Development And Cherecterization Of Pulsatile Release Tablet Of Nizatidine

[1]Chandranil D.Ishi, [2]Mr.Sagar R.Koli

KVPS's Maharani Ahilyabai college of pharmacy (M.A.H.) ,Boradi,Tal-Shirpur,Dist.Dhule.[MH],India.Department of Pharmaceutics,

Abstract: The objectives of pulsatile release tablet of nizatidine are pulsatile.it is inhibit the peptic secretion. 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®) 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. TheNizatidine 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 croscarmellose 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,cross crosscarrmellose sodium,evalution

1.0 INTRODUCTION:

1.1 Pepticulcer

A peptic ulcer, also known as PUD or peptic ulcer disease, is the most common ulcerof 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 acidsproduced in your stomach. If this protective lining stops working correctly and thelining breaks down, it results in inflammation (gastritis) or an ulcer. Most ulcers occurin the first layer of the inner lining. A hole that goes all the way through the stomachorduodenum is called aperforation.[1]

Amajorcausativefactorofgastricandofduodenalulcersischronicinflammationdue to *Helicobacter pylori* that colonizes the antral mucosa. The immune system isunable to clear the infection, despite the appearance of antibodies. Thus, the bacteriumcan cause a chronic active gastritis (type B gastritis), resulting in a defect in theregulation of gastrin production by that part of the stomach, and gastrin secretion caneither 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 acid can contribute to theerosionofthemucosaandthereforeulcerformation.Anothermajorcauseistheuseof NSAIDs.Thegastricmucosa protectsitselffromgastric acidwitha layer ofmucus, the secretion of which is stimulated by certain prostaglandins. NSAIDs blockthefunctionofcyclooxygenase1(cox-1),whichisessentialfortheproductionofthese 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 declinesdue to increased medical treatment, a greater proportion of ulcers will be due toincreasing NSAID use among individuals with pain syndromes as well as the growthofaging populations that develop arthritis.

A major causative factor of gastric and of duodenal ulcers is smoking and ulcerformation.[2] others have been more specific in exploring the risks involved and havefoundthatsmokingbyitselfmaynotbemuchofariskfactorunlessassociatedwithH. pylori infection.[3,4,5] Similarly, while studies have found that alcohol consumptionincreasesriskwhenassociatedwith*H.pylori*infection,itdoesnotseemtoindependentlyincreaserisk, and even whencoupled with*H. pylori*infection.[6]

Typesofulcerbasedonlocation:(Duodenum)Duodenalulcer,(Oesophagus)Oesophagealulcer,(Stomach)Gastriculcer,

1.2 Medicationstreating pepticulcer

Antiulcerreferstothepropertyofasubstancesortreatmentthatreducethegastricacidsecretions, duodenalulcerischronicremittingandrelapsingdieses. Goalsofantiulcertherapyare

- Reliefofpain,
- Ulcerhealing,
- Preventionofcomplication,
- Preventionofrelapse.

1.2.1 Classificationofdrugsforpepticulcer

1. **Gastricacidsecretioninhibitor**
   - H_2antihistamines: Cimetidine,Ranitidine,Famotidine, Roxatidine,Loxatidine,Nizatidine
   - Protonpumpinhibitors(PPI):Omeprazole,Esomeprazole,lansoprazole,pantoprazole,Rabeprazole
   - Prostaglandinanalogues (PA):Misoprostol
   - Anticholinergics:Pirenzepine,Propanthelne,Oxyphenoniun
2. **Gastricacidneutralizers(Antacids)**
   - Systemicantacids:Sodiumbicarbonate,Sod.citrate
   - Nonsystemic antacids: Magnesium hydroxide, Mag. trisilicate,Aluminiumhydroxidegel,Calcium carbonate,Magaldrate
3. **Ulcerprotective**:Sucralfate,colloidalbismuthsubcitrates(CBS)
4. **Anti-H pylori drugs**: Amoxicillin,Clarithromycin, Metronidazole,Tetracycline.[7]

H_2antagonist

Peptic ulcer occur in that part of gastrointestinal tract which is exposed to gastric acidand pepsin i.e. stomach and duodenum. It is result probably due to an imbalancebetween aggressive (acid, pepsin, bile and *H pylori*) and defensive factor (gastricmucus, bicarbonate secretion, prostaglandin, innate resistance of the mucosal cell)factor.[8]

Normal gastric acid secretion follows circadian rhythm with a sudden surge of gastricacidity when gastric pH level goes far below 4 for at least 1 hour in the midnight. Thispathophysiological condition is termed as nocturnal acid breakthrough (NAB). Butsteady reveals that up to 70% patients appears to be resistance to even high doses ofproton pump inhibitor taken twice daily. It is observed that adding a bed time dose ofH_2 antagonistprovidenocturnalrecoveryofgastricacidsecretion.[9]H_2receptorantagonistsrelievesymptomsof duodenal ulcers and promoteulcer healing.

MechanismofAction[10]

The H_2-receptor antagonists inhibit acid production by reversibly competingwith histamine for binding to H_2 receptors on the basolateral membrane of parietalcells. Four different H_2-receptor antagonists, who differ mainly in these drugs, are lesspotent than proton pump inhibitors but still suppress 24-hour gastric acid secretion byabout 70%. The H_2-receptor antagonists predominantly inhibit basal acid secretion,which accounts for their efficacy in suppressing nocturnal acid secretion. Because themost important determinant of duodenal ulcer healing is the level of nocturnal acidity,eveningdosingof H_2-receptor antagonistsis adequate therapyin mostinstances.

TherapeuticUses

The major therapeutic indications for H_2-receptor antagonists are to promotehealing of gastric and duodenal ulcers, to treat uncomplicated GERD and to preventtheoccurrenceof stress ulcers.

Pharmacologicalaction

H_2blockade:H_2antagonistblockhistamineinducedgastricsecretion,cardiacstimulation uterine relaxation and bronchial relaxation, they attenuated fall in BP dueto histamine, especially the late phase response seen with high doses they are highlyselective, and have no effect on H_1 mediated responses or on the action on the otherautacoids.

Gastric secretion: They only significant in vivo action of H_2 blockers inhibition ofgastric secretion. All phases of secretion are suppressed dose dependently, but thebasal nocturnal secretion suppressed more completely. Secretary responses to not onlyhistamine but all other stimuli are attenuated. This reflects the permissive role ofhistamine in amplifying responses to other secretagogues. The volume, pepsin contentandintrinsic factor secretion arealso reduced.

1.0 IntroductiontoPulsatileDrugDeliverySystem

During the past several decades, conventional drug dosage forms have beenwidely used for treatment of various conditions. These drug dosage forms typicallyprovide an immediate or rapid medication release, and supply a given concentration orquantityofthedrugtothebody'ssystemiccirculatorysystemwithoutanyratecontrol. To maintain the effective plasma drug concentration, frequent administrationis required. Due to poor drug efficacy, the incidence of side effects, frequency ofadministration and patient compliance of these conventional drug preparations, manytraditionaldrugdosageformsareundergoingreplacementbysecond-generation,modified drug-release dosage forms (Fig. 1). Treatments of numerous diseases usingtraditional drug products are often inconvenient and impractical if disease symptomsoccur during the night or early morning. During the early 1990s, second-generationmodified-release drug preparations achieved continuous and constant-rate drug de-livery, in which constant or sustained drug output minimize drug concentration “peakand valley” levels in the blood, so promoting drug efficacy and reducing adverseeffects. Modified-release drug preparations are expected to provide reduced dosingfrequencyandimprovedpatientcompliancecomparedtoconventionalreleasepreparations.Second-generationmodified-releasedosageformsincludeslowed-release,delayed-release,andprolonged-releaseextended-release,repeated-release,sustained-release, andcontrolled release drugpreparations.[11,12]

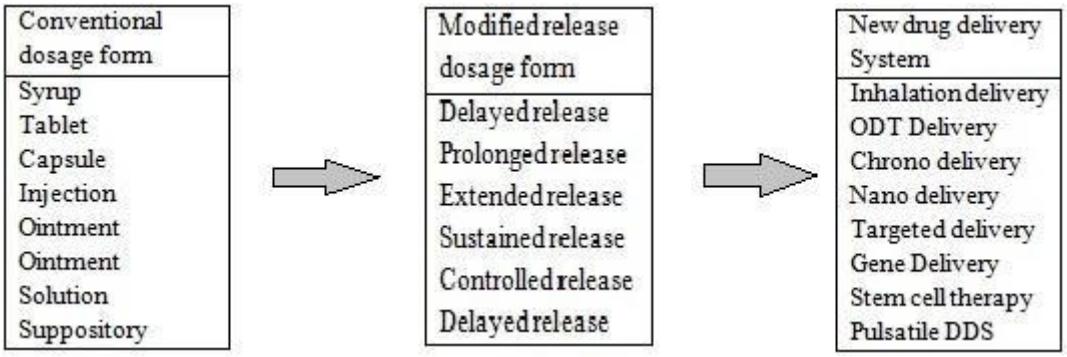


Figure1:Progressofpharmaceuticalpreparation

Several controlled-release preparations present numerous problems such as resistanceanddrugtolerance,andactivationofthephysiologicalsystemduetolong-termconstant drug concentrations in the blood and tissues. Physiological tolerance maydevelop as an organism builds resistance to the effects of a drug substance afterrepeated exposures. This indicates strongly that it is not always desirable to maintainconstantbloodlevelsofadrugoverlongperiods.Pulsatiledrugdeliverysystemalso reveal that the body's biological rhythm may affect normal physiological function,including gastrointestinal motility, gastric acid secretion, gastrointestinal blood flow,renalbloodflow,hepaticbloodflow,urinarypH,cardiacoutput,drug-proteinbinding,andliverenzymaticactivity,andbiologicalfunctionssuchasheartrate,blood pressure, body temperature, blood plasma concentration, intraocular pressureandplateletaggregation.[1]Most organ functions vary with the time of the day, particularly when therearerhythmic and temporal patterns in the manifestation of a given disease state. Thesymptoms of many diseases, such as bronchial asthma, myocardial infarction, anginapectoris, hypertension, and rheumatic disease have followed the body's biologicalrhythm. Day-night variation in asthmatic dyspnea and variations in the incidence ofmyocardial infarction occur throughout the early morning hours. Controlled-releasemedications deliver continuous treatment, rather than providing relief of symptomsand protection from adverse events solely when necessary, the development of athird-generation of advanced drug delivery systems (DDSs) to optimize and createnew innovative DDSwhich providea defineddose, atachosenrate,ata selectedtime, to a targeted site isnow a growing challenge. A chronodelivery system, basedonbiologicalrhythms,isastateofthearttechnologyfordrugdelivery.Chronomodulated DDSs not only increase safety and efficacy levels, but also improveoveralldrugperformance.Chronomodulated drug delivery systemalsoknown aspulsatile drug delivery system.[14]The oral controlled-release system shows a typicalpatternofdrugreleaseinwhichthedrugconcentrationismaintainedinthetherapeuticwindowforaprolongedperiodoftime,therebyensuringsustainedtherapeutic action. However, there are certain conditions for which such a releasepattern is not suitable. These conditions demand release of drug after a lag time. Inother words, it is required that the drug should not be released at all during the initialphase of dosage form administration. Such a release pattern is known as pulsatilerelease.

Recent studies have revealed that diseases have a predictable cyclic rhythm and thatthe timing of medication regimens can improve the outcome of a desired effect.[15]Thiscondition demands release of drug as a "pulse" after a time lag and such system has tobed designed in a way that complete and rapiddrug release should follow the lagtime.Suchsystemsareknownaspulsatiledrug delivery systems(PDDS),time-controlledsystems, or sigmoidal releasesystems (Fig2).

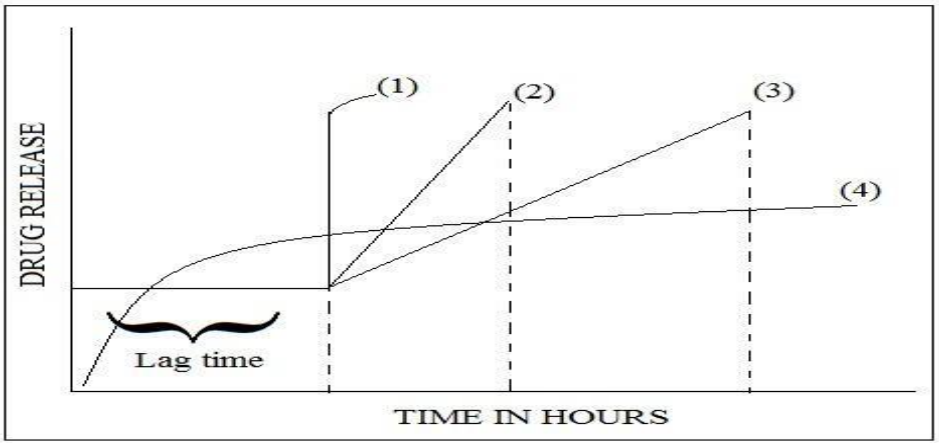


Figure2: Schematic representation of different drug delivery system (1)Sigmoidal release after lag time (2) Delayed release after lag time (3) Sustainedreleaseafterlag time(4) Extended releasewithoutlag time

PDDS have been developed in close connection with emerging Chronotherapeuticsviews. In this respect, it is well established that the symptoms of many pathologies, aswellasthepharmacokineticandpharmacodynamicsprofilesofmostdrugs,aresubjectto circadian variation patterns.

Asfaraswidespreadchronicpathologieswithnightorearlymorningsymptomsareconcerned,suchascardiovasculardisease(CVD),bronchialasthmaandrheumatoidarthritis(RA),remarkableefficacy,tolerabilityandcompliancebenefitscouldarisefrommodifiedreleasemedications.Afterbedtimeadministration,wouldallowtheonsetoftherapeuticdrugconcentrationstocoincidewiththetimeatwhichdiseasemanifestationsaremorelikelytooccur.Performanceofpulsatiledeliveryfulfilssuchgoals.Inadditiontobeingpotentiallysuitableforchronothera

py,pulsatilereleaseisalso exploited to target proximal as well as distal colonic regions via the oral route.[16]Followingarethereasonswhichforcetheinventorstothinkabouttheshiftfromconventionalsustained releaseapproach tothemodern pulsatiledeliveryof drugs.

- **First passmetabolism:**Some drugs like betablockers, and salicylamide,undergoesextensivefirstpassmetabolism.Tominimizethepre-systemicmetabolism,thesedrugsrequirefastdruginputforthesaturationofmetabolizing enzymes. Thus, a constant/sustained oral delivery would reducetheoral bioavailability.
- **Biological tolerance:** The pharmaco-therapeutic effect of the drug declineswith the continuous release of drug plasma profiles. For example biologicaltoleranceof trans-dermalnitro-glycerin.
- **Chrono-pharmacological needs:** According to circadian rhythms, it has beenobserved that symptoms and inception of disease occur during specific timeperiods of the 24 hours a day. For example Asthma, rheumatoid arthritis andanginapectorisattacks aremost frequentlyinthemorninghours.
- **Local therapeutic need:** For the local disorders treatment of such as crohn'sdisease,InflammatoryBowelDisease(IBD),ulcerativecolitisandInflammatory Bowel Syndrome (IBS). The absorption in the small intestine ishighlyadvantageousto attainthetherapeutic effect andto reducesideeffects.
- **Instability of the drugs in GI fluid:** In case of such compounds, the uses of asustainedreleasepreparationarewidelysuggestedandacceptablefromtherapeuticpoint of view.
- **Different drug absorption behavior in GIT:** In common, drug absorption issomewhat slow in the stomach rapid in the small intestine than stomach, andsharplyminimizesinthelargeintestinetocompensatethechangesinabsorption characteristics.[17]

Circadianrhythmsandtheirimplications:

Circadian rhythms are self-sustaining, endogenous oscillation, exhibiting periodicitiesofaboutonedayor24hours.Normally,circadianrhythmsaresynchronizedaccording to the body's pacemaker clock, located in the suprachiasmic nucleus of thehypothalamus.Thephysiology andbiochemistryofhumanbeingisnotconstantduring the 24 hours, but variable in a predictable manner as defined by the timing ofthe peak and through of each of the body's circadian processes and functions.

