.6. Drug-excipients compatibility study**

The proper design and the formulation of a dosage form require consideration of the physical, chemical, and biological characteristics of the drug and excipients used in fabricating the product. The drug and excipients must be compatible with one another to produce a product that is stable, efficacious, attractive, easy to administer and safe. The compatibility studies provide the framework for the drug combination with excipients in the fabrication of the dosage form. The study was carried out to establish that the therapeutically active drug has not undergone any changes, after it has been subjected to processing steps during formulation of tablets.

Prepared powder mixture in 1:1 ratio for bulk excipients and in 1:10 for lubricants or for trace excipients. Ground excipients in mortar and screen through suitable screen for thorough mixing. Fill in vial and seal. Keep samples at 55°C for 10 days. Remove samples after every two days and analyze for drug content, TLC, UV spectra for drug content, Rf value and λmax.

**Table 9: Codes of mixture for drug-excipients compatibility study**

<table>
<thead>
<tr>
<th>Name</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nizatidine</td>
<td>N</td>
</tr>
<tr>
<td>Nizatidine + MCC</td>
<td>NM</td>
</tr>
<tr>
<td>Nizatidine + Lactose</td>
<td>NL</td>
</tr>
<tr>
<td>Nizatidine + crosspovidone</td>
<td>NC</td>
</tr>
<tr>
<td>Nizatidine + SSG</td>
<td>NS</td>
</tr>
<tr>
<td>Code</td>
<td>Nizatidine+Mg.stearate</td>
</tr>
<tr>
<td>------</td>
<td>------------------------</td>
</tr>
<tr>
<td></td>
<td>Nizatidine+Talc</td>
</tr>
<tr>
<td></td>
<td>Nizatidine+Aerosil</td>
</tr>
<tr>
<td></td>
<td>Nizatidine+all excipients</td>
</tr>
<tr>
<td></td>
<td>Nizatidine+croscarmellose sodium</td>
</tr>
</tbody>
</table>

**Table 10: Data for R value of drug excipients compatibility study**

<table>
<thead>
<tr>
<th>Code</th>
<th>0days</th>
<th>2Days</th>
<th>5Days</th>
<th>10Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>0.73</td>
<td>0.728</td>
<td>0.729</td>
<td>0.728</td>
</tr>
<tr>
<td>NM</td>
<td>0.73</td>
<td>0.731</td>
<td>0.73</td>
<td>0.729</td>
</tr>
<tr>
<td>NL</td>
<td>0.73</td>
<td>0.73</td>
<td>0.732</td>
<td>0.028</td>
</tr>
<tr>
<td>NC</td>
<td>0.73</td>
<td>0.73</td>
<td>0.73</td>
<td>0.73</td>
</tr>
<tr>
<td>NCS</td>
<td>0.73</td>
<td>0.725</td>
<td>0.729</td>
<td>0.729</td>
</tr>
<tr>
<td>NS</td>
<td>0.73</td>
<td>0.728</td>
<td>0.728</td>
<td>0.73</td>
</tr>
<tr>
<td>NM</td>
<td>0.73</td>
<td>0.73</td>
<td>0.731</td>
<td>0.728</td>
</tr>
<tr>
<td>NT</td>
<td>0.73</td>
<td>0.73</td>
<td>0.729</td>
<td>0.729</td>
</tr>
<tr>
<td>NA</td>
<td>0.73</td>
<td>0.734</td>
<td>0.73</td>
<td>0.728</td>
</tr>
<tr>
<td>NAE</td>
<td>0.73</td>
<td>0.732</td>
<td>0.727</td>
<td>0.728</td>
</tr>
</tbody>
</table>

**Table 11: Data for max value in 01.N HCl of drug excipients compatibility study**

<table>
<thead>
<tr>
<th>Code</th>
<th>0days</th>
<th>2Days</th>
<th>5Days</th>
<th>10Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>314</td>
<td>314</td>
<td>314</td>
<td>314</td>
</tr>
<tr>
<td>NM</td>
<td>314</td>
<td>314</td>
<td>315</td>
<td>315</td>
</tr>
<tr>
<td>NL</td>
<td>314</td>
<td>314</td>
<td>314</td>
<td>314</td>
</tr>
<tr>
<td>NC</td>
<td>315</td>
<td>314</td>
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<td>314</td>
</tr>
<tr>
<td>NCS</td>
<td>314</td>
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<td>99.18</td>
<td>98.91</td>
<td>98.58</td>
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</table>

2.1.1. FTIR Studies:
Drug excipients compatibility study was performed by mixing drug with polymer in equal proportion and the mixture was kept under accelerated stability condition (i.e. 40°C and 75% R.H.) for a period of 21 days in a glass vial. It was hermetically sealed with rubber stopper using carnauba wax. Same mixture under control condition (i.e. 5% H₂O) was kept. IR spectrum was noted for mixture after 21 days. The IR Spectrum of previously dried samples were recorded by KBr dispersion technique. 2-3 mg of samples was mixed with previously dried IR grade potassium bromide and kept in sample cell, the cell was then fitted on sample holder and spectrum were recorded with FTIR.

Figure 31: IR spectra of pure crosspovidone, cross carmaolsesodium, sodiumstarchglycolate, pure Nizatidine and physical mixture of Nizatidine
2.1.1.9 Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) was performed using Shimadzu DSC 60 instrument. The samples were hermetically sealed in aluminum pans and heated over the temperature range 35˚C to 300˚C with a heating rate of 10 C/min. Inert atmosphere was provided by purging nitrogen gas flowing at 10 ml/min.

![DSC thermogram](image)

Figure 32: DSC thermogram of (a) pure Nizatidine, (b) pure microcrystalline cellulose, (c) pure croscarmellose sodium, (d) pure crosspovidone, (e) pure lactose, (f) pure sodium starch glycolate, (g) physical mixture of Nizatidine with all excipients

2.2 Development of formulation

During the past several decades, conventional drug dosage forms have been widely used for treatment of various conditions. These drug dosage forms typically provide immediate or rapid medication release, and supply a given concentration or quantity of the drug to the body's systemic circulatory system without any rate control. To maintain the effective plasma drug concentration, frequent administration is required. Due to poor drug efficacy, the incidence of side effects, frequency of administration, and patient compliance of these conventional drug preparations, many traditional drug dosage forms are undergoing replacement by modified drug-release dosage forms. Treatments of numerous diseases using traditional drug products are often inconvenient and impractical if disease symptoms occur during the night or early morning. During the early 1990s, modified-release drug preparations achieved continuous and constant-rate drug delivery, in which constant or sustained drug output minimized drug concentration "peak and valley" levels in the blood, promoting drug efficacy and reducing adverse effects. Modified-release drug preparations are expected to provide reduced dosing frequency and improved patient compliance compared to conventional release preparations. Several controlled-
release preparations present numerous problems such as resistance and drug tolerance. Controlled-release medications deliver continuous treatment, rather than providing relief of symptoms and protection from adverse events solely when necessary. The development of advanced drug delivery systems (DDSs) i.e. pulsatile drug delivery system to optimize and create new innovative DDS which provide a defined dose, at a chosen rate, at a selected time, at a targeted site is now a growing challenge.

2.2.1 Formulation of core tablets of Nizatidine
The core tablets containing Nizatidine (150 mg per tablet), lactose, microcrystalline cellulose (Avicel® PH101), polyvinyl pyrrolidone (PVP k30) and superdisintegrant like crosspovidone, croscarmellose sodium (Ac-Di-Sol®) and sodium starch glycolate, were prepared by direct compression. Initially, the core tablet excipients were dry blended in polybags for 10 min, followed by the addition of Talc, magnesium stearate and Aerosil® 200. The powder components were further blended for 5 min. The core tablets (diameter, 9 mm; biconvex; average tablet weight, 360 mg) were compressed using an eight station tablet machine (Karnavati, Ahmadabad, India).

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>CT1</th>
<th>CT2</th>
<th>CT3</th>
<th>CT4</th>
<th>CT5</th>
<th>CT6</th>
<th>CT7</th>
<th>CT8</th>
<th>CT9</th>
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<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
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<td>79.6</td>
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<td>100</td>
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<td>Ac-Di-Sol</td>
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<td>10.8</td>
<td>14. 4</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>7.2</td>
<td>10.8</td>
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<td>SSG</td>
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<td>-</td>
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<td>2</td>
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<tr>
<td>Wt of core tablets (mg)</td>
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<td>360</td>
<td>360</td>
<td>360</td>
<td>360</td>
<td>360</td>
<td>360</td>
<td>360</td>
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Table 13: Formulation Code for Core Tablets

<table>
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<tr>
<th>Material</th>
<th>% weight ratio</th>
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<tr>
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</tr>
<tr>
<td>EudragitNE30D</td>
<td>10 25 40 - - - - - -</td>
</tr>
<tr>
<td>Methocel</td>
<td>- - - 10 25 40 - -</td>
</tr>
<tr>
<td>EudragitS100</td>
<td>- - - - - - 10 25 40</td>
</tr>
<tr>
<td>Triethylcitrate</td>
<td>20 20 20 20 20 20 20 20 20 20</td>
</tr>
</tbody>
</table>
2.2.2 Time-Lagged Coating of Core Tablets for Pulsatile Release of Nizatidine

Coating solutions of ethylcellulose (rupturable polymer) combined with hydroxypropyl methylcellulose (erodible polymer) were prepared in isopropyl alcohol. The weight ratios of ethylcellulose (Aqualon ECN10) to hydroxypropyl methylcellulose (Methocel E15), ethylcellulose to eudragit 100 (erodible polymer) and ethyl cellulose to eudragit NE 30 D (erodible polymer) were 60:40%, 75:25% and 90:10% (w/w) based on the trials batches. The solution was plasticized with triethyl citrate (20%, w/w, with respect to dry polymer), and then talc was added as glidant (5%, w/w, related to dry polymer). The homogeneous dispersion was gently stirred throughout the coating process. The polymer solution was sprayed onto the core tablets in a conventional pan coating apparatus till the desired weight gain (5%, w/w). Coating conditions are listed in Table 14. At each stage the coated tablets were further dried in the coating pan for 15 min at 40°C. The tablets were then placed in the oven at 40°C for 2 h to remove the residual solvent.

Table 14: Coating solution

*Triethyl citrate and talc used in % w/w with respect to dry polymer coating of the tablets

The polymer solution was sprayed onto the core tablets in a conventional coating pan. Fixed numbers of tablets were coated each time by atomizing the polymeric coating solution through coating gun. The coating pan operated at fixed RPM (35) for all polymeric solution. The coating solution was applied when the tablet bed in the coating pan reached up to 60°C.

Table 15: The process condition for coating

<table>
<thead>
<tr>
<th>Process condition for coating</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Inlet temperature</td>
<td>50º-60ºC</td>
</tr>
<tr>
<td>Product temperature</td>
<td>35-40ºC</td>
</tr>
<tr>
<td>Spray rate</td>
<td>4-8 ml min⁻¹</td>
</tr>
<tr>
<td>Spray nozzle diameter</td>
<td>1 mm</td>
</tr>
<tr>
<td>Distance between tablet bed</td>
<td>10-15 cm</td>
</tr>
<tr>
<td>Spray gun</td>
<td>35 RPM</td>
</tr>
<tr>
<td>The level of coating</td>
<td>5%</td>
</tr>
</tbody>
</table>

3.1 Evaluation of Powder Blend

Tablet powder blends of core were evaluated for various pre compression parameters such as Angle of repose, loose bulk density, Tapped bulk density, Compressibility index and Hausner’s ratio.

- **Angle of repose**

  The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surfaces of a pile of powder or granules and the horizontal plane. Angle of repose is to be measured by following method: A funnel was filled to the brim and the test sample was allowed to flow smoothly through the orifice under gravity. From the cone formed on a graph sheet was taken to measure the area of pile, thereby evaluating the flow ability of the granules. Height of the pile is then measured. Angle of repose is calculated by formula:

  \[ r = \left( \frac{\text{area}}{\pi} \right)^{1/2} \] .......................... (a)

  \[ \theta = \tan^{-1} \left( \frac{h}{r} \right) \] .......................... (b)

- **Bulk density**

  Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape and the tendency of the particles to adhere to one another. Both loose bulk density and tapped bulk density were determined. A quantity of 10 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas.
Compressibility Index
The compressibility index of the powder or granules was determined by Carr’s compressibility index. This is a simple index that can be determined on small quantities of powder.

\[
Carr\text{'s Index (\%)} = \left(\frac{TBD - LBD}{TBD}\right) \times 100
\]

Hausner’s Ratio: Hausner’s ratio can be defined as ‘it is the ratio of tapped density by loose density’

\[
Hausner\text{ Ratio} = \frac{\text{Tapped Density}}{\text{Loose Density}}
\]

3.2 Evaluation of Core Tablets
The result of evaluation of core tablets for thickness, weight variation, hardness, and friability and drug content were shown in table from these tables it is concluded that all core tablets prepared and passed the official evaluation test criteria.