Thepeakintherhythmsofbasalgastricandsecretion,whitebloodcells(WBC),lymphocytes,prolactin,melatonin,eosinophil,adrenalcorticotrophinhormone(ACTH),folliclestimulatinghormone(FSH),andluteinizinghormone(LH),ismanifestedatspecific timesduring the nocturnalsleepspan. The peakinserumcortisol,aldosterone,testosteroneplusplateletadhesivenessandbloodviscosityfollows later during the initial hours of diurnal activity.Hematocrit is the greatest andairway caliber the best around the middle and afternoon hours, platelet numbers anduricacidpeaklaterduringthedayandevening.Hence,severalphysiologicalprocessesinhumansvary inarhythmicmanner,insynchrony withtheinternalbiologicalclock, as shown in fig.3.[18]

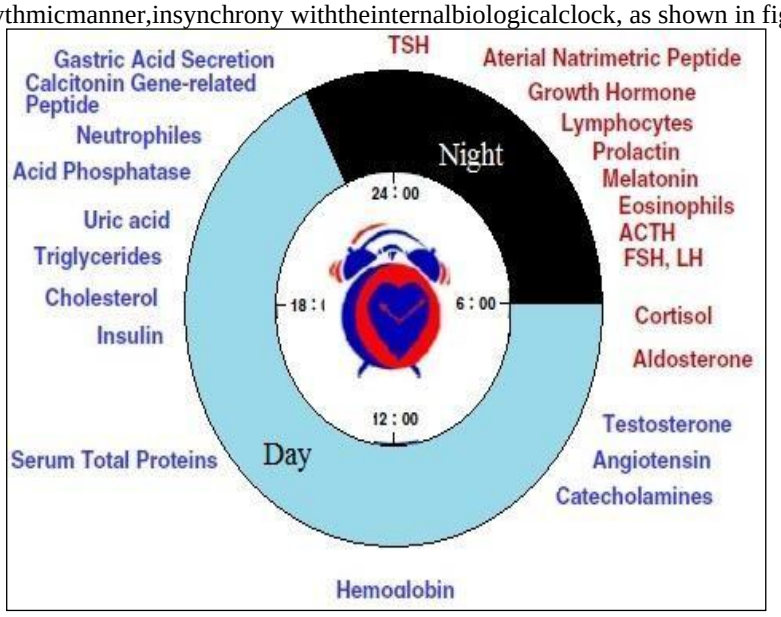


Figure3:Humancircadiantimestructuredependentpulsatilehormonesecretion

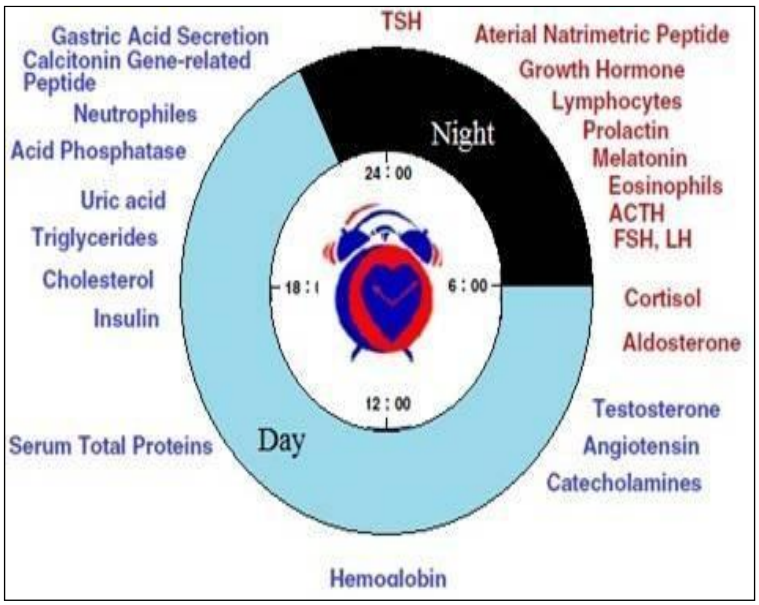


Figure4:Thecircadianpatternof diseases

Through a number of clinical trials and epidemiological studies, it has become evidentthatthelevelsofdiseaseactivity ofnumberofclinicaldisordershaveapatternassociated with the body's inherent clock set according to circadian rhythms. Infectjustasthetimeofdayinfluencesnormalbiologicprocesses,soitaffectsthepathophysiology of disease and its treatment. Examples of some of the diseases areshown inTable 1.

Table1:Circadian rhythmandmanifestation of clinicaldiseases

Diseaseorsyndrome	Circadianrhythmicity
AllergicRhinitis	Worsein themorning/upon rising
Asthma	Exacerbationmorecommonduringthesleep period
RheumatoidArthritis	Symptomsmore commonduringthesleepperiod
Osteoarthritis	Symptomsworseinthemiddle/laterportion ofthe day
AnginaPectoris	ChestpainandECGchangesmorecommoninearly morning
MyocardialInfraction	Incidencegreatestinearlymorning
Stroke	Incidencehigherin themorning
Suddencardiacdeath	Incidencehigherinthemorningafterawakening
Pepticulcerdisease	Worsein lateeveningand earlymorninghours

Chronopharmacotherapy

Recent studies have revealed that diseases have predictable cyclic rhythms andthatthetimingofmedicationregimenscanimproveoutcomeinselectedchronicconditions."Chronopharmaceutics"consistoftwoword sChronobiologyandpharmaceutics.Chronobiologyisthestudyofbiologicalrhythmsandtheirmechanisms.Therearethreetypesof mechanicalrhythms inourbody. Theyare:

i. Circadian
ii. Ultradian
iii. Infradian

Circadian*:*
ThiswordcomesfromLatinword"circa"meansaboutand"dies"meansdayUltradian
OscillationofshorterdurationaretermedasUltradian(morethanonecycleper24h)Infradian
Oscillationsthat arelongerthan 24 h (lessthan onecycle perday.[19]

1.3.2 Diseaseswithestablishedcircadianrhythms

The diseases recently targeted for pulsatile drug delivery are those which have enoughscientific background to justify chronopharmaceutical drug delivery system

comparedtoconventionaldrugadministrationTheseincludeasthma,arthritis,duodenalulcer, Cancer,cardiovasculardiseases,diabetes,hypercholesterolemia,neurologicaldisordersetc. which havegood circadianrhythm.[20]

- **Duodenalulcer**

Generallygastricacidsecretionishighestintheeveninginduodenalulcerpatientsand decreases in the early morning.[21]One group of authors studied incidence of ulcerperforation for daily (circadian), weekly (circaseptan) and yearly (circannual) timeeffects. A circadian rhythm has been found overall that was reproducible and fairlystable across seasons, decades, and days of the week. Duodenal perforations showedhighest incidence in the afternoon, while gastric perforations showed a major peakaround noon and a secondary peak near midnight. For duodenal ulcer perforation, thecircannual pattern was characterized by a 6-month rhythm, with significantly higherincidencein May–June–Julyand in November– December in most subgroups.[22]

- **Bronchialasthma**

It is characterized by airway inflammation resulting in hyper responsiveness of lowerrespiratorytracttovariousenvironmentalstimuli.[23]Airwayresistanceincreasesprogressively at night in asthmatic patient. This asthma known as nocturnal asthma isan exacerbation of asthma with increase in symptoms, airway responsiveness andlungfunction.Indaytimeantigenprovokesthereleaseofpro-inflammatorymediators from mast and eosinophils cells over the span of long hours resulting inexacerbation of inflammation, smooth muscle bronchospasm and contraction, over-stimulation of mucus glands with mucus hypersecretion of the small airways of thelung.Itisagoodtargetforchronotherapybecausebronco-constrictionandexacerbation ofsymptoms varyon circadian fashion.[24]

- **Allergicrhinitis**

Common symptoms of allergic rhinitis are sneezing, nasal rhinorrhea red itchy eyes,nasal pruritus and nasal congestion.[25] Each of the symptoms was found to occur mostfrequentlybeforebreakfastandinthemorningandleastfrequentlyinthemiddleoftheday.Therearetwophasesofoccurrenceofallergicrhinitisi.e.earlyphase(developing within minutes) and late phase (manifesting after 12–16 h). The earlyphasehappensduetoreleaseofhistamine,prostaglandins,cytokines,TNF-α,Chemotactic factors etc resulting in sneezing, nasal itch, rhinorrhea. On the other handlatephaseisshownduetoelaboration,adhesionandinfiltrationofcirculatingleukocytes, T cells and eosinophils evoking nasal congestion, obstruction due to theexacerbationofinflammation ofthe nasal,sinus andothertissueoftheupper airway.

- **Pain**

Pain control is one of the most important therapeutic priorities. Although numerousclinical practiceguidelinesfor pain management have been published, inadequatepain relief remains a significant health care issue. It was reported that the highestthreshold occurred at the end of the resting period, while the least threshold was seenat the end of the activity period. In arthritis there is circadian rhythm in the plasmaconcentrationofC-reactiveproteinandinterleukin-6ofpatientwithrheumatoidarthritis.Besides,differentopioidpeptideslike5-hydroxytryptamine,bradykinin,glutamate, NO, substance P, cytokines and prostanoids are involved in the activationof receptors. Brain concentration of substance P in rat model is highest in night withcompared to daytime. It was reported that levels of endogenous opioid peptides arehigher at the starting point of the day and lower in the evening both in neonate andadult human volunteers. Patients with osteoarthritis tend to have less pain in themorning and more at night. While patients with rheumatoid arthritis have pain thatusuallypeaksinthemorninganddecreasesthroughoutday.Thesymptomsareswelling of finger and pain at joint.[26] Patients with gastro-esophageal reflux diseasefeel night time pain. But renal colic shows morning peak independent of gender andpresence or absence of visible kidney stones. The choice of analgesics and the route oftheiradministrationdependonthenatureanddurationofthepain.Aspirin,paracetamol, NSAIDs and morphinomimetics are indicated against nociceptive pain,while anticonvulsants, tricyclic antidepressants and local anesthetics are used againstneurogenic pain.[27]

- **Cardiovasculardiseases**

In cardiovascular disease capillary resistance and vascular reactivity are higher in themorninganddecreaseslatterintheday.Plateletagreeabilityisincreasedandfibrinolyticactivityis decreased in themorning, leadingto astateofrelativeHypercoagulability of the blood. Because of this reason the frequencies of myocardialinfarction and of sudden cardiac death are more prone during from morning to noon.Ambulatory blood pressure measurements show a significant circadian variation tocharacterize blood pressure. This variation is affected by a variety of external factorssuchasethnicity,gender,autonomicnervoussystemtone,vasoactivehormones,hematologicandrenalvariables.Increasedheartrate,bloodpressure,imbalancedautonomictone,andcirculatinglevelofcatecholaminecontrollingthecardiacarrhythmias show important circadian variation and trigger the genesis of the circadianpattern ofcardiacarrhythmias.[28]Atrial arrhythmias appear to exhibit circadian pattern usually with a higher frequencyin the daytime and lower frequency in the night time with the abnormal foci under thesame long-term autonomic regulation as normal pacemaker tissue. According to studyventricular tachyarrhythmia show late morning peak in the patients with myocardialinfarction sometime in the distant past morning peak and afternoon peak in patientswithrecentmyocardialinfarction.Myocardialischemia,anginapectoris,acutemyocardial infarction, and sudden cardiac death are also unevenly distributed duringthe 24 h with greater than expected events during the initial hours of the daily activityspan,inthelateafternoonorearlyevening.[29]Bothpharmacokineticsandpharmacodynamics of some oral nitrates, calcium channel blocker and β-adrenoceptorantagonistmedicationshavebeenshowntobeinfluencedbythecircadiantimeoftheiradministration.

- **RheumatoidArthritis(RA)**

The Chronobiology, chronopharmacology and Chronotherapeutics of pain have beenextensivelyreviewed.Forinstance,thereisacircadianrhythmintheplasmaconcentration of C-reactive protein 26 and interleukin-627 of patients with rheumatoidarthritis. Patients with osteoarthritis tend to have less pain in the morning and more atnight,whilethosewithrheumatoidarthritis,havepainthatusuallypeaksinthemorning and decreases throughout the day. Chronotherapy for all forms of arthritisusing NSAIDs such as Ibuprofen should be timed to ensure that the highest bloodlevelsof

the drugcoincide with peak pain.

- **Sleepdisorder**

Many biological signaling e.g. sleep disorder occurring in the central and autonomousnervous systems show complex time structure with rhythm and pulsatile variations inmultiple frequencies. The time of sleep required by each person is usually constant,although there is a wide variation among individuals.[30] Sleep consists of a rhythmic(circadian)combinationofthechangesinphysiological,biochemicalandpsychologicalprocesses.Whenthecircadianrhythmisdisturbed,orwhentheindividual 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 severesleep-onset insomnia) normally, sleep is impossible until 3 a.m. or later until there isgreatdifficultyinawakeninginthemorningsatthenormaltime.Theabilitytocopeupwithcircadianrhythmdisturbancesalsodiffersfrompersontoperson.Identificationoftheindividualvariationwouldbeofimportanceindealingwithcertainsleep disorders.

1.3.3 ClassificationofPDDSdependingonTargetrelease.

Fromtechnologypointofviewpulsatiledrugdeliverysystemarefurtherdividedtosingleand multiple units system

a) Singleunitsystem

- **Capsularsystem:**

Different single-unit capsular PDDS have been developed (Fig 5). A generaldesign of such systems consists of an insoluble capsule body housing a drug and aplug. The plug is removed after a predetermined time lag due to swelling, erosion ordissolution. The Pulsincap® system is an example of such a system that is made up ofa water-insolublecapsule body filled with drugformulation.[33]The body is closedattheopenendwithaswellablehydrogelplug.Uponcontactwithdissolutionmediumor gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a timelag. This is followed byaspontaneous releaseof thedrug(Fig5).

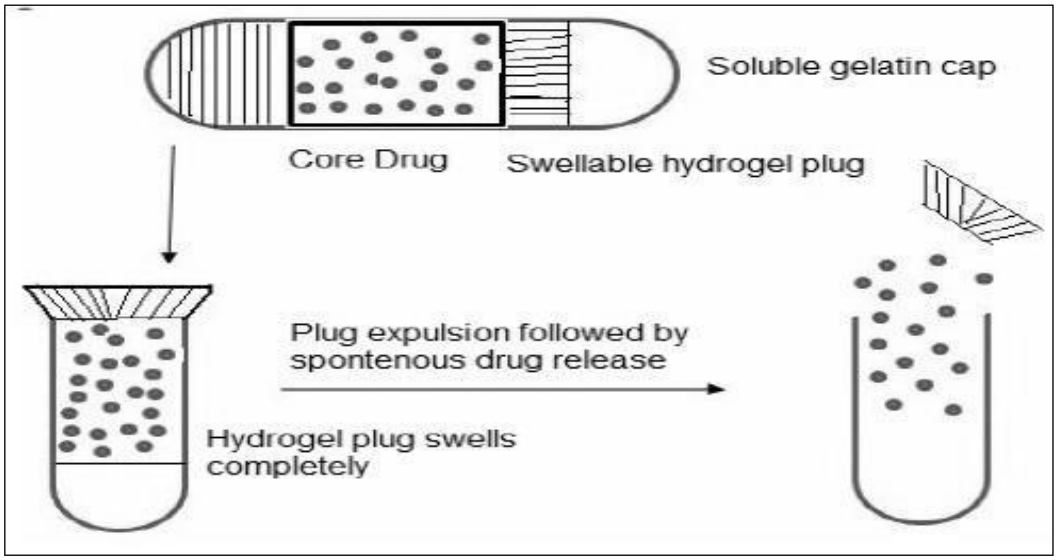


Figure5:Schematicdiagramof capsularsystem

The time lag can be controlled by manipulating the dimension and the position of theplug. For water insoluble drugs, a spontaneous release can be ensured by inclusion ofeffervescentagentsordisintegrants.Theplugmaterialconsistsofinsolublebutpermeableandswellablepolymers[34](e.g.polymethacrylates) erodiblecompressedpolymers (e.g. hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide),congealed melted polymers (e.g. saturated polyglycolated glycerides, glycerylmonooleandenzymaticallycontrollederodiblepolymere.g.pectin).Theseformulationsare
well tolerated in animals and healthy volunteers, and there have been no reports ofgastro-intestinal irritation. However, there was a potential problem of variable gastricresidencetime,whichwasovercomebyentericcoatingthesystemtoallowitsdissolution onlyin thehigher pHregion of small intestine.[35]

- **Portsystems**

The PortSystemconsistsof agelatincapsulecoated witha semipermeablemembrane (e.g.celluloseacetate)housing aninsoluble plug (e.g.lipidic) andanosmotically active agent along with the drug formulation. When it comes in contactwiththeaqueousmedium,waterdiffusesacrossthesemipermeablemembrane,resulting in increased inner pressure that ejects the plug after a lag time. The lag timeis controlled by the thickness of semi permeable membrane. The system showed goodcorrelation in lag times of *in-vitro* and *in-vivo* experiments in humans. In order todeliver drug in liquid form, an osmotically driven capsular system was developed. Inthis system, liquid drug is absorbed into highly porous particles, which release thedrug throughan orifice of a semi permeable capsulesupported by anexpandingosmotic layer after the barrier layer is dissolved. The capsular system delivers drug bythe capsule's osmotic infusion of moisture from the body. The capsule wall is made upof an elastic material and possesses an orifice. As the osmosis proceeds, the pressurewithinthecapsulerises,causingthewalltostretch.Theorificeissmallenoughsothat when the elastic wall relaxes, the flow of the drug through the orifice

essentiallystops,butwhentheelasticwallisdistendedbeyondthresholdvalue,theorificeexpands sufficiently to allow drug release at a required rate. Elastomers, such asstyrene-butadienecopolymerhavebeen suggested.[36]

- **Osmoticbasedpumpcapsule**

Osmotic delivery capsules ("osmotic pumps") function by virtue of walls whichselectively pass water into the capsule reservoir. Absorption of water by the capsulethrough these walls is driven by a water-attracting agent in the capsule interior whichcreates osmotic pressure across the capsule wall. The water-attracting agent may bethe beneficial agent itself whose controlled release is sought, but in most cases, it is aseparateagentspecifically selectedfor itsability todrawwater,andthisseparateagentisbeingisolatedfromthebeneficialagentatoneendofthecapsule.Ineither
Case, the structure of the capsule wall does not permit the capsule to expand, and as aresult, the water uptake causes discharge of the beneficial agent through an orifice inthe capsuleat thesame rate that water enters byosmosis.