- **Thickness**
The thickness of the individual tablets is measured by use of the Vernier Calipers, which provides accurate information on the variation of thickness between the tablets. Tablets thickness should be controlled with in a ±5% variation of the average thickness. In addition to thickness, the uniformity of the tablets must be controlled to get consistent tablet weight in the lot. From six tablets from each batch of formulation of core tablets were used, and the mean thickness value and standard deviation were calculated for each formulation.

- **Hardness**
The hardness which is called the crushing strength for tablet is measured to determine its strength and endurance during transport. The hardness also has an indirect effect on the disintegration of the tablets as more hardness delays the disintegration time. The hardness or the crushing strength of the tablets are determined by using Monstanto hardness tester. For each formulation, the hardness of six tablets was measured using Monstanto hardness tester and mean value and standard deviation were calculated.

- **Weight Variation**
To study weight variation, 20 tablets of each formulation were weighed using an electronic digital balance. The average weight of each tablet was calculated and from the percentage deviation in weight was calculated.

- **Friability**
It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of laminating or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed (Initial Wt) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (Final Wt). The % friability was then calculated by,

\[
F\text{ (\%)} = \frac{\text{Initial Wt} - \text{Final Wt}}{\text{Initial Wt}} \times 100
\]

- **Drug Content**
Five tablets were weighed accurately and powdered. The drug content was determined by following procedure.
Standard solution: 10µg/ml of Nizatidine solution in 0.1N HCl
Sample solution: an accurately weight amount of powder equivalent to 100 mg of Nizatidine was extracted with 100 ml of 0.1N HCl to get final concentration of 10µg/ml. Measure the absorbance of standard and sample solution at 314 nm using 0.1N HCl solution as blank.
The drug Nizatidine that belongs to the H₂ antagonist class has been reported in the monograph to have ‘Nizatidine contains not less than 97.0% percent and not more than the equivalent of 101.0% per cent of the stated amount of the drug.’

- **Disintegration Test**
It is determined by using USP device which consist of 6 glass tubes that are 3 inches long, open at one end and held against 10 meshscreen at the bottom end of basketrack assembly. To test for disintegration time, one tablet is placed in each tube and the basket arch is positioned in a 900 ml beaker of water at 37°C ± 2°C. A standard motor driven device is used to move the
basket assembly up and down. To be in compliance with the USP standard, all tablets must disintegrate and all particles must pass through the 10 mesh in the timespecified.
**Dissolution of core tablets**
The test was carried out in USP dissolution basket assembly (Model TDL Electrolab, India) in 900 ml medium at 37±0.5 °C at a rotation speed of 100 rpm using pH 6.8 phosphate buffer for 1 hr. The aliquots of dissolution fluid were removed at specific time intervals and assayed for the amount of Nizatidine released by spectrometer (model Shimadzu-UV 1700, Japan) at wavelength 341 nm.

**3.3 Evaluation of coated tablets for pulsatile release of Nizatidine**
Prepared pulsatile release tablet was evaluated for official parameters like, Thickness, Hardness, and weight variation, Lag time of coating tablets and content uniformity and in-vitro dissolution studies.

**Thickness**
The thickness of the individual tablets is measured by use of the Vernier Calipers, which provides accurate information on the variations of thickness between the tablets. Tablets thickness should be controlled with in ±5% variation of the average thickness. In addition, thickness must be controlled to get uniform tablet weight in thelot. From six tablets from each batch of dissolution medium to tablet were used and mean thickness and standard deviation were calculated for each formulation.

**Hardness**
The hardness which is called the crushing strength for tablet is measured to determine its strength and endurance during transport. The hardness also has an indirect effect on the disintegration of the tablets as more hardness delays the disintegration time. The hardness or the crushing strength of the tablets are determined by using Monsanto hardness tester. For each formulation, the hardness of six tablets was measured using Monsanto hardness tester and mean value and standard deviation were calculated.

**Weight variation**
Tostudy weight variation, 20 tablets of each formulation were weighed using an electronic digital balance. The average weight of each tablet was calculated and from the percentage deviation in weight was calculated.

**Lag time of coating tablets:**
Coating tablets were placed into USP dissolution paddle apparatus at rotation speed 50 rpm with phosphate buffer IP pH 6.8, 37±0.5°C and observed visually. The lag time was defined as the point, when the outer coating ruptured due to swelling.

**Drug content**
Twenty coated tablets were weight accurately and powdered. The drug content was determined by following procedure.

Standard solution: 10µg/ml of Nizatidine solution in 0.1 N HCl

Sample solution: an accurately weight amount of powder equivalent to 100 mg of Nizatidine was extracted with 100 ml 0.1 N HCl to get final concentration of 10µg/ml. Measure the absorbance of standard and sample solution at 314 nm using 0.1 N HCl solution as blank.

**Dissolution methodology for coated tablets for pulsatile release of Nizatidine**
To verify how the composition of the core and the barriers interfere with the drug release profile from the cores, in vitro dissolution studies were carried out using USP Type I dissolution apparatus I (basket method; Electrolab India Pvt. Ltd., Mumbai, India) in 900 ml medium at 37±0.5°C at a rotation speed of 100 rpm. To mimic gastric pH conditions, test was carried out in 0.1N hydrochloric acid (pH 1.2) for 2 hr. simulated intestinal fluid pH 6.8 for 3 hr and simulated colonic fluid pH 7.4. The buffersystem having pH 6.8 and pH 7.4 was selected to simulate the condition in small intestine and colon. 5 ml sample was withdrawn every 1 hr, filtered through and immediately replaced by the fresh dissolution medium. All the dissolution samples were filtered through filter paper and analyzed immediately after the completion of dissolution test in Vilnis scanning spectrophotometer (Shimadzu-UV-1700, UV–visscanning spectrophotometer, Japan). Nizatidine released in 0.1N HCl was estimated at 314 nm. In this dissolution studies the USP type I dissolution apparatus I was quite suitable for carrying the samples in the next medium and dissolution is continued without disturbing and touching the surface of coated tablets.