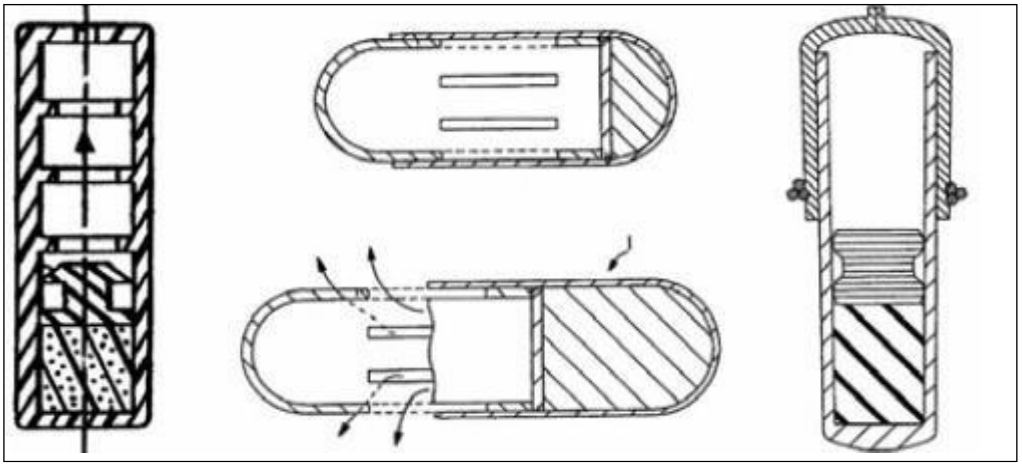


Figure6:Differenttypeof osmoticpumpsusedforPDDS

Linkwitz and co-workers proposed a drug delivery capsule where drug delivery isdriven by the osmotic infusion of moisture from a physiological environment. Thecapsulehasadeliveryorificewhichopensintermittentlytoachieveapulsatiledelivery effect. The wall in which the orifice is formed is constructed of an elasticmaterial(Elastomers) which stretchesunder a pressure differentialcausedby thepressure rise inside the capsule as the osmotic infusion progresses. The orifice is sosmall that when the elastic wall is relaxed, the flow rate of drug through the orifice issubstantiallyzero,butwhentheelasticwallisstretchedduetothepressuredifferential across the wall exceeding a threshold, the orifice expands sufficiently toallow the release of the drug at a physiologically beneficial rate. The selection of thematerials from which the device is constructed and the configuration of the device anditsdimensions controls thelength of time between pulses.[37]

- **Drugdeliverysystemwitheroding orsolublebarrier coating**

In this systems drug reservoir surrounded a soluble barrier layer that dissolves withtime, and the drug releases at once after this lag time. Chronotropic system consists ofa core containing drug reservoir coated by a hydrophilic polymer HPM[38,39]Anadditional enteric coated variability in gastric emptying this layer to overcome intrasubjectvariabilityingastricemptyingrates.Thelagtimeandtheonsetofactionare
controlledbythe thickness andtheviscositygradeofHPMC. Thetime clocksystem isadeliverydevicebased onsolid dosageform thatis coated byanaqueous dispersion.

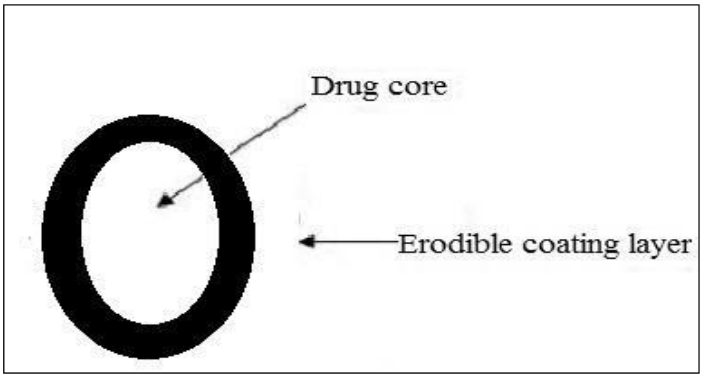


Figure7: Schematicdiagramof delivery systemoferodiblecoating layer

This coating is a hydrophobic surfactant layer which a water-soluble polymer is addedto improve adhesion to the core. Contact with the dissolution fluid, the dispersionrehydrates and redisperses. The lag time could be controlled by the thickness of thefilm. After the lag time, i.e., the time required for rehydration, the core immediatelyreleases the drug. This system has shown reproducible results in vitro and in vivo. Theeffect of low calorie and high calorie meal on the lag time was studied using gagmanscinintigraphy. The mean lag time of drug releases was 345 and 333 min respectively.Midha et al developed palatial a pulsatile delivery system for d-threomethyl phenidatean additional CNS stimulant in a dosage form comprising at least two individual drugscontaining dosage limit housed in a closed capsule. The dosage units are designed inthe formof compressed tablets[40]

The first drug release pulse occurs within 1-2h, followed by a lag period during whichnoreleaseoccurs.Seconddoseisreleasedin-3-5hofingestion.Seconddoseisreleases in-3-5h of ingestion. This is again followed by a second no-release interval.Release of third dose occurs within 7-9 h of ingestion. To provide such delayed-releasedosageunits,coatingisdonewithoutbioerodiblegraduallyhydrolysablepolymers. The release amount of coating material per dosage unit decides the timeinterval between interval and drug release. Dittigen et. al. invented a multiple unitdosage form Comprising of compressed compositions having different amounts ofingredientsandcombination.[41]Hormones,viz.,progesterone,testosterone,dehydroepiamdrsteron,theirconcentrationinbloodvariesover24h.oftheanalogues andinhibitorysubstancesforthesehormonesalsofollowacircadianrhythm.Examples of such classes include antihistamines. Glucocorticoids, mineral corticoidsandantihistamines. The formulation comprises of four compressed in a capsule. Thefirst composition is formed to provide rapid releases ina capsule.Inwhich at least75% of the effective ingredients are delivered within 45 min the second compressedcombinationprovidesauniformlymaintainedreleaseprofileinwhich100%ofeffective ingredient is released within 3 of ingestion. Third compressed combinationdelivers at least 75% of effective ingredient within 45 min of reaching duodenum andintestine at a pH of 6 to 7.5 Coating is given by gastric-resistant agents (PMMA orshellac). Fourth compressed composition releases 100% of the effective ingredient 3 hafter reachingpH of6-7.[42]

- **Drugdeliverysystemwithrupturablelayer:**

A novel formulation for once daily administration (prior to sleeping) that provides aninitial delay followed by controlled release of the drug. A method for preparing a timespecificdelayed,controlledreleaseformulationodosageisalsoprovidedwhichmethod includes coating a single pellet with at least one dosage layer, which is coatedby at least one seal coat and at least one outer rate controlling layer of a water solublepolymercoat.

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 drugto onlyoncedaily.

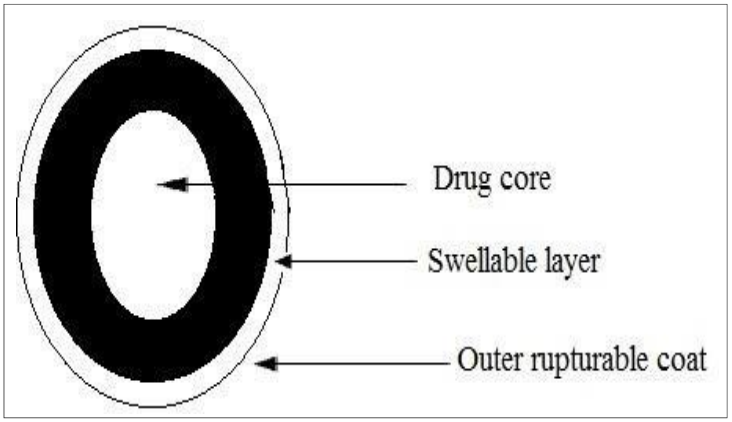


Figure 8: Schematic diagram of delivery system with rupturable coatinglayer

b) MultipleUnits

- **SystemsBasedonChangeinMembranePermeability**

Numerouspharmaceuticalformswithavailable.Asalreadymentioned the delayedreleasefororaladministrationarereleaseofthedrugmustbecontrolled according to therapeutically purposeandthe pharmacological properties of theactive ingredient. In consequence, it is not always desirable the blood levels to beconstant. On thecontrary, inordertoavoidany habituationand in ordertolimitthesideeffectsprovokedbytheactiveingredient,itwouldbeabsolutelyadvantageousfortheplasmaticratetofollowthemetabolicrhythmandthespecificneedsofthepatientduringcertainperiods.Forinstance,inordertodiminishthenocturnalsymptomsorthesymptomsuponawakeninginthecaseofcertainchronicdiseasessuchasischemicheartdisease,asthmaand arthritis,the drugs should be administered in such awaythatthedesiredtherapeuticalplasmaticlevelisreached only at the desired moment, i.e. during sleep orat themomentofawakeningDosageformforPulsatilereleaseproposedbyChencontainingapluralityofdifferentpelletscomposedwithacoreandseveralcoatinglayers.Chendescribedadosageformfordeliveringdrugsintothebodyinaseriesofsequential,pulsatilereleasing events.Thesystem canbeusedwithdrugs which cannot be released by diffusion through a porous coating, such as waterinsoluble drugs. A plurality of populations of pellets is provided within a unit dosageform such as a capsule or tablet Fig. (9) Dosageformfor pulsatile release proposedby Chen containing a plurality of different pellets composed with acore and severalcoatinglayers.Thepelletsarecomposedofacorecontainingthedrugandawelling agentwhichexpandsinvolumewhenexposedtowater.Thecoreisenclosedwithinamembraneorcoatingwhichis permeabletowater.Themembraneiscomposedofawaterinsolubleandpermeablefilmformingpolymer,a watersolublefilmformingpolymerandapermeability reducing agent.Whenthe unit dose releases the pellets intothedigestivetract,water diffuses throughthe coatingandintothecore.Aswateristakenupbythe swellingagent,thecoreexpands,exertingforceonthe coating until it bursts, releasing thedrug. The permeabilityreducingagentreducestherateatwhich water reachestheswellingagent,therebydelaying releasetime.

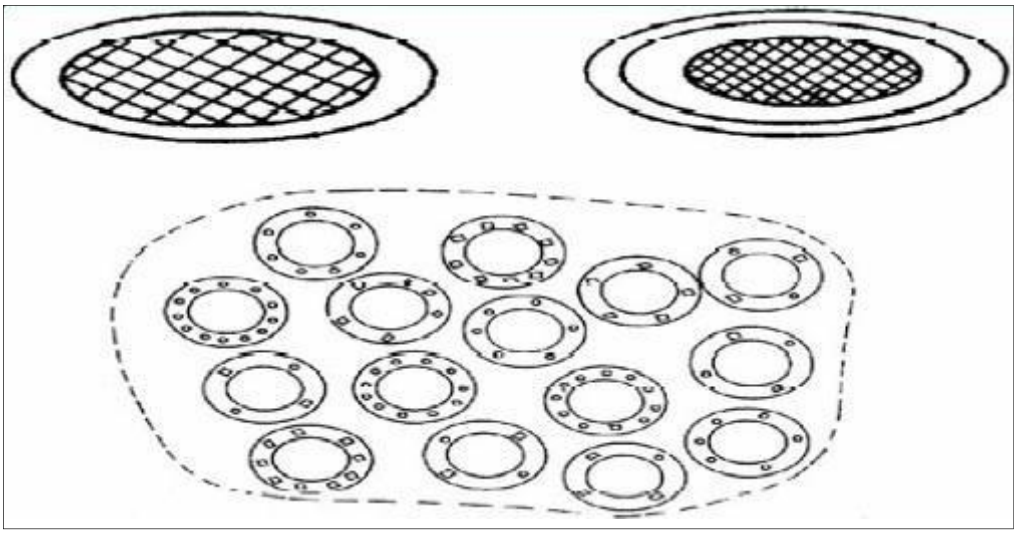


Figure9: Pulsatilereleasedosageformproposedby Chen

Thewatersolublepolymerdissolves,weakeningthecoating sothatitburstssooner. By varying the proportionsofthethreecoating ingredientsand/or coatingthicknessfromonepelletpopulationtoanother, thereleasetimingofthepelletscanbeveryeffectivelycontrolled.[43]

1.3.4 ApproachesofPulsatileDrugDeliveryDependingonTargetRelease

- **Timecontrolleddeliverysystem:**

The principle of time controlled drug delivery systems is that the release of the drughappens according to a predetermined rate so to achieve maximum therapeutic andminimum toxic effect. Systems having a lag phase (delayed release systems) andsystems where the release is following a biological circadian rhythm are the mostcommonly used controlled release systems. As already mentioned the delayed drugrelease for meeting chronotherapeutical needs provides optimum drug delivery for anumber of widespread chronic pathologies. Most delayed release delivery systems arereservoir devices covered with a barrier coating, which dissolves, erodes or rupturesafter a lag phase. Well known coating techniques are applied to pellets and tablets todelay drug's release. Conventional coatings dissolve slowly to release drugs into theintestine.Anotherwell-knowncoatingtechniqueemploysawater-permeablebutinsoluble film which encloses the active ingredient and an osmotic agent. As waterfrom the gut slowly diffuses through the film into the core, the core swells until thefilm bursts, releasing the drug. The film coating may be adjusted for selecting suitablerates of water permeation, and thereby, release time. Alternatively, the tablet coatingmay be impermeable, and water enters through a controlled aperture in the coatinguntilthecorebursts.Whenthetabletbursts,thecontentisreleasedimmediatelyor overalongerperiodoftime.Theseandothertechniquesmaybeemployedtoformulatetabletsorcapsuleswiththe requisitetimeintervalbeforedrugrelease.