**Drug release kinetics**
In model dependent approaches released data were fitted to five kinetics model including zero order, first order, Higuchi equation, Korsemeyer–Peppas equation and Hixon–Crowell release equation to find the higher correlation (r>0.98), release exponent (n) and rate constant (k).

**Stability Testing of the Best Formulation**
Stability studies are an integral part of the drug development program and are one of the important areas in the registration of pharmaceutical products. The purpose of Stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of various factors such as temperature, humidity, and light and to evaluate the shelf life of the drug product. Stability assessment started with studies on the substance to determine degradation products and degradation pathway. Temperature dependent stability studies were carried out on the best batches. They were packed in Low Density Polyethylene (LDPE) bags enclose in High Density Polyethylene (HDPE) container. And stored under the following conditions for 3 months at 37±0.5°C ±5%RH (14±2°C and RH 75%±5%)

Tables were withdrawn after a period of initial, 1, 2, 3 months and analyzed for Hardness, Drug content (%), Lag time and Dissolution study.

**Table 16: Physical parameters of powder blend**
<table>
<thead>
<tr>
<th>Batch no</th>
<th>Angle of Repose (θ)</th>
<th>Bulk Density gm/cm³</th>
<th>Tapped Density gm/cm³</th>
<th>Hausner’s Ratio (HR)</th>
<th>Carr’s index (%)</th>
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<tr>
<td>CT1</td>
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Table 17: Evaluation parameters of core tablets

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<tr>
<th>Batchno</th>
<th>Thickness (mm)</th>
<th>Friability (%)</th>
<th>Hardness (Kg/cm²)</th>
<th>Weight Variation (mg)</th>
<th>Drug content (%)</th>
<th>Disintegration time (Sec)</th>
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<tbody>
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<td>4.8±0.2</td>
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<tr>
<td>CT8</td>
<td>3.45±0.03</td>
<td>0.42</td>
<td>4.9±0.5</td>
<td>0.357±0.6</td>
<td>98.89</td>
<td>121</td>
</tr>
<tr>
<td>CT9</td>
<td>3.45±0.04</td>
<td>0.58</td>
<td>4.7±0.3</td>
<td>0.356±0.6</td>
<td>98.98</td>
<td>110</td>
</tr>
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</table>
### Table 18: Dissolution test data for core tablets

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>CT1</th>
<th>CT2</th>
<th>CT3</th>
<th>CT4</th>
<th>CT5</th>
<th>CT6</th>
<th>CT7</th>
<th>CT8</th>
<th>CT9</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>22.48±0.04</td>
<td>25.18±0.12</td>
<td>30.45±0.05</td>
<td>43.59±0.11</td>
<td>47.73±0.02</td>
<td>49.97±0.21</td>
<td>23.48±0.8</td>
<td>24.18±0.05</td>
<td>29.45±0.04</td>
</tr>
<tr>
<td>10</td>
<td>45.3±0.08</td>
<td>46.53±0.13</td>
<td>51.51±0.04</td>
<td>63.3±0.24</td>
<td>65.69±0.06</td>
<td>67.48±0.22</td>
<td>39.3±0.22</td>
<td>40.53±0.05</td>
<td>49.51±0.11</td>
</tr>
<tr>
<td>15</td>
<td>66.24±0.25</td>
<td>67.47±0.08</td>
<td>68.29±0.01</td>
<td>71.95±0.08</td>
<td>78.25±0.04</td>
<td>79.25±0.18</td>
<td>61.24±0.14</td>
<td>65.47±0.09</td>
<td>66.29±0.07</td>
</tr>
<tr>
<td>20</td>
<td>78.08±0.07</td>
<td>78.09±0.17</td>
<td>83.54±0.05</td>
<td>78.16±0.01</td>
<td>88.25±0.10</td>
<td>89.28±0.04</td>
<td>72.08±0.13</td>
<td>77.09±0.13</td>
<td>80.54±0.23</td>
</tr>
<tr>
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<td>87.24±0.04</td>
<td>95.54±0.08</td>
<td>87.16±0.21</td>
<td>92.25±0.02</td>
<td>93.54±0.11</td>
<td>84.77±0.05</td>
<td>85.24±0.12</td>
<td>91.54±0.04</td>
</tr>
<tr>
<td>30</td>
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<td>91.51±0.23</td>
<td>97.51±0.13</td>
<td>94.87±0.04</td>
<td>96.75±0.03</td>
<td>97.11±0.10</td>
<td>85.26±0.09</td>
<td>90.51±0.21</td>
<td>96.51±0.18</td>
</tr>
<tr>
<td>45</td>
<td>94.94±0.14</td>
<td>96.02±0.12</td>
<td>97.85±0.04</td>
<td>97.14±0.16</td>
<td>97.48±0.23</td>
<td>98.48±0.14</td>
<td>94.04±0.15</td>
<td>97.02±0.13</td>
<td>96.85±0.01</td>
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<tr>
<td>60</td>
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<td>96.66±0.05</td>
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<td>97.45±0.09</td>
<td>98.42±0.06</td>
<td>99.68±0.02</td>
<td>95.02±0.12</td>
<td>97.56±0.05</td>
<td>98.98±0.08</td>
</tr>
</tbody>
</table>