Ting describeda presscoated, pulsatile drug delivery systemsuitablefororaladministration,havingan immediate-release compartment, made by a compressedblendofanactiveagentandoneormorepolymers, envelopedby an extended-releasecompartment,made byacompressedblendoftheactiveagentandhydrophilic and hydrophobic polymers, able to provide a first order delivery of theactiveagent,interrupted by a timed,pulseddeliveryofanincreasedamountoftheactiveagent.Whentheextendedreleasecompartmentisenvelopedbyanoptionalinstantreleasecompartment, canprovideadose sufficient to exceedtheliver'smetaboliccapacityandtomaintaintherapeuticlevels,preferablythroughout a 24-hourperiod.[44]

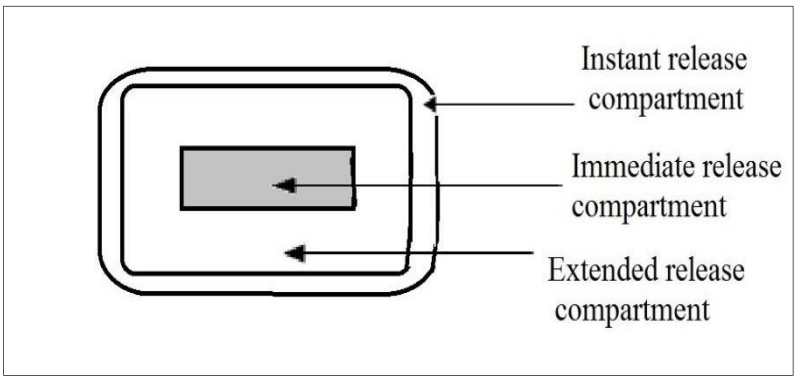


Figure10:PressCoateddrugdeliverysystemdescribedbyTing

- **pHsensitivedrugdeliverysystem**

This type of PDDS contains two components. The first is fast release type while theother is pulsed release which releases the drug in response to change in pH. In case ofpHdependentsystem,advantagehasbeentakenofthefactthatthereexistsdifferentpHenvironmentatdifferentpartsofthegastrointestinaltract.ByselectingthepHdependentpolymers drug release at specific location can be obtained. Examples of pH

dependentpolymersincludecelluloseacetatephthalate,polyacrylates,andsodiumcarboxymethylcellulose. These polymers are used as enteric coating materials so as toprovidereleaseofdruginthesmallintestine.[45]

- **Enzymes PresentintheIntestinalTract**
  Severalprodrugsrelyoncolonicbacteriaforrelease.Inthesesystems,colonicbacteria are utilized to degrade the substrate. The bacterial amount has been estimatedabout1011pergraminthe colon.The bacterialspeciesinthe colonhave beenestimated to be around 400 (anaerobic in nature). In the past, polymers cross linkedwith azo-aromatic groups have been used to achieve colonic drug delivery. The firstsuch compound that came out in the market was sulphasalazine, a prodrug consistingby 5 aminosalycilic acid linked by an azo bond to sulphapyridine. When the chemicalentity was reaching the site of action (colon) a reduction reaction was taking place andthe5aminosalycilicacidwasbecomingavailable.However,duetopotentialcarcinogenicactivityazo-aromaticcompoundshavenowreplacedwithnaturalpolysaccharides.Naturalpolysaccharidessuchasamylosechitosan,dextran,guargum , and pectin are currently investigated for colonic delivery. To overcome problemsof premature release due to their hydrophilic nature they are usually mixed with waterinsoluble polymers. Nevertheless, no granted patents on enzymatic drug delivery havebeen found.[46]
- **Inflammation-inducedpulsatilerelease**
  Onreceivinganyphysicalorchemicalstress,suchasinjury,fractureetc.,inflammation take place at the injured sites. During inflammation, hydroxyl radicalsareproducedfromtheseinflammation-responsivecellsYuiandco-workersfocusedon the inflammatory induced hydroxyl radicals and designed drug delivery systems,whichrespondedtothehydroxylradicalsanddegradedinalimitedmanner.Theyused hyaluronic acid (HA) which is specifically degraded by the hyaluronidase or freeradicals. Degradation of HA via the hyaluronidase is very low in a normal state ofhealth. Degradation viahydroxylradicalshowever, isusually dominantand rapidwhen HA is injected at inflammatory sites. Thus, it is possible to treat patient withinflammatorydiseaseslikerheumatoidarthritis;usinganti-inflammatorydrugincorporated HAgels asnew implantabledrugdeliverysystems.[47]
- **Glucose-responsiveinsulinreleasedevices**
  Incaseofdiabetesmellitusthereisrhythmicincreaseinthelevelsofglucoseinthebodyrequiringinjectionoftheinsulinatpropertime.Several systemshavebeen developed which are able to respond to changes in glucose concentration. One suchsystemincludespHsensitivehydrogelcontainingglucoseoxidaseimmobilizedinthe hydrogel. When glucose concentration in the blood increases glucose oxidaseconverts glucose into gluconic acid which changes the pH of the system. This pHchangeinduces swellingofthe polymer which results in insulin release.[48]
- **Externallyregulatedsystems**
  For releasing the drug in a pulsatile manner, another way can be the externallyregulated systems in which drug release is programmed by external stimuli likemagnetism,ultrasound,electricaleffectandirradiation.Magneticallyregulatedsystem contains magnetic beads in the implant. On application of the magnetic field,drugreleaseoccurs because of magneticbeads.[49]

1.3 DrugandExcipientsProfile

1.4.1 Drugprofile

Name: **NIZATIDINE**[50,51,52]

StructuralFormula:

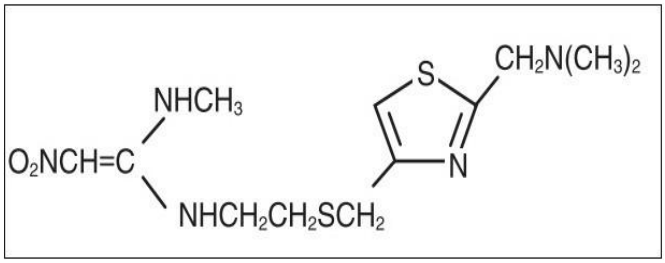


Figure11:structureof Nizatidine

MolecularFormula: $C_{12}H_{21}N_5O_2S_2$

Molecularweight (M_t): 331

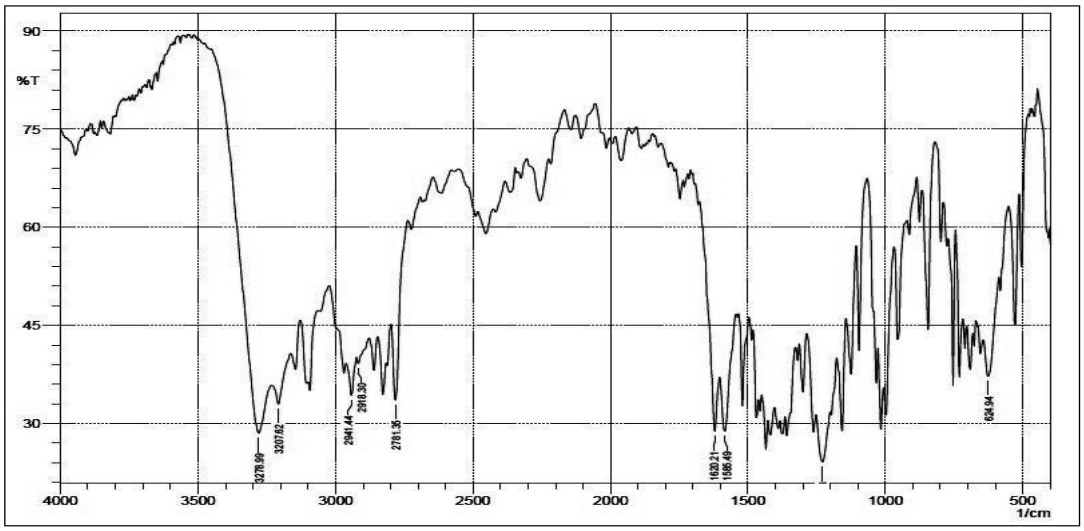
CASnumber: 76963-41-2

1,1-Ethenediamine,N-[2-[[[2-[(dimethylamino)methyl]-4-thiazolyl]methyl]thio]ethyl]-N-methyl-2-nitro

MeltingRange: 131ºC to 134ºC

IRspectra:

Figure12:IRspectraof Nizatidine



Nizatidineoccursinalmostwhiteorslightlybrownish,crystallinepowder.

Solubility: Nizatidine is freely soluble in chloroform, soluble inmethanol,solubleinwaterandbufferedsolutionslightlysolubleinethylacetateandosopropranolol

Nizatidineisessentiallyinsolubleinbenzene,diethyletherand octanol

λ_{Max}: 314nm.

Half life: The elimination half-life is 1 to 2 hours**Volumeof Distribution:** Thevolumeofdistributionis0.8to1.5L/kg.**Protein Binding**: 35%

Bioavailability: 70-80%

The recommended oral dosage for adults is 300 mgonce daily at bedtime. An alternative dosage regimenis150 mgtwicedaily.

Pharmacokinetics: The absolute oral bioavailability of Nizatidine exceeds70%.Peakplasmaconcentrationsoccurfrom 0.5to3hoursfollowingthedose.Plasmaconcentrations 12 hours after administration are lessthan 10 mcg/L. The elimination half-life is 1 to 2hours,plasmaclearanceis40to60L/h,andthevolume of distribution is 0.8 to 1.5 L/kg. Because ofthe short half-life and rapid clearance of Nizatidine,accumulation of the drug would not be expected inindividualswithnormalrenalfunctionwhotakeeither 300 mg once daily at bedtime or 150 mg twicedaily.Nizatidine exhibitsdose proportionality overthe recommended dose range. The oral bioavailabilityof Nizatidine is unaffected by concomitant ingestionofPropanthelne.Antacidsconsistingofaluminumandmagnesiumhydroxideswithsimethiconedecrease the absorption of Nizatidine by about 10%.Withfood,theAUCandCmaxincreasebyapproximately 10%. In humans, less than 7% of anoraldoseismetabolizedasN2-monodesmethylNizatidine, an H_2-receptor antagonist,whichistheprincipalmetaboliteexcretedintheurine. Other likely metabolites are the N2-oxide (lessthan 5%ofthedose)andtheS-oxide(lessthan6% of

thedose).Morethan90%ofanoraldoseofNizatidine is excreted in the urine within 12 hours.About 60% of an oral dose is excreted as unchangeddrug. Renal clearance is about 500 mL/min, whichindicates excretion by active tubular secretion. Lessthan 6% of an administered dose is eliminated in thefeces.Moderatetosevererenalimpairmentsignificantly prolongs the half-life and decreases theclearanceofNizatidine.Inindividualswhoarefunctionally anephric, the half-life is 3.5 to 11 hours,and the plasma clearance is 7 to 14 L/h. To avoidaccumulationofthedruginindividualswithclinicallysignificantrenalimpairment,theamountand/orfrequency ofdosesofNizatidineshouldbereducein proportion to theseverityof dysfunction

Approximately 35% of Nizatidine is bound to plasmaprotein,mainlytoα1-acidglycoprotein.Warfarin,diazepam, acetaminophen, propantheline,phenobarbital, and propranolol did not affect plasmaprotein bindingof Nizatidinein vitro.

MechanismofAction: Nizatidine(H_2receptorantagonists)inhibitacid productionby reversibly competing withhistamineforbindingtoH_2receptorsonthebasolateralmembraneofparietalcells.Thesedrugsarelesspotent than proton pump inhibitors but still suppress24-hourgastricacidsecretionbyabout70%.Nizatidineispredominantlyinhibitingbasalacidsecretion,whichaccountsfortheirefficacyinsuppressingnocturnalacidsecretion.Becausethemost important determinant of duodenal ulcer healingisthelevelofnocturnalacidity,eveningdosingof Nizatidineisadequatetherapyinmostinstances.Nizatidine also maystimulate GImotility

NizatidineisanH_2antagonistusedinmanagementofbenigngastricandduodenalulcerandNSAIDassociatedulceration.Ingastro-esophagealrefluxdisease an oral dose of150 to 300mg twice daily for12 week.for theshortterm symptomaticreliefofdyspepsia an oral dose of75 mg

The major therapeutic indications for Nizatidine (H_2receptor antagonists)isto promote healing of gastricand duodenal ulcers, to treat

uncomplicated GERD,andto prevent theoccurrenceofstress ulcers.

Contraindications: Nizatidineiscontraindicatedinpatientswithknown hypersensitivitytothedrug.Becausecross-sensitivityinthisclassofcompoundshasbeenobserved,H_2-receptorantagonists,includingNizatidine,shouldnotbeadministeredtopatientswith a history of hypersensitivity to other H_2-receptorantagonists.

Headache,dizziness,drowsiness,constipation,diarrohea,stomachpain,runnynose,sneezing,coughing,sweating

Nizatidine should be used with caution in: patientswithkidneyorliverproblems,womenwhoarepregnantor whoare breastfeeding,andcare shouldbe taken in those whose symptoms change and whoare middle-aged or older as this drug can mask thesymptomsofgastric cancer.

DosageForm: Tablet,capsule,solution.

Storeinatightlyclosedcontaineratroomtemperature between 59-86 degrees F (15-30 degreesC)awayfrom moistureand light.

1.4.2 Name: CROSCARMELLOSESODIUM[53]

Synonyms: Ac-di-sol,Modifiedcellulosegum

CASRegistryNumber: 74811-65-7

FunctionalCategory: Tabletandcapsuledisintegrant.

IRspectra:

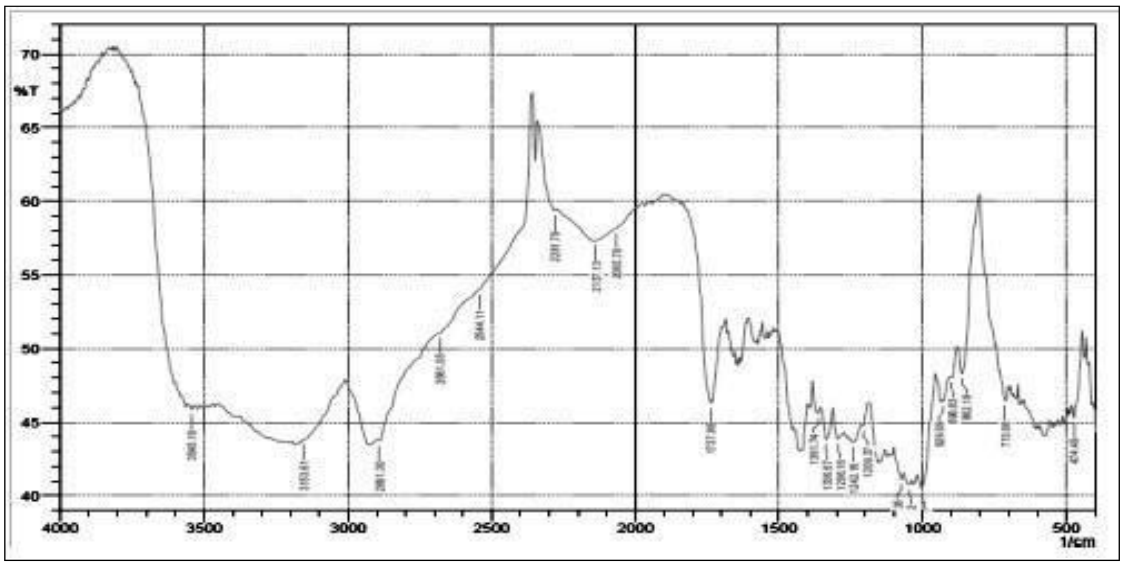


Figure13:IRspectraof croscarmellosesodium

Croscarmellose sodium is used in oral pharmaceuticalformulations as a disintegrant for capsules, tablets,and granules. In tablet formulations, croscarmellosesodium may be used in both direct-compression andwet-granulationprocesses.Whenusedinwetgranulations,thecroscarmellosesodiumshouldbeadded in both the wet and dry stages of the process(intra- and extra granularly) so that the wicking andswelling ability of the disintegrant is best utilized.Croscarmellose sodium at concentrations up to 5%w/wmaybeusedasatabletdisintegrant,although

normally 2% w/w is used in tablets prepared by directcompression and 3% w/w in tablets prepared by awet-granulationprocess.Croscarmellosesodiumisusedinoralpharmaceuticalformulationsasadisintegrantfor capsules,andgranules,

Disintegrant in tablets in 0.5-5.0% concentration,Disintegrantincapsulein10-25%concentration

Croscarmellose sodium occurs as an odorless, whiteorgrayish white powder.

Insoluble in water, although croscarmellose sodiumrapidly swells to 4–8 times its original volume oncontact with water. Practically insoluble in acetone,ethanoland toluene.

StabilityandStorage: Croscarmellose sodium is a stable though hygroscopicmaterial.Amodeltabletformulationprepared by direct compression, with croscarmellosesodiumasadisintegrant,showednosignificantdifferenceindrugdissolutionafterstorageat308Cfor14months.Croscarmellosesodiumshouldbestored in a well-closedcontainer in acool,dryplace.

Incompatibilities: Theefficacyofdisintegrants,suchascroscarmellose sodium,maybeslightlyreducedintabletformulationspreparedby either the wet-granulationordirect-compressionprocessthatcontainhygroscopicexcipientssuchassorbitol.Croscarmellose sodium is not compatible with strongacids or with soluble salts of iron and some othermetalssuch asaluminum, mercury,andzinc.

1.4.3 Name: LACTOSE [53]

Lactochem, lactosum monohydricum, MonohydratePharmatose.