### Table 19: Evaluation parameters of pulsatile release Nizatidine tablets:

<table>
<thead>
<tr>
<th>Batch no.</th>
<th>Thickness (mm)</th>
<th>Hardness (Kg/cm²)</th>
<th>Weight Variation (mg)</th>
<th>Lag time (Hr)</th>
<th>Drug content %</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>3.63±0.04</td>
<td>5.1±0.4</td>
<td>0.382±1.6</td>
<td>5.39±0.03</td>
<td>98.28</td>
</tr>
<tr>
<td>F2</td>
<td>3.66±0.02</td>
<td>5.3±0.5</td>
<td>0.378±1.4</td>
<td>6.18±0.06</td>
<td>98.48</td>
</tr>
<tr>
<td>F3</td>
<td>3.75±0.03</td>
<td>5.2±0.8</td>
<td>0.374±0.4</td>
<td>7.17±0.07</td>
<td>99.20</td>
</tr>
<tr>
<td>F4</td>
<td>3.81±0.06</td>
<td>5.0±0.2</td>
<td>0.382±3.5</td>
<td>2.27±0.07</td>
<td>98.22</td>
</tr>
<tr>
<td>F5</td>
<td>3.62±0.07</td>
<td>5.5±0.12</td>
<td>0.377±1.6</td>
<td>3.12±0.02</td>
<td>98.97</td>
</tr>
<tr>
<td>F6</td>
<td>3.71±0.06</td>
<td>5.6±0.3</td>
<td>0.377±2.8</td>
<td>3.28±0.04</td>
<td>99.86</td>
</tr>
<tr>
<td>F7</td>
<td>3.62±0.05</td>
<td>5.3±0.8</td>
<td>0.380±0.3</td>
<td>3.38±0.06</td>
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</tr>
<tr>
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<td>3.55±0.03</td>
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<td>0.375±1.5</td>
<td>4.24±0.04</td>
<td>98.89</td>
</tr>
<tr>
<td>F9</td>
<td>3.65±0.04</td>
<td>5.1±0.3</td>
<td>0.376±2.4</td>
<td>4.35±0.05</td>
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### Table 20: Dissolution test data for pulsatile release Nizatidine tablets
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<th>Time (hr)</th>
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<th>F2</th>
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<td>±0.06</td>
<td>±0.01</td>
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<td>±0.08</td>
<td>±0.07</td>
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<td>8</td>
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<td>94.72</td>
<td>92.51</td>
<td>96.58</td>
<td>97.16</td>
<td>99.58</td>
<td>98.13</td>
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<td>96.13</td>
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<td>±0.07</td>
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<td>±0.13</td>
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<td>92.50</td>
<td>96.58</td>
<td>97.16</td>
<td>99.62</td>
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<td>97.18</td>
<td>96.14</td>
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<td>±0.13</td>
<td>±0.03</td>
<td>±0.10</td>
<td>±0.02</td>
<td>±0.01</td>
<td>±0.13</td>
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</table>

Table 21: Kinetic Release Data for pulsatile release Nizatidine tablets

<table>
<thead>
<tr>
<th>Batch</th>
<th>Zero order</th>
<th>First order</th>
<th>Hixon</th>
<th>Higuchi</th>
<th>Korsemeyer-Peppas</th>
</tr>
</thead>
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<td>$r^2$</td>
<td>$r^2$</td>
<td>$r^2$</td>
<td>$r^2$</td>
<td>$r^2$</td>
</tr>
<tr>
<td>F1</td>
<td>0.819</td>
<td>0.837</td>
<td>0.835</td>
<td>0.750</td>
<td>0.818</td>
</tr>
<tr>
<td>F2</td>
<td>0.719</td>
<td>0.713</td>
<td>0.713</td>
<td>0.621</td>
<td>0.636</td>
</tr>
<tr>
<td>F3</td>
<td>0.613</td>
<td>0.568</td>
<td>0.581</td>
<td>0.503</td>
<td>0.722</td>
</tr>
<tr>
<td>F4</td>
<td>0.627</td>
<td>0.876</td>
<td>0.788</td>
<td>0.725</td>
<td>0.762</td>
</tr>
<tr>
<td>F5</td>
<td>0.862</td>
<td>0.803</td>
<td>0.845</td>
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<td>0.877</td>
</tr>
<tr>
<td>F6</td>
<td>0.751</td>
<td>0.810</td>
<td>0.852</td>
<td>0.803</td>
<td>0.928</td>
</tr>
<tr>
<td>F7</td>
<td>0.753</td>
<td>0.824</td>
<td>0.862</td>
<td>0.804</td>
<td>0.868</td>
</tr>
<tr>
<td>F8</td>
<td>0.806</td>
<td>0.888</td>
<td>0.858</td>
<td>0.748</td>
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</table>

n value
Table 22: Evaluation parameters of the best batch F6 after stability

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Initial</th>
<th>1 Month</th>
<th>2 Month</th>
<th>3 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardness (kg/cm²)</td>
<td>5.6</td>
<td>5.4</td>
<td>5.4</td>
<td>5.6</td>
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<tr>
<td>Drug content (%)</td>
<td>99.86</td>
<td>99.12</td>
<td>99.15</td>
<td>99.54</td>
</tr>
<tr>
<td>LagTime (h)</td>
<td>3.28</td>
<td>3.21</td>
<td>3.30</td>
<td>3.25</td>
</tr>
<tr>
<td>% Drug Release</td>
<td>99.62</td>
<td>99.05</td>
<td>98.90</td>
<td>98.81</td>
</tr>
</tbody>
</table>

Figure 33: Drug release profile of core tablets.
Figure 34: Drug release profile of pulsatile release Nizatidine tablets.

4.1 Preformulation studies for Nizatidine

- Nizatidine was observed to be most white powder with a sulphur mercaptonour with a metallic bitter taste. The results are shown in Table 2.
- The melting point was found to be 131-134°C.
- The solubility studies of Nizatidine were performed in various solvents.
- The drug was found to be freely soluble in chloroform; soluble in methanol; soluble in water and buffered solution slightly soluble in ethyl acetate. The solubility studies of Nizatidine were performed in various solvents summarised in Table 3.
- The UV spectrum was recorded in the range of 200-400 nm as shown in Figure 24, 25, 26.
- Maximum absorption of wavelength was determined in 0.1 N HCl, pH 6.8 phosphate buffer, pH 7.4 phosphate buffer. The results are shown in Table 4.
- IR spectrum of Nizatidine is shown in Figure 27. The principal peak of maximum absorbance along with interpretation are shown in Table 5.
- A linear relationship was obtained in Beer-Lambert's plot of Nizatidine. The absorbance values were shown in Table 6, 7, 8. A straight line was obtained in the concentration range of 0.05 to 2.0 mg/mL. The drug content was also good. The results are shown in Table 10, 11, 12.