MolecularWeight: 360.31

CASRegistryNumber: 64044-51-5

Structure:

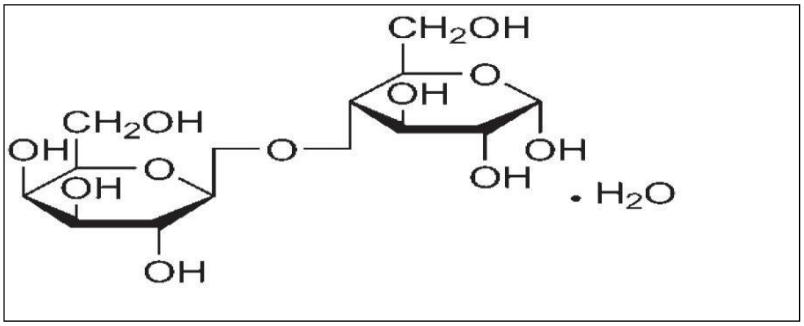


Figure14:Structureof lactose

EmpiricalFormula: $C_{12}H_{22}O_{11}\cdot H_2O$

IRspectra:

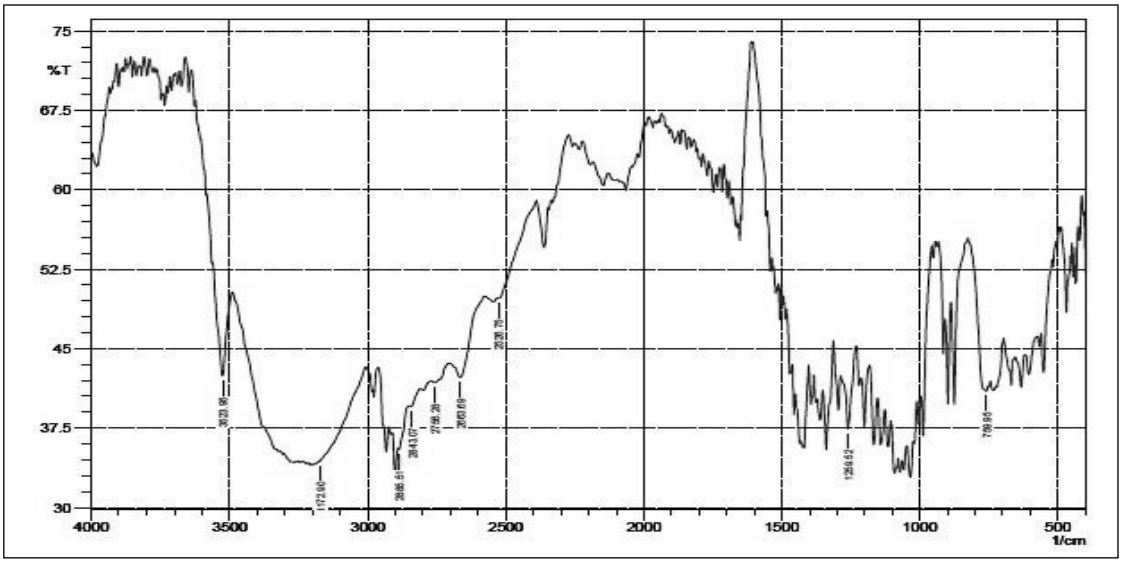


Figure15:IR spectraof lactose

FunctionalCategory: Bindingagent, diluentsfordry-powderinhalers, tabletbinder,tabletandcapsulediluents.

Lactose is widely used as filler or diluents in tabletsandcapsules,andtoamorelimitedextentinlyophilized products and infant formulas. Lactose isalsousedasadiluentindry-powderinhalation.Variouslactosegradesarecommerciallyavailablethat have different physical properties such as particlesizedistributionandflowcharacteristics.Thispermits the selection of the most suitable material fora particular application; for example, the particle sizerange selected for capsules is often dependent on thetypeofencapsulatingmachineused.Usually,finegrades of lactose are used in the preparation of tabletsbythewet-granulationmethodorwhenmillingduring processing is carried out, since the fine sizepermitsbettermixingwithotherformulationingredientsandutilizesthebindermoreefficiently.

In the solid state, lactose appears as various isomericforms,depending on the crystallization and dryingconditions,i.e.α-lactosemonohydrate,β-lactoseanhydrous,andγ-lactoseanhydrous.Thestablecrystallineformsoflactosareα-lactosemonohydrate,β-lactoseanhydrousandstableγ-lactose anhydrous. Lactose occurs aswhite tooff-whitecrystallineparticlesorpowder.Lactoseisodorlessandslightlysweet-tasting;α-lactoseisapproximately20%assweetassucrose,whileβ-lactoseis 40% as sweet.

StabilityandStorage: Moldgrowthmayoccurunderhumidconditions (80%relativehumidityandabove).Lactosemaydevelop a brown coloration on storage, the reactionbeingacceleratedbywarm,dampconditions.Thepuritiesofdifferentlactosecanvaryandcolor evaluationmaybeimportant,particularlyifwhitetablets are being formulated. The color stabilities ofvariouslactosealsodiffer.Solutionsshowmutorotation;Lactoseshouldbestoredinawell-closedcontainer in acool, dryplace.

Incompatibilities: AMaillard-typecondensationreactionislikelyto occur between lactose and compounds with a primaryamine group to form brown, or yellow-brown-coloredproducts.Lactoseisalsoincompatiblewithaminoacids,aminophylline, amfetaminesandlisinopril.

RelatedSubstances: Lactoseanhydrous

1.4.4 Name **CROSSPOVIDONE**[53]
Synonym: Crospovidonum,Crospophar,
CASRegistryNumber: 9003-39-8
EmpiricalFormula: (C6H9NO)n**FunctionalCategory:** Tabletdisintegrant.**IRSpectra:**

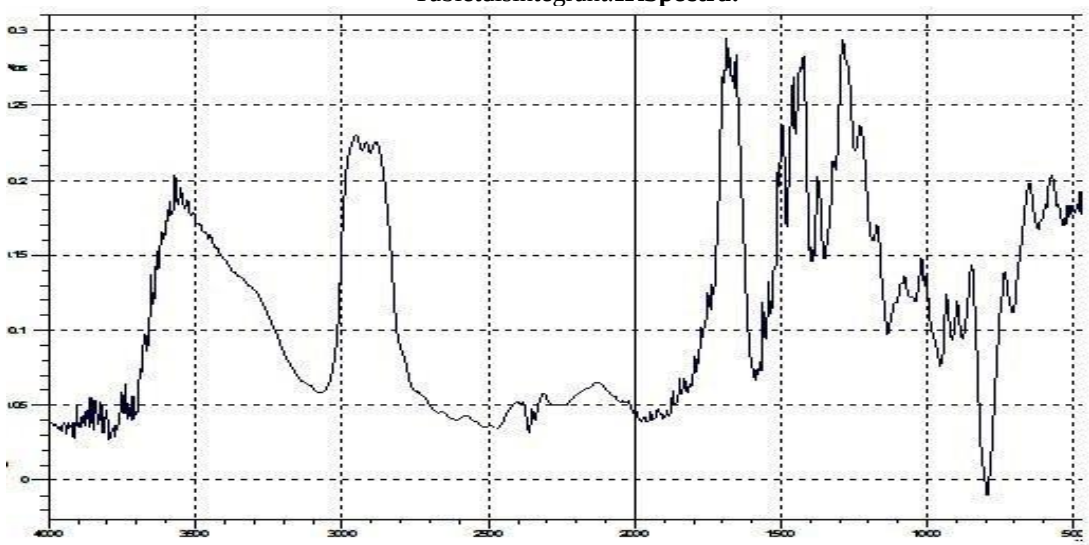


Figure16:IRspectraofcrosspovidone

Applications: Crosspovidone is a water-insoluble tablet disintegrantand dissolution agent used at 2–5% concentration intabletspreparedbydirectcompressionorwet-and dry-granulationmethods.Itrapidlyexhibitshighcapillary activity and pronounced hydration capacity,with little tendency to form gels. Studies suggest thatthe particle size of crosspovidone strongly influencesdisintegrationofanalgesictablets.Largerparticlesprovide a faster disintegration than smaller particles.Crosspovidonecanalsobeusedasasolubilityenhancer.Withthetechniqueo fco-evaporation,crosspovidonecanbeusedtoenhancethesolubilityof poorly soluble drugs. The drug is adsorbed on tocrosspovidone in the presence of a suitable solventand the solvent is thenevaporated. This techniqueresultsinfasterdissolution rate.

Description: Crosspovidoneisawhitetocreamy-white,finelydivided,freeflowing,practically tasteless,odorlessornearlyodorless, hygroscopic powder.

StabilityandStorage: Crosspovidoneishygroscopic,itshouldbestoredin anairtightcontainerinacool,dryplace.

Incompatibilities: Crosspovidoneiscompatiblewithmostorganicand inorganic pharmaceutical ingredients. When exposedtoahighwaterlevel,crosspovidonemayformmolecularadduct with somematerials.

1.4.5 Name **SODIUMSTARCHGLYCOLATE**[53]
Synonyms: Carboxymethylstarch.
Structure:

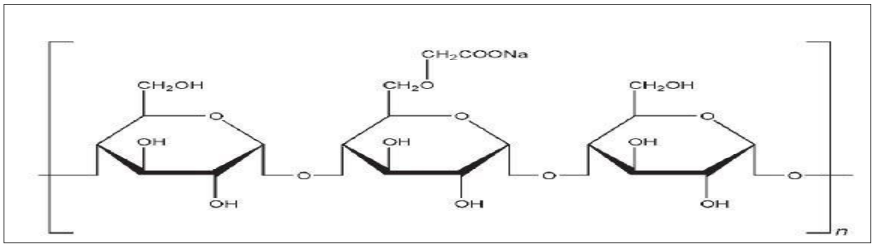


Figure17:structureof sodiumstarchglycolate

CASRegistryNumber: 9063-38-1
Description: Sodiumstarchglycolateisawhitetooff-white,odorless,tasteless, free-flowingpowder.

FunctionalCategory: Tabletandcapsuledisintegrant.

IRSpectra:

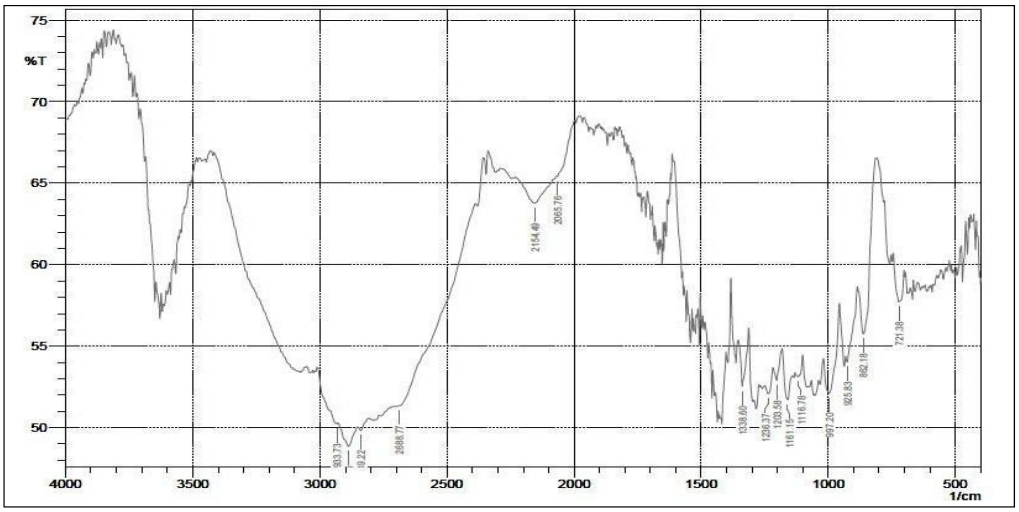


Figure18:IRspectraofsodiumstarch glycolate

Applications:

Sodiumstarchglycolateiswidelyusedinoralpharmaceuticalsasadisintegrantincapsuleandtabletformulations..Theusualconcentrationemployed in a formulation is between 2% and 8%,withtheoptimumconcentrationabout4%,althoughin many cases 2% is sufficient. Disintegration occursbyrapiduptakeofwaterfollowedbyrapidandenormousswelling.
Although the effectiveness of many disintegrants isaffected by the presence of hydrophobic
excipientssuchaslubricants,thedisintegrantefficiencyofsodiumstarch glycolate is unimpaired.

StabilityandStorage: Sodiumstarchglycolateisstableandshouldbe stored in a well-closed container in order to protect itfromwidevariationsofhumidityandtemperature,

which may cause caking. The physical properties ofsodium starch glycolate remain unchanged for upto3–5 years if it is stored at moderate temperatures andhumidity.

Incompatibilities: Sodiumstarch glycolate is incompatible with ascorbicacid.

1.4.6 **Name** **MICROCRYSTALLINECELLULOSE** [53]

Synonyms: AvicelPH,Cellets,Celex,Celphere,crystallinecellulose;Emcocel.

ChemicalName: Cellulose

Structure:

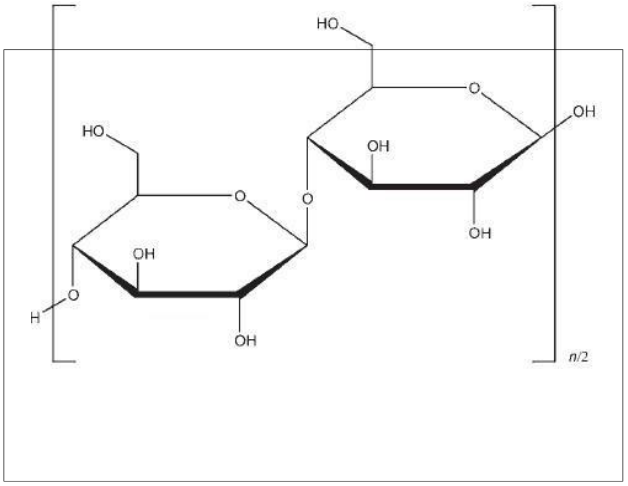


Figure19:StructureofMicrocrystallinecelluloseCASRegistryNumber: 9004-34-6

EmpiricalFormula: $(C_6H_{10}O_5)_n$.

FunctionalCategory: Adsorbent;suspendingagent;tabletandcapsule diluents;tabletdisintegrant.

Description:

Microcrystallinecelluloseispurified,partiallydepolymerizedcellulosethatoccursasawhite,odourless, tasteless, crystalline powder composed ofporousparticles.Itiscommerciallyavailableindifferent particle sizes and moisture grades that havedifferentpropertiesand applications.

IRSpectra:

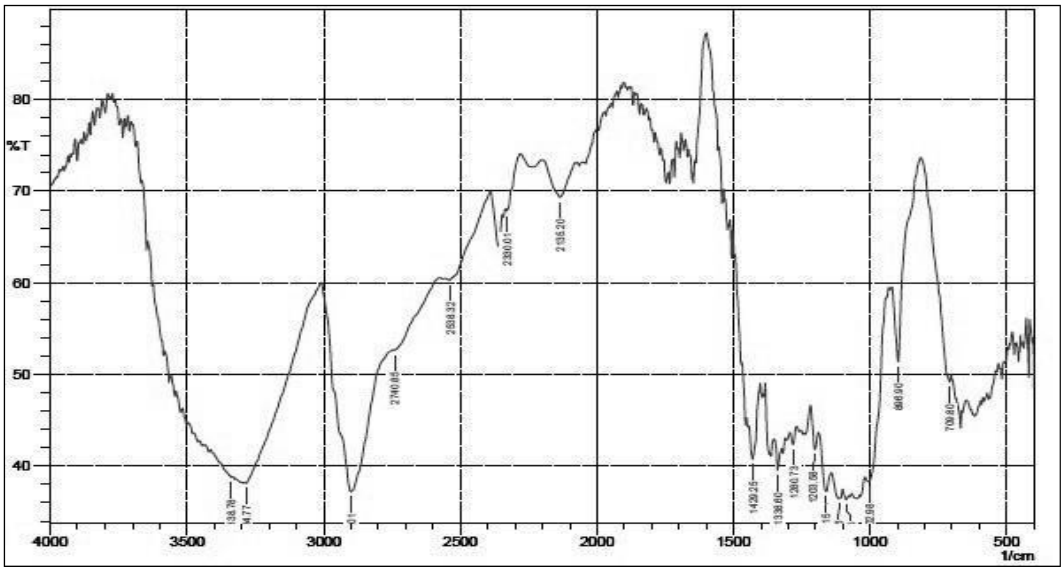


Figure20:IRspectraof microcrystallinecellulose

Applications: Microcrystallinecelluloseiswidelyusedinpharmaceuticals, primarily as a binder/diluents in oraltablet and capsule formulations where it is used inbothwet-granulationanddirect-compressionprocesses. In addition to its use as a binder/diluents,microcrystalline cellulose also has some lubricant anddisintegrantpropertiesthatmakeitusefulintableting.

Solubility: Slightlysolublein5%w/vsodiumhydroxidesolution; practically insoluble in water, dilute acids,andmost organic solvents**.**

StabilityandStorage: Microcrystalline cellulose is a stable though hygroscopicmaterial.Thebulkmaterialshouldbestored in a well-closed container in acool, dryplace.

Incompatibilities: Microcrystalline cellulose isincompatible withstrong oxidizingagents.

1.4.7 Name: **MAGNESIUMSTEARATE**[53]

Synonyms: Dibasicmagnesiumstearate;magnesiumdistearate.

CASRegistryNumber: 557-04-0**Empiricalformula:** $C_{36}H_{70}MgO_4$

Molecularweight: 591.34

Functionalcategory: Tabletandcapsulelubricant.

Application:

Magnesiumstearateiswidelyusedincosmetics,foods,andpharmaceuticalformulationsprimarilyusedaslubricantincapsuleandtabletataconcentrationbetween 0.25% -5.0%w/w.

Description: Magnesiumstearateisveryfine,lightwhite,precipitated or milled impalpable powder of low bulkdensityhavingafaintorderofstearicacidandcharacteristictaste.