FTIR Spectroscopy Study:
The IR spectrum measurements were performed shown in Figure 31. The infrared spectra of pure Nizatidine exhibited IR signals showing characteristic peaks at 3280 cm⁻¹ (N-H stretching), 3107 cm⁻¹ (C-H stretching), 1521 cm⁻¹ (Thiazole), 2945 cm⁻¹ (C-H stretching in NCH₃, CH₂), 1377 cm⁻¹, 1359 cm⁻¹ (Thiazole ring frequency sym NO₂, H-bonded, conjugated).

The Infrared Spectra of physical mixture of Nizatidine exhibited IR signals showing characteristic peaks at 1354 cm⁻¹ (Thiazole ring for one frequency is sym NO₂, H-bonded, conjugated), 2860 cm⁻¹ (C-H stretching in NCH₃, CH₂), 3094 cm⁻¹ (C=CH stretching in thiazole ring) 3280 cm⁻¹ (N-H stretching).

Differential Scanning Calorimetry Study:
The DSC thermogram obtained of pure drug and excipients are shown in Figure 32. The DSC curve of pure Nizatidine exhibited a single endothermic curve corresponding to the melting of drug. Onset of melting was observed at 131°C shown in Figure 30a. The super disintegrant croscarmellose sodium, crosspovidone, sodium starch glycolate shows broad endothermic fusion peaks at 96.11°C, 94.96°C and 84.48°C respectively shown in Figure 30c, 30d, 30e which is due to glass transition state. The DSC spectrum of physical mixture of Nizatidine and mixture of other excipients has also shown same endothermic peaks like pure drug shown in Figure 30. These observations of DSC study indicate absence of significant interactions between drug and excipients used in tablet formulations and coating materials.

Evaluations of Powder Blend:
Powder characteristics for all batches were evaluated for various precompression parameters such as Angle of Repose, Loose Bulk Density (LBD), Tapped Bulk Density (TBD), Compressibility index and Hausner’s ratio. The results are shown in Table 16. All prepared batches exhibited good flow properties and compression characteristics as compared to pure drug. The angle of repose for batches CT1 to CT8 exhibited a range of 24.70º to 29.66º indicating good flow properties for the powder blend ready for compression. Carr’s index for all the prepared batches showed a value of 1.33 to 1.69 indicating good compression characteristics for the granules ready for compression. Hausner’s Ratio for all the batches was found to be between 1.22 to 1.86 indicating good compression characteristics.

4.2 Evaluation of Core Tablets:
Routine pharmacopeial physical evaluation tests for uncoated tablets were performed like tablet thickness, weight variation, tablet hardness, friability and drug content. Results obtained for these tests are summarised in Table 17. Thickness of all uncoated tablets varied from 3.42±0.05 mm to 3.61±0.02 mm. Friability for all batches ranged between 0.26% to 0.61%. Tablets hardness varied from 4.7±0.3 Kg/cm² to 5.4±0.3 Kg/cm². Weight Variation for all batches was between 0.354±0.4 mg to 0.364±0.3 mg. Drug content from all batches was 98.28% to 99.86%. While the disintegration time for uncoated tablets varied from 13.33 to 37.26 seconds. All the prepared batches passed the routine physical evaluation tests per limits of pharmacopeia.

From these results it is observed that all core tablets prepared and passes the official evaluation test criteria. The thickness of the individual tablets is measured by use of...
the Vernier Calipers, which provides accurate information on the variations of thickness between tablets. (Tablet thickness should not be less than 5% of the average thickness.)

Batch CT6 contained 4% concentration of crosspovidone, giving a lowest lag time of 1.7±0.07 hr. Results for dissolution time obtained for various batches are given in Table 17.

### Dissolution of Core Tablets:

Dissolution data of core tablets of Nizatidine are reported in Table 18. Drug dissolution at specific time periods was plotted as percent drug release versus time (hr). Release profile of core tablet of Nizatidine with different concentration of superdisintegrants are shown in Figure 33.

All the core tablets showed complete drug release within 60 min. The percent of the drug release versus time plots show that the dissolution rate was directly proportional to the amount of superdisintegrant in the core tablet shown in Figure 33. A significant difference was observed in the percent of the drug release for different concentration of superdisintegrant in core tablet.

### 4.2 Evaluation of Pulsatile Release Tablets of Nizatidine

Pharmaceutical evaluation tests for coated tablets were performed like tablet thickness, weight variation, tablethardness, drug content uniformity, and content uniformity.

Results are shown in Table 19. From these results, it is concluded that all core tablets prepared and passed the official evaluation test criteria. The tablethardness of all the core tablets was determined and it was found in the range 5.1–5.6 kg/cm². Evaluation parameters of pulsatile release are shown in Figure 33.

Routine pharmaceutical physical evaluation tests for coated tablets were performed like tablet thickness, weight variation, tablethardness, and drug content. Results obtained for these tests are summarized in Table 19. Thickness of all coated tablets varied from 3.63±0.04 mm to 3.81±0.06 mm. Tablets hardness varied from 5.1±0.3 Kg/cm² to 5.6±0.3. Weight Variation for all batches was between 0.37±0.4 mg to 0.38±0.3 mg. Drug content from all batches was 98.22% to 99.86%.

All the prepared tablets passed the routine physical evaluation tests as per limits of pharmacopoeia. From these results, it is observed that all core tablets prepared and passed the official evaluation test criteria. The thickness of the individual tablets is measured by use of the Vernier Calipers, which provides accurate information on the variations of thickness between the tablets. (Tablets thickness should not less and not more than in ±5% variation of the average thickness.) The weight variation test was carried out as per official method and the results are shown in Table 19. The content uniformity test was also carried out as per official method and it was found that all batches showed good content uniformity.

### Lag time for Coated Tablets

The lag time for all prepared batches was found to be dependent on the core ratio of coating component. Ethyl cellulose and Eudragit NE 30D was used in the ratio of 60:40%, 75:25% and 90:10% (w/w). The lag time of all batches of was found to be in between 5.39±0.03 to 7.37±0.07 hr. Ethyl cellulose and Methocel was used in the ratio of 60:40%, 75:25% and 90:10% (w/w). The lag time of all batches of was found to be in between 2.27±0.07 to 3.28±0.04. Ethyl cellulose and Eudragit S100 was used in the ratio of 60:40%, 75:25% and 90:10% (w/w). The lag time of all batches of was found to be in between 3.38±0.06 to 4.35±0.05. As the concentration of rupturable polymer increased proportionally increases the lag time. In this study formulation having F6 containing (60:40) w/w amount of coating ratio shows the lag time having a 3.28±0.04 hr.