StabilityandStorage: Magnesiumstearateisstableandshouldbestoredin awell-closedcontainer in acool, dryplace.

Incompatibility: Incompatiblewithstrongacids,alkalisandironsalts. Avoidmixingwithstrongoxidizingmaterials.Magnesiumstearatecannotbeusedinproductcontaining aspirin, some vitamins and most alkaloidalsalts.

RelatedSubstances: Calciumstearate; magnesium aluminum silicate; stearicacid;zincstearate

1.4.8 Name **COLLOIDAL SILICON DIOXIDE**[53]

Synonyms: Aerosil, colloidal silica; fumed silica, fumed silicondioxide.

CASRegistryNumber: 7631-86-9

EmpiricalFormula: SiO2

MolecularWeight: 60.08

FunctionalCategory: Adsorbent,Anticakingagent,Emulsionstabilizer; glidant, suspending agent, tablet disintegrant, thermalstabilizer,viscosity-increasingagent.

Applications:

Colloidalsilicondioxideiswidelyusedinpharmaceuticals,cosmetics,andfoodproducts,Itssmall particle size and large specific surface area giveit desirable flow characteristics that are exploited toimprovetheflowpropertiesofdrypowdersinanumber of processes such as tableting and capsulefilling.Colloidalsilicondioxideisalsousedtostabilize emulsions and asa thixotropic thickeningandsuspendingagentingelsandsemisolidpreparations.Withotheringredientsofsimilarrefractive index, transparent gels may be formed. Thedegree of viscosityincrease depends on the polarity ofthe liquid (polar liquids generally require a greaterconcentrationofcolloidalsilicondioxidethannonpolar liquids). Viscosity is largely independent oftemperature. However, changes to the pH of a systemmayaffect theviscosity

Description: Colloidal silicon dioxide is sub microscopic fumedsilica with a particle size of about 15 nm. It is a light,loose,bluish-white-colour,odourless,tasteless,amorphouspowder.

StabilityandStorage: Colloidalsilicondioxideishygroscopicbutadsorbs large quantities of water without liquefying. WhenusedinaqueoussystemsatapH0–7.5,colloidalsilicon dioxide is effective in increasing the viscosityof a system. However, at a pH greater than 7.5 theviscosityincreasingpropertiesofcolloidalsilicon dioxide are reduced; and at a pHgreater than10.7this ability is lost entirely since the silicon dioxidedissolves to form silicates. Colloidal silicon dioxidepowdershould bestoredina well-closed container.

Incompatibilities: Incompatiblewithdiethylstilbestrolpreparations.

1.4.9 Name **TALC**[53]

Synonyms: Hydrousmagnesiumcalciumsilicate,hydrousmagnesiumsilicate,purifiedFrenchchalk,Purtalc,soapstone,steatite.

CASRegistryNumber: 14807-96-6

MolecularWeight: $Mg_6(Si_2O_5)_4(OH)_4$.

FunctionalCategory: Anticakingagent,glidant,tabletandcapsulediluents, tabletandcapsulelubricant.

Applications:

Talcwasoncewidelyusedinoralsoliddosageformulationsasalubricantanddiluentsalthoughtoday it is less commonly used. However, it is widelyused as a dissolution retardant in the development ofcontrolled-releaseproducts.Talcisalsousedasalubricant in tablet formulations; in a novel powdercoatingforextended-releasepellets;andasanadsorbent. In topical preparations, talc is used as adusting powder,although it should not beusedtodust surgical gloves; Talc is a natural material; it maythereforefrequentlycontainmicroorganismsandshould be sterilized when used as a dusting powder.Talc is additionally used to clarify liquids and is alsoused in cosmetics and food products, mainly for itslubricantproperties.

Description: Talc is a very fine, white to grayish-white, palpable,unctuous, crystalline powder. It adheres readily to theskinand issoft tothe touchand freefromgrittiness.

Solubility: Practicallyinsolubleindiluteacids,alkalisandwater.

StabilityandStorage: Talcisastablematerialandmaybesterilizedby heating at 160°C for not less than 1 hour. It may alsobe sterilized by exposure to ethylene oxide or gammairradiation.Talc should be stored in a well-

closedcontainer in a cool, dryplace.

Incompatibilities: Incompatible with quaternary ammonium compounds.

Safety: Talcisnotabsorbedsystemicallyfollowingoralingestion and is therefore regarded as an essentiallynontoxic material. However, intranasal or intravenousabuse of products containing it can cause granulomasin body tissues, particularly the lungs. Although talchas been extensively investigated for its carcinogenicpotential, and it has been suggested that there is anincreased risk of ovarian cancer in women using talc,theevidenceisinconclusive.However,talccontaminated with asbestos has been proved to becarcinogenicinhumans,andasbestos-freegradesshould therefore be used in pharmaceutical products.Also,long-termtoxiceffectsoftalccontaminatedwithlargequantitiesofhexachlorophenecausedseriousirreversibleneurotoxicityininfantsaccidentallyexposedto thesubstance.

1.4.10 Name **POLYMETHACRYLATES** [53]

Synonyms: Methacrylicacid,Eudragit

Description: Whitepowderswithafaintcharacteristicodour

MolecularWeight: Averageapprox.135,000.

StructuralFormula: EUDRAGIT® is anionic copolymers based on Methacrylicacidandmethylmethacrylate

Structure:

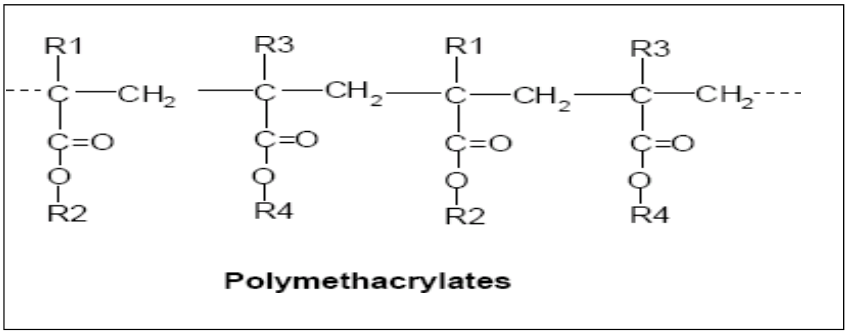


Figure21:structureofpolymethacrylatesFunctionalCategory: Film former,tablet binder.

Solubility: 1 g of EUDRAGIT® dissolves in 7 g methanol, ethanol,inaqueousisopropylalcoholandacetone(containingapprox. 3 % water), as well as in 1 N sodium hydroxidetogivecleartoslightlycloudysolutions.EUDRAGIT®ispracticallyinsolubleinethylacetate,methylenechloride,petroleumether and water.

Stability: Minimum stability dates are given on the product labelsandbatch-relatedCertificatesofAnalysis.StorageStabilitydataareavailableupon request.

Storage: Storeatcontrolledroomtemperatures(USP,GeneralNotices). Protect against moisture.Any storage between8°Cand 25°C fulfils thisrequirement.

Incompatibilities: Incompatibilities occur with acid and/or alkaline conditiondependinguponwhich polymeris beingused.

Application: Eudragit L, S types are used as enteric coating agentsbecause they are resistant to gastric fluid. Different typesare available that are soluble at different pH values: e.g.Eudragit L is soluble at pH > 6; Eudragit S is soluble atpH>7.WhileEudragitRSisusedtoformwater-

insolublefilmcoatsforsustained-releaseproducts.Binder – Eudragit E (concentration between 5 to 20%).Film former – Eudragit L form acid-insoluble film coatsforentericpurpose.

1.4.11 Name **HYDROXYPROPYL METHYLCELLULOSE**[53]

Synonyms: Hydroxypropylmethylcellulose,HPMC,Methocel,methyl hydroxypropylcellulose

CASRegistryNumber: 9004-65-3

FunctionalCategory: Coatingagent;film-former;rate-controllingpolymer forsustainedrelease;stabilizingagent;suspendingagent;tablet binder; viscosity-

increasingagent.

Applications: Hypromellose is widely used in oral, ophthalmic andtopical pharmaceutical formulations. In oral products,it is primarily used as a tablet binder, in film-coating,andasamatrixforuseinextended-releasetabletformulations.Concentrationsbetween2%and5%w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may beused to retard the release of drugs from a matrix atlevelsof 10–80%w/w intabletsand capsules.

Description: Hypromellose is an odorless and tasteless, white orcreamy-whitefibrous or granularpowder.

Solubility: Solubleincoldwater,forminga viscouscolloidalsolution; practically insoluble in chloroform, ethanol(95%), and ether, but soluble in mixtures of ethanolanddichloromethane,mixturesofmethanolanddichloromethane, and mixtures of water and alcohol.Certaingradesofhypromellosearesolubleinaqueousacetonesolutions,mixtureso f

dichloromethane and propan-2-ol, and other organicsolvents.

StabilityandStorage: Hypromellosepowderisastablematerial,althoughit is hygroscopic after drying. Solutions are stable at pH3–11. Increasing temperature reduces the viscosity ofsolutions.Itundergoesareversiblesol–geltransformationuponheatingandcooling,respectively.Thegelpointis50–90°C,dependingupon the grade and concentration of material. Thispowdershouldbestoredinawell-closedcontainer,in a cool, dryplace.

Incompatibilities: Hypromelloseisincompatiblewithsomeoxidizing agents. Since it is nonionic, it will not complex withmetallicsaltsorionicorganicstoforminsolubleprecipitates.

Safety: Hypromellose is widely used as an excipient in oralandtopicalpharmaceuticalformulations.Itisalsoused extensively in cosmetics and food products. It isgenerallyregardedasanontoxicandnonirritantmaterial, although excessive oral consumption mayhave a laxative effect. The WHO has not specified anacceptabledailyintakeforhypromellosesincethelevels consumed were not considered to represent ahazardto health.

1.4.12 Name **POLYVINYLPYRROLIDONEK30**[53]

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

Nonproprietarynames: BP-povidone,JP-Povidone,PHEur-povidonum, USP-povidone.

Chemicalname: 1-Ethenyl-2-pyrrolidonehomopolymer.

Category: Disintegrant,dissolutionaid,suspendingagent,tabletbinder.

Structure

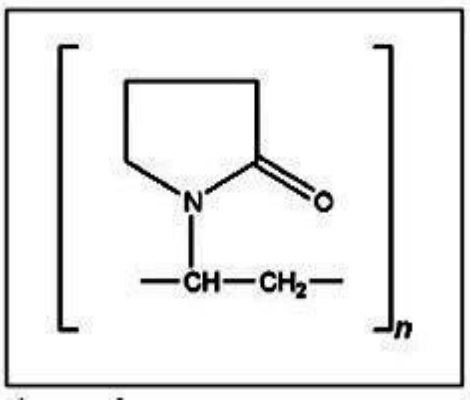


Figure22:structureof vinylpolyvinylpyrrolidoneK30

Molecularweight: 50,000

FTIR-spectra

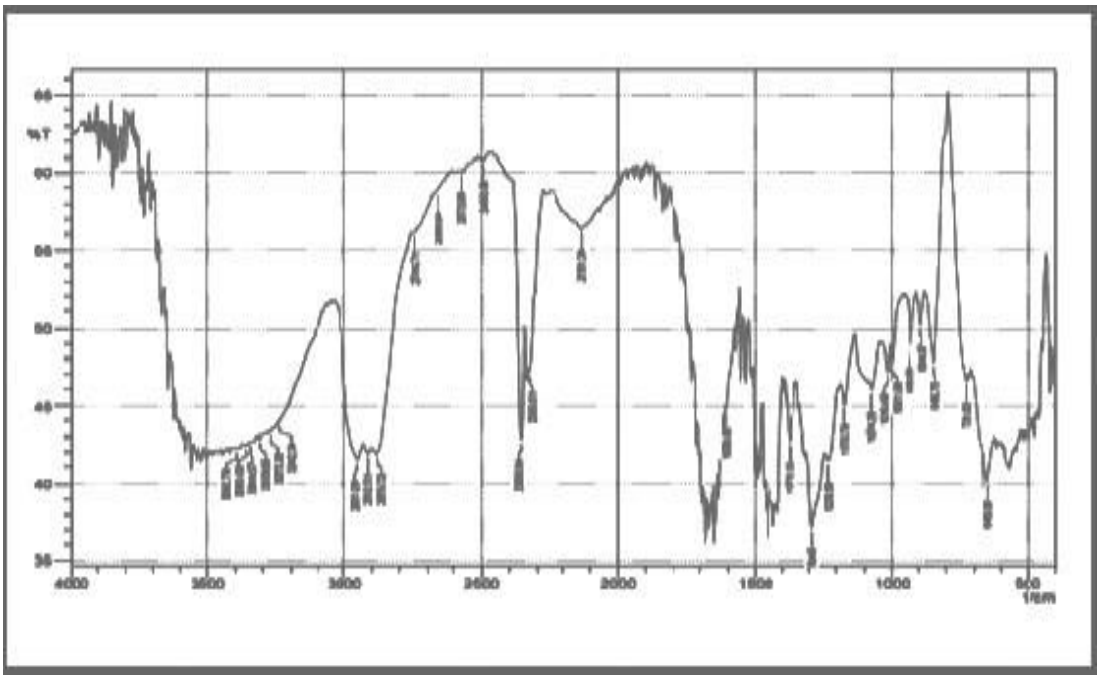


Figure23:FTIR-spectraofPVPK-30

Description: Itoccursasafine,whitetocreamywhitecolored,odorless,hygroscopic powder.

Solubility: Freely soluble in acids, chloroform, ethanol, ketones,methanolandwater.Practically insolubleinether,hydrocarbonsand mineral oil.

5.5to 8.5 m Pas (aqueous solution)

Stability: Darkens to some extent on heating at 150 ºC, with areduction in aqueous solubility. It is stable to a shortcycle ofheat exposurearound 110-130 °C.

Itshouldbestoredinanairtightcontainerinacool, dryplace.

Safety:

Generallyregardedasnontoxic,nonirritantbutadversereactionsmaytakeplaceift akenintramuscularlyor subcutaneously.

Itis incompatible with sulfathiazole, sodium salicylate,salicylicacid, Phenobarbital,tannin.

1.4 ReviewofLiterature

Akhter, et al. 2011.[54] A time controlled two pulse dosage form of Amoxicillin wasdeveloped. The compression coating inlay tablet approach was used todeliver thedrug in two pulses to different parts of the GIT after a well-defined lag time betweenthe two releases. This was made possible by formulating a core containing one of thetwo drug fractions, which was spray coated with a suspension of ethyl cellulose and ahydrophilic 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 correspondinglagof3,5, 7 and 12 h.

Bauskar, et al. 2011.[55]A tablet system consisting of cores coated with two layers ofswelling and erodible coatings was prepared and evaluated as pulsatile drug deliverysystem. Cores containing Doxofylline were prepared by direct compression of lactose,microcrystalline cellulose and containing a superdisintegrant (croscarmellose sodium,crosspovidone)andanoutererodiblelayerofHydroxypropylmethylcellulose(Methocel E 50). The effect of core composition and magnesium stearate in erodiblelayer was investigated. Erodible and dissolution tests were performed using the paddlemethod at 50 rpm in Simulated Gastric Fluid and Simulated Intestinal Fluid. The lagtimeofthepulsatilereleasetabletsdecreasedwithincreasingamountofmicrocrystalline cellulose in the cores and increased with increasing level of erodibleHydroxypropylmethylcellulose(MethocelE50)coating.IncreasinglevelsoftheHydroxypropylmethylcellulose (Methocel E 50) coating retarded the water uptake orerodesin presenceof aqueous environment andthus prolonged thelagtime.

Gami,et al.2011.[56] prepare pulsatile drug delivery system of Metoprolol succinate.In this work pulsatile drug delivery system was prepared by using swellable andrupturable polymer. The polymers like Ac-di-sol and crosspovidone were selected asswellablepolymerwhileethylcellulosewasselectedasrupturablepolymer.Inpresent work,core tablet (150 mg) containing 100 mg Metoprolol succinate wasprepared by wet granulation technique. This prepared core tablet was coat by using2.5% ethyl cellulose containing triethyl citrateas plasticizer. This coating solutionwas sprayed to core tablet to achieve different percentage of weight

gain into the coretablet. The preparedfilm coated tablet wasevaluated for in vitro drug dissolutionstudytoget desirable immediate releaseofdrugafter lagtime of6hour.

NaikandZine,2011.[57]Chronopharmaceuticsisabranchofpharmaceuticsdevotedtothedesignandevaluationofdrugdeliverysystemsthat releaseabioactiveagentata rhythm that ideally matches the biological requirement of a given disease therapy. Amajor objective of chronotherapy in the treatment of several diseases is to deliver thedruginhigherconcentrationsduringthetimeofgreatestneedaccordingtothecircadian onset of diseases or symptoms.. The main objective of the present study wasto develop single-unit floating-pulsatile drug delivery system for obtaining no drugrelease during floating and in the proximal small intestine followed by pulsed drugrelease in distal small intestine to achieve Chronotherapeutic release of Aceclofenacfor treatment of rheumatoid arthritis, osteoarthritis, spondylitis and to improve thepatientcompliance.

Shirsagar,etal.2011.[58]Developedhollowcalciumalginatebeadsforfloatingpulsatile release of valsartan intended for chronopharmacotherapy. Floating pulsatileconcept was applied to increase the gastric residence of the dosage form having lagphase followed by a burst release. To overcome the limitations of various approachesfor imparting buoyancy, hollow porous beads were prepared by simple process ofacid-base reaction during ionotropic cross linking by low viscosity sodium alginateand calcium chloride asa cross linking agent.In this study, investigation of thefunctionalityof thesodium alginate to predict lagtime.

Latha,etal.2011.[59]Todevelopanoptimisedpress-coatedtabletsoflosartanpotassiumusinganadmixtureofahydrophilicpolymer,Hydroxypropylmethylcellulose(HPMC)andmicrocrystallinecellulose(MCC)inorder to achieve a predetermined lag time for chronotherapy. The press-coated tablets(PCT) containing losartan potassium in the inner core were prepared by compression-coating with HPMC 100KM alone and admixed with MCC as the outer layer indifferent ratios. The effect of the outer layer on the lag time of drug release wasinvestigated.

Reddy,etal.2011.[60]Thepurposeofthisresearchstudywastodevelopandoptimizeacontrolled-releasefloating tabletofhighly watersoluble drug Nizatidineinaneffort to increase its gastric retention time in the stomach. The tablets were preparedbydirectcompressionmethodandHydroxypropylmethylcellulose(HPMC)ofdifferentviscositygrades,CarboxymethylcelluloseSodium(NaCMC)wereincorporatedasretardingpolymers.Sodiumbicarbonatewasincorporatedaseffervescentagent.Formulationswereevaluatedforweightvariation,thickness,hardness, percentage swelling, friability, and in vitro drug release, and floating lagtime, total duration of floating, dissolution efficacy and in vivo Mean Residence Time(MRT)in thestomach.

PannalaandRathnanand,2011.[61]Prepareandevaluate(invitro)Nizatidineimmediatereleasetablets.Thedevelopeddrugdeliverysystemdeliversaprogrammeddoseofdrugintendedforexcessivelysecretedgastricacidandforpromoting healing of duodenal ulcers thereby spontaneously delivering the drug whenexposed into GIT for producing an anti-ulcer effect. Accordingly, immediate releasedrug-containingcoretablets of Nizatidine wereprepared bywetgranulation method.

Patil,et al.2011.[62] Prepaidandevaluatedapress-coated pulsatile drug deliverysystem intended for treatment of early morning stiffness and symptomatic relief frompain in patients with rheumatoid arthritis. The formulation involved press coating of arupturable coat around a rapidly disintegrating core tablet of Aceclofenac. A three-factor, two-level, full factorial design was used to Investigate the influence of amountof glyceryl behenate, amount of sodium chloride in the coating composition, and thecoating level on the responses, ie, lag time to release and amount of Aceclofenacreleased in 450 minutes. Glyceryl behenate and the coating level had a significantinfluence on lag time,while sodium chloride helped in the rupture ofthe coatbyactingas a channelingagent

Jagdale, et al. 2010.[63]A tablet system consisting of cores coated with two layers ofswellingandrupturablecoatingswaspreparedandevaluatedaspulsatiledrugdelivery system. Cores containing Atenolol as model drug were prepared by directcompression of different ratios of lactose and microcrystalline cellulose and were thencoatedsequentiallywithaninnerswellinglayercontainingasuperdisintegrantKYRON T 314 and an outer rupturable layer of ethyl cellulose. The effect of level ofswelling layer and rupturable coating was investigated. Rupture and dissolution testswere performed using the USP Type II paddle method at 50 rpm in 0.1N HCl. Thelagtimeofthepulsatilereleasetabletsdecreasedwithincreasingamountofmicrocrystalline cellulose in the cores and increased with increasing levels of bothswellinglayerandrupturableethylcellulosecoating.Increasinglevelsoftheethyl cellulose coatingretarded the wateruptakeand thus prolonged thelagtime.

Shah,etal.2010.[64]Advancementindrugdeliverycouldcomefrominnovateimprovementtoexistingdrugdeliverysystem.Becauseofreducefrequencyofadministration sustain release dosage from enjoy convenience and ambulatory patientcompliance.Developedformulaisamultipleunitbasedpulsatiledeliveryof Salbutamol Sulphate which can offer a solution for exhibiting chronopharmacologicalbehaviorofasthma,extensivefirst-passmetabolismandnecessityofnight-timedosing.Sowecanconcludethatitcanunderliethechronokineticsofnocturnalasthma. Among five Batches Specific amount 4% CAP and 2% EC batch gives laterelease than predetermined time. They release their higher dose after 6 hours. So thatbatch SF2 is accurate batch for Nocturnal Asthma according to pulsatile drug deliverysystem.

Roy and Shahiwala, 2009.[65] Present works 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 beachieved by using a programmed delivery of ranitidine hydrochloride from a floatingtablet with time-lagged coating. In this study, investigation of the functionality of theouter polymer coating to predict lag time and drug release was statistically analyzedusingthe responsesurfacemethodology(RSM).

Zou, et al. 2008.[66]The objective of this work was to develop and evaluate a floatingpulsatile drug delivery system intended for chronopharmacotherapy. Floating pulsatileconcept was applied to increase the gastric residence of the dosage form having lagphase followed by a burst release. To overcome limitations of various approaches forimparting buoyancy, we generated the system which consisted of three different parts,a core tablet, containing the active ingredient, an erodible outer shell and a top coverbuoyant layer. The dry coated tablet consists in a drug-containing core, coated by ahydrophilic erodible polymer which is responsible for a lag phase in the onset ofpulsatilerelease.Thebuoyantlayer,preparedwithMethocel®K4M,Carbopol®934P and sodium bicarbonate, provides buoyancy to increase the retention of the

oraldosageforminthestomach.Theeffectofthehydrophilicerodiblepolymercharacteristicson thelagtime and drugreleasewas investigated.

ShajiandPatole,2007.[67]Preparationofamultiple-unit,floating-pulsatiledrugdelivery systemfor obtaining nodrug releaseduring floating andintheproximalsmall intestine followed by pulsed, rapid drug release in distal small intestine toachieve Chronotherapeutic release of indomethacin. The system developed consists ofdrugcontainingcorepelletspreparedbyextrusion-spheronizationprocess,whichwerecoatedwithaninnerpH-dependentlayerofEudragitS100andoutereffervescentlayerofsodiumbicarbonateandHPMCK100M.Pelletsshowedinstantaneous floating with no drug release in acidic medium followed by pulsed drugreleaseinbasicmedium.ConcentrationofHPMCK100Mandlayeringlevelofeffervescent agent significantly affected performance of pellets. The system showedexcellent lag phase followed by burst release in the distal small intestine which givessiteandtimespecificdeliveryofindomethacinactingasperchronotherapyofrheumatoidarthritis.

Gothoskar,etal.2004.[68]ReviewedDiseaselikeBronchialasthma,Myocardialinfarction, angina pectoris, Rheumatic disease, Ulcer, & Hypertension display timedependence. In Asthmatic disease reported sharp increase in asthmatic attack duringearly morning hours. Such a condition demands consideration of diurnal progress ofdisease rather than maintaining constant plasma drug level, a drug delivery systemadministered at bed time, but releasing drug well after the time of administration,wouldbeideal in this case

Lin, et al. 2004.[69]An oral press-coated tablet was developed by means of directcompression to achieve the time-controlled disintegrating or rupturing function with adistinct predetermined lag time. This press-coated tablet containing sodium diclofenacin the inner core was formulated with an outer shell by different weight ratios ofhydrophobic polymer of micronized ethyl- cellulose (EC) powder and hydrophilicexcipientssuchasspray-driedlactose(SDL)orhydroxypropylmethylcellulose(HPMC). The effect of the formulation of an outer shell comprising both hydrophobicpolymerandhydrophilicexcipientsonthe timelagof drugreleasewas investigated.

Sungthongjeen, et al. 2004.[70]A tablet system consisting of cores coated with twolayersofswellingandrupturablecoatingswaspreparedandevaluatedaspulsatiledrug delivery system. Cores containing buflomedil HCl as model drug were preparedbydirectcompressionofdifferentratiosofspray-driedlactoseandmicrocrystalline cellulose and were then coated sequentially with an inner swelling layer containing asuperdisintegrant(croscarmellosesodium)andanouterrupturablelayerofethylcellulose.Theeffectofcorecomposition,levelofswellingl ayerandrupturablecoating, and magnesium stearate in rupturable layer was investigated. Mechanicalproperties of ethyl cellulose films in the dry and wet state were characterized with apuncturetest. Ruptureand dissolution tests wereperformed

Bodmeier, et al. 2003.[71] Investigate the swelling characteristics of various swellablepolymers in swelling layers that induce the rupturing of an outer polymer coating inpulsatiledrugdeliverysystems.Anapparatuswasdesignedtomeasuresimultaneouslytheswellingenergy/forceandwateruptakeofdiscs, madeofpolymers. The swelling energy of several excipients decreased in the following order:croscarmellosesodium.Low-substitutedhydroxypropylcellulose.sodiumstarchglycolate. Crosspovidone.hydroxypropyl methylcellulose. A linear correlation existedbetweenthe swelling energyand the wateruptake.

Fan, et al.2001.[72] To develop new pulsatile release tablets, which can suppress drugrelease in stomach and release the drug rapidly after a predetermined lag time of about3 h in intestine, the use of tablets with ethyl cellulose/Eudragit L as a coating film andcross-linked polyvinylpyrrolidone in the core tablets was investigated. The release ofdiltiazemhydrochlorideasa modeldruginthecoretablets wasinvestigatedinvitro.

Fukui, et al. 2001.[73] In this study Dissolution profiles of diltiazem hydrochloridecontainedincoretabletsfrompress-coated(PC)tabletswithHydroxypropylmethylcelluloseacetatesuccinate(HPMCAS)andplasticizers–adsorbentin the outer shell wereinvestigated.

Ping, et al. 1999.[74]Non-cross linked and cross linked chitosan microspheres werepreparedbyaspraydryingmethod.Themicrospheressopreparedhadagoodsphericityandasmoothbutdistortedsurfacemorphology. Theywerepositivelycharged. The particle size ranged from 2 to 10 µm. The size and seta potential of theparticles were influenced by the cross linking level. With decreasing amount of crosslinking agent (either glutaraldehyde or formaldehyde), both particle size and zetapotentialwereincreased.Preparationconditionsalsohadsomeinfluenceontheparticlesize.DSCstudiesrevealedthattheH$_2$antagonist drugCimetidine,aswellas Famotidine was molecularly dispersed inside the microspheres, in the form of a solidsolution. The release of model drugs (Cimetidine, Famotidine and Nizatidine) fromthesemicrospheres wasfast, and accompanied byaburst effect.

RESEARCH ENVISAGED

Oral drug delivery has been known for decades .The most widely utilized route ofadministration among all the routes that have been explored for the systemic deliveryof different dosage form. Pulsatile drug delivery systems are gaining a lot of interestand attention these days. These systems have a particular mechanism of delivering thedrug rapidly and completely after a "lag time," i.e., a period of "no drug release."Thoughmostdeliverysystemsaredesignedforconstantdrugreleaseoveraprolongedperiodoftime,pulsatiledeliverysystemsarec haracterizedbyaprogrammed drug release, as constant blood levels of a drug may not always bedesirable. Pulsatile systems are designed in a manner that the drug is available at thesiteof action at therighttime in the right amount.[75]

Circadianrhythmregulatesmanybodyfunctionsinhumans,viz.,metabolism,physiology,behavior,sleeppatterns,hormoneproduction,et c.Ulcerisonesuchdisease where pulsatile drug delivery system can be useful. Because pH of the gastricjuicedecreasein midnight hours.[76,77]Delivery of H$_2$ antagonist through PDDS is very effective, but because Study revealsthat up to 70% patients appear to be resistant to even high doses of PPIs taken twicedaily;andthusbringsfailureofPPIinprovidingnecessarynocturnalacidsuppression.[78,79] It is demonstrated that adding a bed-time dose of H$_2$ antagonist to anevening dose of proton pump inhibitor provides nocturnal

recovery of gastric acidsecretion Hence the present study, the Pulsatile drug delivery system of tablets will beadapted to achieve time-controlled drug delivery system using selective Anti ulcerdrug(Nizatidine)with suitable polymer.[80,81]Nizatidine is a potent histamine H_2 receptor antagonist, has been a market leader forsymptoms like erosive esophagitis and active gastric ulcers; until when proton pumpinhibitors came to replace it. However, the recent failure of PPIs to prevent night-timegastric 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 onsetofsymptoms.[65]

TheoralabsolutebioavabilityofNizatidinemorethan70%peakplasmaconcentration occurs from 0.5 to 3 hours. Elimination half life is 1 to 2 hours andvolumeof distribution is0.8 to 1.5L/kg.The aim of this study was to design a pulsatile release Nizatidine tablets, intended forchronotherapy in nocturnal acid breakthrough. This approach will be achieved byusingaprogrammeddeliveryofNizatidinefromacoretabletwithtime-laggedcoating. The prepared tablet will not give release of drug for desired period of timeafteritsadministrationaftermealandthenwillreleasethedrugwhentheacidsecretionishigherinmidnighthoursafterthelagtimeofthree tofourhoursimprovingthe efficacyofdrugand henceimproved patient compliance.

PLANOFWORK

- LiteratureSurvey
- SelectionofDrugandExcipients
- CharacterizationofDrug
- PreformulationStudies
- SelectionofUVSpectroscopicMethodForEstimationofNizatidineandPreparation of Calibration Curve
- FormulationofCoreTabletsofNizatidine
  - PreparationofPowder Blend
  - EvaluationofPowder Blend
- Evaluation ofCoreTablets ofNizatidine
  - Thickness
  - Hardness
  - WeightVariation
  - Friability
  - DrugContent
  - DisintegrationTime
  - Dissolution Study
- FormulationofPulsatileReleaseTablet
- EvaluationofPulsatileReleaseTablet
  - Thickness
  - Hardness
  - WeightVariation
  - LagTime.
  - DrugContent
  - Dissolution Study
- KineticModelling
- StabilityTesting

2.1. Preformulationstudies

Preformulation testing is the first step in the rationale development of dosage forms ofa drug substance. It can be defined as an investigation of physical and chemicalproperties of a drug substance alone and when combined with excipients. The overallobjective of preformulation testing is to generate information useful to the formulatorindevelopingsafe and stable dosageforms.

The Preformulation studies performed include the study of organoleptic properties,meltingpoint,solubilityetc.ItalsoincludestheUVspectroscopy,IRcharacterization,DSC,ConstructionofBeer-Lambert'splotanddrug-excipientsinteraction.

2.1.1. Analysisof Nizatidine[51]

The obtained drug sample was used without further purification. Characterization ofdrugwas donebyphysicochemical methods. Thedetails areas givenbelow.

2.1.1.1. OrganolepticPropertiesandDescription[51]

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

Table2:OrganolepticCharacteristics ofNizatidine

Test	Specification	Observation
Colour	Yellowish	Yellowish
Taste	Bitter	Bitter
Odour	Sulpher-mercapton	Sulpher-mercapton

2.1.1.2. Melting Point determination[51]

It is one of the parameters to judge the purity of drugs.In case of pure chemicals orphotochemical, melting points are very sharp and constant.Since thedrugs containthe mixed chemicals, they are described with certain range of melting point. Meltingpointwasdeterminedusingcapillarymethod;itisessentialparameterforanidentification of drug. It is a temperature at which substance from solid to liquid. Themelting point was determined by open capillary method and the uncorrected meltingpoint found in rangeof 131^0cto 134^0c.