### Dissolution Studies:

Dissolution data of pulsatile release Nizatidine tablets are reported in Table 20. Drug dissolution at specific time periods was plotted as percent drug release versus time (hr) curve. Release profile of Nizatidine with different polymer content is shown in Figure 34.

All polymers show no drug or small amount of drug release in the first two hours after words a different drug release profile was evident for each polymer in different ratio. The time at which rupture of the polymer layer in the dissolution medium was taken as indication for the beginning of the drug release into the medium. The lag time and drug release was directly related to concentration ratio to the polymer in coatingsolution and the coating level. Percent drug release Vs time plots show that the dissolution rate was inversely proportional to the combination of polymer in coatingsolution shown in Figure 34. A significant difference was observed in the percent of the drug release for different combination of polymer in coatingsolution. All the coated tablets with variable coating combination showed nearly complete drug release in 6-8 hr.

The percent of the drug release versus time plot shows that the dissolution rate was inversely proportional to the amount of film forming (erodible) polymer in the coatingsolution. The lag time and in vitro drug release profile for all three polymers combinations with ethylcellulose in different ratio is different

### Kinetic Modelling of Drug Release

To analyze the in vitro release data various kinetic models were used to describe the release kinetics. Data obtained from the in vitro release studies were subjected to kinetic treatment to know the order of release. The ‘r’ values for zero order, first order, and second order are shown in Table 21. From these tables it is observed that the release profile was as follows: zero order that was confirmed by low ‘r’ values of 0.613 – 0.8163. Higuchi plots of all the formulations were non linear because ‘r’ values are not near about 1 in all the cases. The formulations were subjected to Higuchi plots by taking log cumulative % drug released versus log time. The plots are found to be linear and slope value was calculated (n value) which was range of 0.243 to 0.767 or F1 – F9 indicating the drug was released by Fickian diffusion mechanism. A non-Fickian mechanism was evident for each polymer in different ratio. The time at which rupture of the polymer layer in the dissolution medium was taken as indication for the beginning of the drug release into the medium. The lag time and drug release was directly related to concentration ratio to the polymer in coatingsolution and the coating level. Percent drug release Vs time plots show that the dissolution rate was inversely proportional to the combination of polymer in coatingsolution shown in Figure 34. A significant difference was observed in the percent of the drug release for different combination of polymer in coatingsolution. All the coated tablets with variable coating combination showed nearly complete drug release in 6-8 hr.

The percent of the drug release versus time plot shows that the dissolution rate was inversely proportional to the amount of film forming (erodible) polymer in the coatingsolution. The lag time and in vitro drug release profile for all three polymers combinations with ethylcellulose in different ratio is different.
release from system where release rate is concentration dependent. According to Higuchi release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion. The Hixson-Crowell cube root law describes the release from systems where there is anchage in surface area and diameter of particles or tablets. 53. Korsmeyer et al derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug released was fitted in Korsmeyer–Peppas model:

$$\frac{Q_t}{Q_{\infty}}=kt^n$$

Where $Q_t / Q_{\infty}$ is fraction of drug released at time t, k is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms according to Table 23 for cylindrical shaped matrices.

Table 23: Diffusion exponent and dissolution mechanism for cylindrical shape

<table>
<thead>
<tr>
<th>Exponent (n)</th>
<th>Overall solutediffusion mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>Fickian diffusion</td>
</tr>
<tr>
<td>0.5 &lt; n &lt; 0.89</td>
<td>Anomalous (non-Fickian) diffusion</td>
</tr>
<tr>
<td>1.0</td>
<td>Case-II transport</td>
</tr>
<tr>
<td>Higher than 1.0</td>
<td>Supercase-II transport</td>
</tr>
</tbody>
</table>

According to Korsmeyer where n is the release exponent, indicative of mechanism of drug release. Fickian diffusional release and a case-II relaxational release are the limits of this phenomenon. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxational release is hydrodrug transport mechanism associated with stress release and transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymer disentanglement and erosion. 57 Table 23 describes the limits of this analysis for cylindrical shape, e.g. a tablet. The value of the release exponent in tablet formulation is 0.243 indicating Fickian diffusion.

**Stability Study**

The best batch F6 was stored at 40°C (±5°C) and 75% RH (±5%) for 3 months to analyze various physical parameters, results were showed in Table 22. No major differences were found between evaluated parameters before and after and all are within acceptable limits. 89

**SUMMARY AND CONCLUSION**

Nizatidine was to be freely soluble in chloroform, in methanol; soluble in water and buffered solution slightly soluble in ethyl acetate and isopropyl. The melting was observed at 131³C. The DSC spectra of pure Nizatidine exhibited a single endothermic response corresponding to the melting of drug. Onset of melting was obtained at 135³C. The Super disintegrant cross caromellose sodium, crosspovidone, sodium starch glycolate showed broad endothermic fusion peaks at 96.11°C, 94.96°C and 84.48°C respectively which is due to glass transition state. The DSC spectra of physical mixture of Nizatidine and mixture of other excipients showed a single endothermic peak at 135°C. These observations of DSC study indicate absence of significant interaction between drug and excipients used in tablets formulation.

The Infrared spectra of pure Nizatidine exhibited IR signals show characteristic peaks on at 3280 cm⁻¹ (N-H stretching), 3107 cm⁻¹ (C-H stretching in NO₂-CH₂), 3094 cm⁻¹ (C-H stretching in NO₂-CH₃), 1521 cm⁻¹ (Thiazole ring), 2945 cm⁻¹ (C-H stretching in NCH₂,CH₂), 1377 cm⁻¹, 1359 cm⁻¹ (Thiazolering for one frequency is symmetric NO₂-H bonded, conjugated). The Infrared Spectra of physical mixture of Nizatidine exhibited IR signals show characteristic peaks on at 1359 cm⁻¹ (Thiazoling for one frequency is symmetric NO₂-H bonded, conjugated), 2860 cm⁻¹ (C-H stretching in NCH₂,CH₂), 3094 cm⁻¹ (C-H stretching in thiazoling), 3280 cm⁻¹ (N-H stretching). The IR spectrum of physical mixture shows the major peaks of Nizatidine. These observations of IR spectra indicate that there was no chemical interaction between Nizatidine and other excipients.

Powder blends for all batches of core tablet were evaluated for various precompression parameters such as Angle of repose, loose bulk density, Tapped bulk density, Compressibility index and Hausner’s ratio where these observations concluded that, the core tablets powder blend shows good flow property and good compressibility index. The core tablets of Nizatidine were complied the official tests for thickness, weight variation, hardness, friability, drug content and dissolution studies. It was observed that the release from CT1 to CT9 was ranging between 95.02 to 99.08% of the drug release within 60 min. The formulation contained 2-4% w/w of cross caromellose sodium (CT1-CT3) showed the disintegration time from 108 to 140 sec and drug release in the range between 95.02-98.66%. The formulation batches contained 2-4% crosspovidone (CT4-CT6) shows the disintegration time from 101 to 134 sec and drug release in the range between 97.45-99.08%. The formulation batches contained 2-4% sodium starch glycolate (CT7-CT9) shows the disintegration time from 110 to 135 sec and drug release in the range between 95.02-98.98%.

From results obtained from dissolution and disintegration time the best batch was found to be CT6. Core tablets prepared with 4% crosspovidone start disintegrating within few min. It shows 50% drug release in 5 min and 90% drug release in 20 min as the amount of super disintegrant decrease the release was decreased. Pulsatite drug delivery system required fast drug release at initial lag phase. Formulation containing 4% crosspovidone shows fast disintegration and dissolution and hence cored core further lagged time coating formulation. The coated tablets of Nizatidine were evaluated for Thickness, Hardness, Weight variation, disintegration test, and content uniformity and in vitro dissolution studies. It was observed that the release from F1 to F9 was ranging between 92.50 to 99.62% of the drug release up to 10 hr. The formulation coated with ethyl cellulose with the Eudragit NE30D in the ratio of 90:10%, 75:25%, 60:40% (w/w) (F1-
F3)showsthatagetime 5.39±0.03,6.18±0.06and7.17±0.07 hr respectively and drug release in the ranging between 94.52-95.52%. The formulation coated with ethyl cellulose with the Methocel in the ratio of 90:10%;75:25%;60:40%(w/w)(F4- F6)showsthatagetime 2.27±0.07,3.12±0.02and3.28±0.04hrsrespectively anddrugrelease intherangingbetween96.58-99.58%. The formulation coated with ethyl cellulose with the Eudragit S100 in the ratio of90:10%;75:25%;60:40%(w/w)(F7- F9)showsthatagetime 3.38±0.06,4.24±0.04and4.35±0.05hrsrespectively anddrugrelease intherangingbetween96.14- 99.13%. The best batch selected on the basis of drug release after the lag time. Formulation 6 could not release the drug initially but gives very immediate burst release at time of midnight hours. To analyze the in vitro release data various kinetic models were used to describe the release kinetics. The zero order rate describes the systems where the drug release rate is independent of its concentration. The first order describes the release from system where release rate is concentration dependent. According to Higuchi release of drugs from insoluble matrix as a square root of time dependent process based on Ficki and diffusion. The Hixon-Crowell cuberootlaw describesthereleasefromsystemswhere theresis achanginsurfacearea and diameter of particles or tablets.

\[
\text{Mt}/M_\infty = Kt^n
\]

\[
Q_t / Q_0 = Kt^{1/2}
\]

\[
Q_t = Kt^{1/3}
\]

Where, \(K_o\) is zero order rate constant expressed in units of concentration/time and t is the time.

Where, \(C_0\) is the initial concentration of the drug in the tablet and \(K_{RC}\) is the rate constant for Hixon-Crowell rate equation.

The following plots were made: cumulative % drug release vs. time (zero order kinetic model); log cumulative % drug remaining vs. time (first order kinetic model); cumulative % drug release vs. square root of time (higuchi model); log cumulative % drug release vs. log time (Korsmeyer model) and cube root of drug % remaining in matrix vs. time (Hixon-crowell cuberoot law).

Mechanism of drug release

Korsmeyer et al. derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, data was fitted in Korsmeyer-Peppas model:

\[
M_t / M_\infty = K^{n}
\]

Where \(M_t / M_\infty\) is fraction of drug released at time t, \(K\) is the release constant and \(n\) is the release exponent. The n value is used to characterize different release mechanisms as given in table 21 for cylindrical shaped matrices. According to various kinetic models, were giving linear relationship. In Zero order the r2 value obtained is 0.751 and first order gave 0.810 describing the drug release rate relationship with concentration of drug. The dissolution data was also plotted in accordance with Hixon Crowell cuberoot law. Applicability of data (r2 = 0.852) indicates a change in surface area and diameter of tablets with the progressive dissolution of matrix as a function of time. According to Korsmeyer where n is therelease exponent, indicative of mechanism of drug release. Fickian diffusion release andanacase-Irelaxational release, there analysisthis phenomenon. Fickian diffusion release is due to chemical potential gradient. Case-IIrelaxational release is due to the usual molecular diffusion of the drug. Drug transport mechanisms are associated with stresses and transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymerdisentanglement anderosion. Table 21 describes the limits of this analysis for cylindrical shape. The value of the release exponent in Nizatidine was found to be 0.243 which as per Table 23 is beyond the limits of Korsmeyer model so-called power law. The power law can only give limited insight into the exact release mechanism of the drug. Even if values of the exponent n are found that would indicate diffusion controlled drug release mechanism. The best batch F6 was stored at 40°C (±5°C) and 75% RH (±5%) for 3 months to analyze various physical parameters. No major differences were found between evaluated parameters before and after, and all are in acceptable limits. From the stability data for pulsatile release Nizatidine tablet it can be concluded that there were no change in any parameter tested in formulation so best batch F6are said to be stable. Conclusively the present study demonstrates the Nizatidine could be successfully delivered by providing nighttimereleof gastric acid by designing timed aged coating during pharmaceutical formulation (F6). It provides the delivery of drug at midnight hours. The formulation is to be taken after meal it gives burst release at midnight hours. This will provide an ideal therapeutic regimen with enhanced patient compliance.

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