2.1.1.3. SolubilityAnalysis:[51]

The solubility of Nizatidine was determined by adding excess amount of drug in thesolvent (supersaturated) at 37 ^{0}C and kept for 24 hrs for equilibrium with occasionalshaking. Equilibrium solubility was determined by taking supernatant and analyzing itonShimadzuUV-1700,doublebeamspectrophotometerNizatidineisfreelysolublein chloroform; soluble in methanol; soluble in water and buffered solution slightlysoluble inethylacetateandosopropranolol.Nizatidine isessentially insoluble inbenzene,diethylether and octanol

Table3:SolubilityofNizatidine

Solvent	Solubility(mg/ml)
Water	25.11
0.1N HCl	30.75
pH6.8phosphatebuffer	32.11
pH7.4phosphatebuffer	30.19

2.1.1.4. UVSpectroscopy[51]

DeterminationofWavelength(λ_{max})

a. A stock solution of Nizatidine100 µg/ml was prepared in 0.1N HCl. Recordedthe UV spectrum was recorded over the wavelength range of 200-400 nm byShimadzu -1700 as shown in Figure24. Thewavelength ofmaximum absorption (□max)wasfound to be314 nm.

b. A stock solution of Nizatidine 100 µg/ml was prepared in pH 6.8 phosphatebuffer. Recorded the UV spectrum was recorded over the wavelength range of200-400nm byShimadzu -1700 as shown in Figure25. Thewavelength ofmaximum absorption (□max)wasfound to be314 nm.

c. A stock solution of Nizatidine 100 µg/ml was prepared in pH 6.8 phosphatebuffer. Recorded the UV spectrum was recorded over the wavelength range of200-400nm byShimadzu -1700 as shown in Figure26.Thewavelength ofmaximum absorption(□max)was foundto be314 nm

Table4:□maxof NizatidineatdifferentpHconditions

Solvent	λmax (nm)
0.1N HCl	314
pH6.8phosphatebuffer	314
pH7.4phosphatebuffer	314

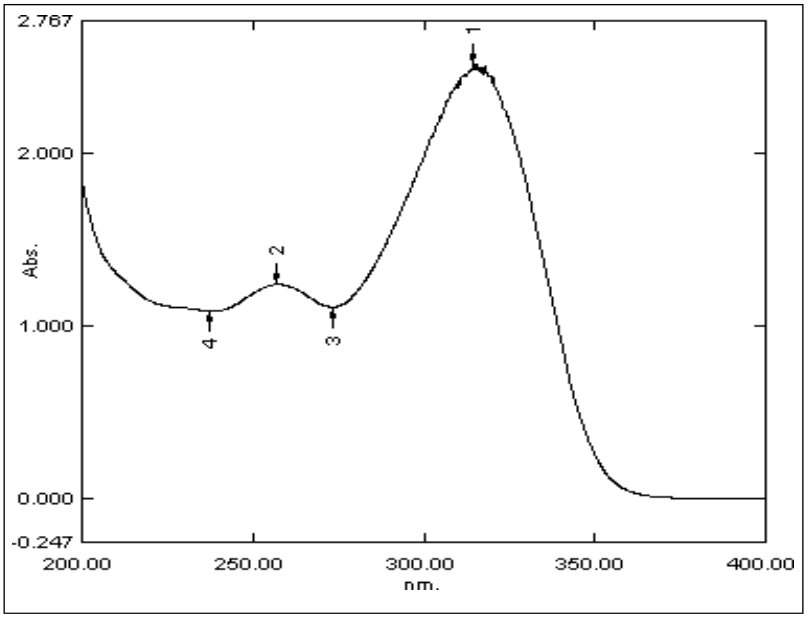


Figure24: UV spectrumof Nizatidinesolution in 0.1N HCl

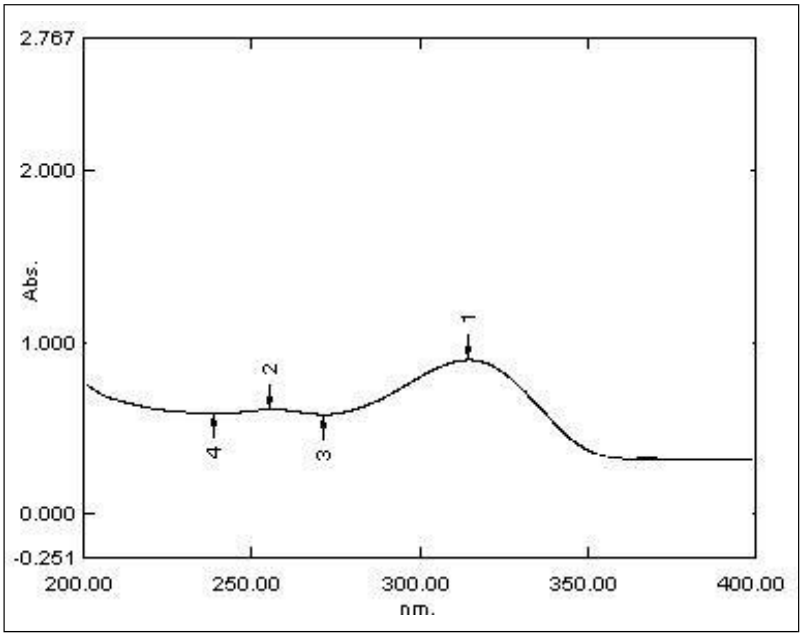


Figure25: UVspectrumof Nizatidinesolutionin pH6.8phosphatebuffer

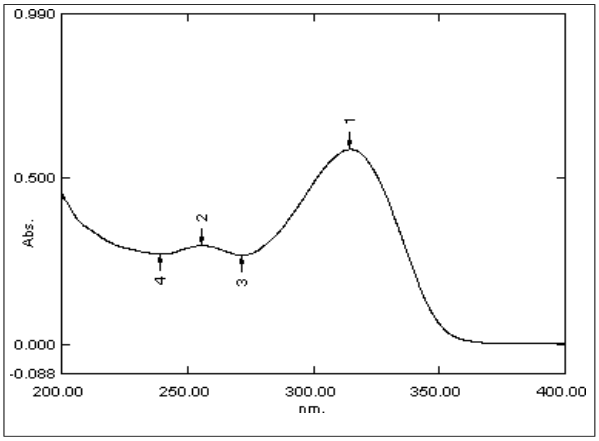


Figure26:UV spectrumofNizatidinesolution in pH7.4phosphatebuffer

2.1.1.5. FTIRSpectrophotometricCharacterization:[82]

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 bromidepowder [1:100] and placed into sample holder in the light path and the spectrum wasobtained.

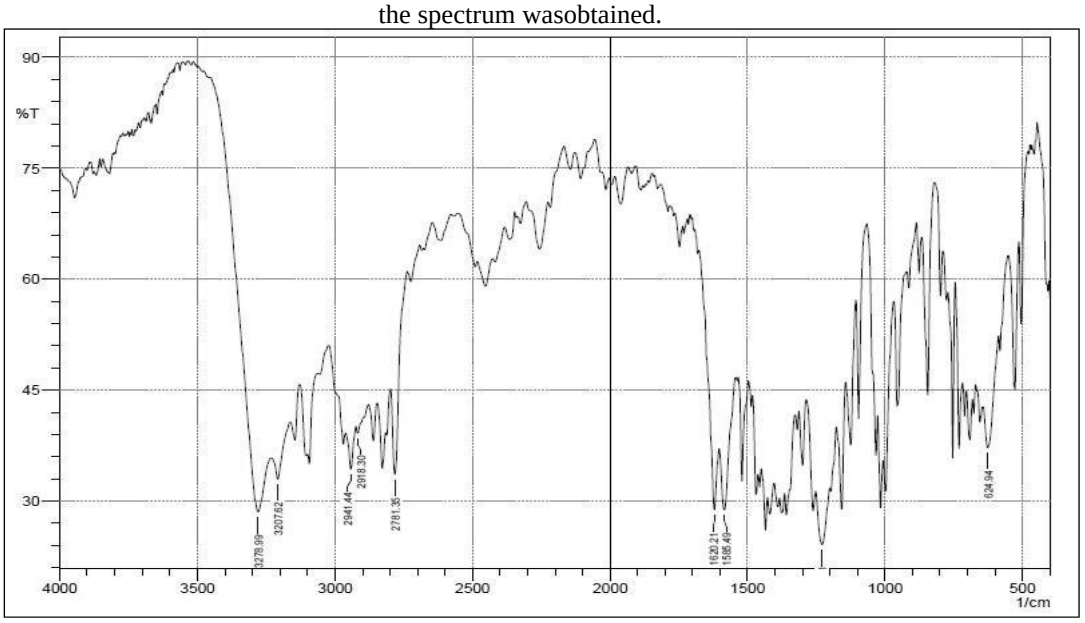


Figure27:IRSpectraofNizatidine

Table5:IRPeaks of Nizatidine

IRsignals(cm^{-1})	Remark
3280,3210	NHstretch,
3107	CHstretch inNO_2-CH
3094	CHstretchinthiazolering
2945,2860	CH stretch in NCH_3,CH_2CH_2
1521	Thiazolering
1435,1422	CHdeformation inNCH_3,CH_2CN stretch
1377,1359	Thiazole ringfor onefrequencyis symNO2,H-bonded,conjugated

2.1.1.1. ConstructionofBeer-Lambert'sPlot[83]

Linearityin 0.1 N HCl:

Nizatidine(10mg)wasdissolvedin100mlof0.1NHCltoobtainedworkingstandard of 100µg/ml. A series of solution of Nizatidine in HCl buffer (pH 1.2)concentration of 2, 4, 6, 8, 10, 12µg/ml was prepared. The absorbance of all thesolutionwasmeasuringusing0.1NHClasblankat314nmusingUVspectrophotometer (Shimadzu 1700). A standard plot of absorbance v/s concentrationof drug was plotted. Correlation coefficient and regression equation were obtainedfromthecalibration curve.

Table6:Beer-LambertsplotinpH 1.2bufferforNizatidine.

Sr.No	Concentration (µg/ml)	Absorbance
1	2	0.171
2	4	0.294
3	6	0.491
4	8	0.594
5	10	0.745

6	12	0.94

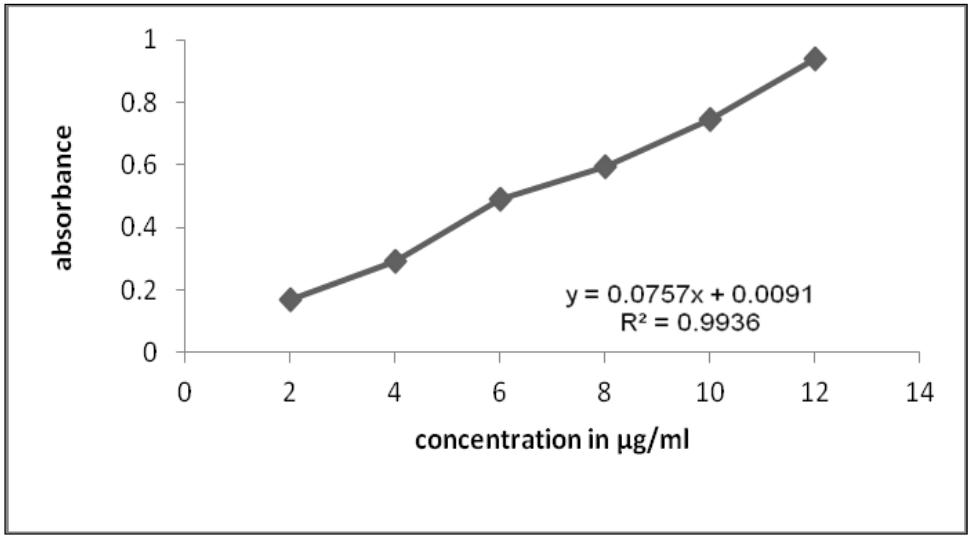


Figure28:Beers-LambertsplotofNizatidinein0.1 NHCl

LinearityinPhosphateBuffer6.8:

Nizatidine (10mg) was dissolved in 100 ml of phosphate buffer (pH 6.8) to obtainedworking 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 allthe solution was measuring using phosphate buffer 6.8 as blank at 314 nm using UVspectrophotometer (Shimadzu 1700). A standard plot of absorbance v/s concentrationof drug was plotted. Correlation coefficient and regression equation were obtainedfromthecalibration curve.

Table7:Beer-LambertsplotinpH6.8phosphatebufferforNizatidine.

Sr.No	Concentration (µg/ml)	Absorbance
1	2	0.14
2	4	0.213
3	6	0.331
4	8	0.439
5	10	0.534
6	12	0.631

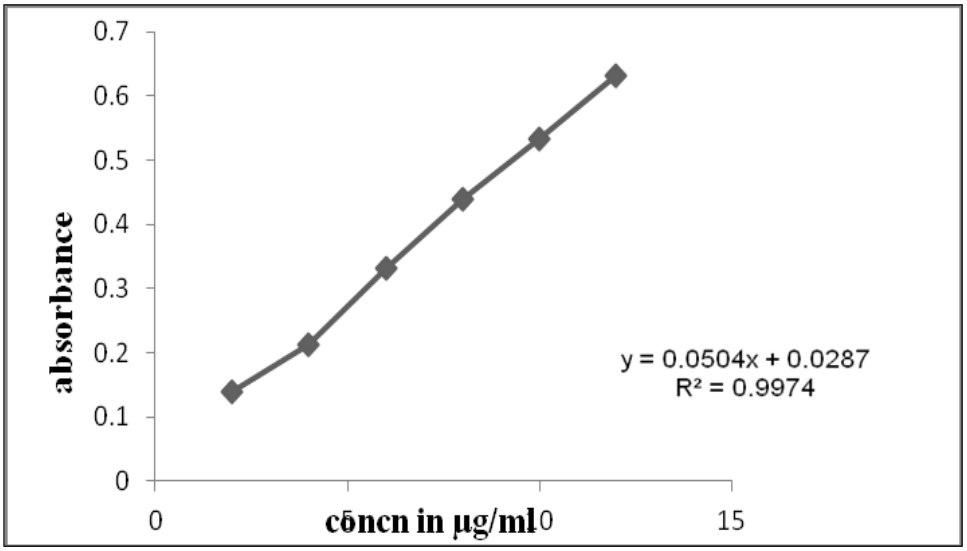


Figure29:Beers-Lambertsplotof Nizatidinein pH6.8phosphatebuffer

Linearityin PhosphateBuffer7.4

Nizatidine (10mg) was dissolved in 100 ml of phosphate buffer (pH 7.4) to obtainedworking standard of 100µg/ml. A series of solution of Nizatidine in phosphate buffer(pH 7.4) concentration of 2, 4, 6, 8, 10, 12µg/ml was prepared. The absorbance of allthe solution was measuring using phosphate buffer 7.4 blank at 314 nm using UVspectrophotometer (Shimadzu 1700). A standard plot of absorbance v/s concentrationof drug was plotted. Correlation coefficient and regression equation were obtainedfromthecalibration curve.

Table8:Beer-LambertsplotinpH7.4phosphatebufferforNizatidine.

Sr.No	Concentration (µg/ml)	Absorbance
1	2	0.117
2	4	0.215
3	6	0.284
4	8	0.391
5	10	0.472
6	12	0.582

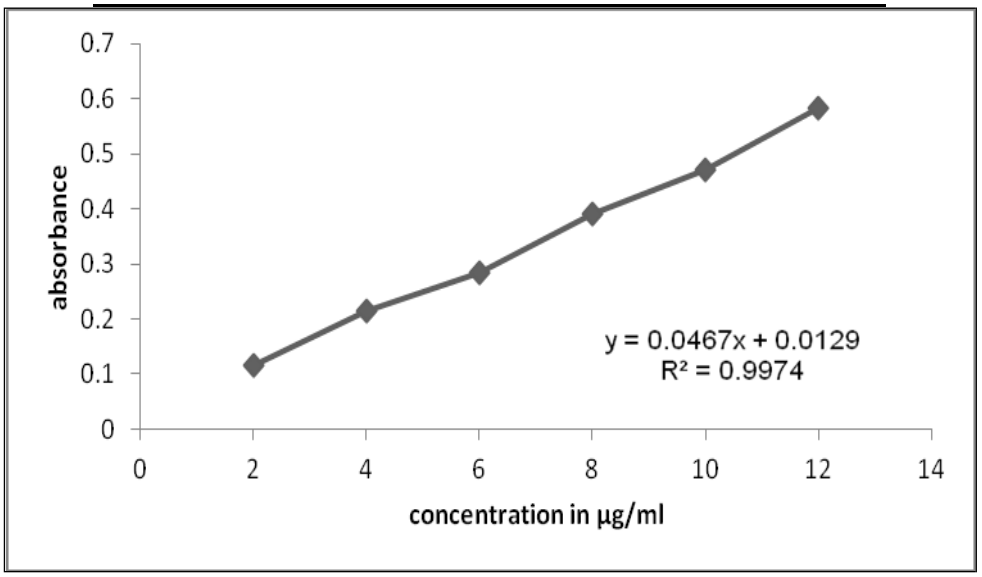


Figure30:Beers-Lambertsplotof Nizatidinein pH7.4phosphatebuffer

2.1.1.6. Drug-excipientscompatibilitystudy

The proper design and the formulation of a dosage form require consideration of thephysical, chemical and biological characteristics of the drug and excipients used infabricating the product. The drug and excipients must be compatible with one anotherto produce a product that is stable, efficacious, attractive, easy to administer and safe.Thecompatibility studiesprovidetheframeworkfor thedrugscombinationwithexcipients in the fabrication of the dosage form. The study was carried out to establishthat the therapeutically active drug has not undergone any changes, after it has beensubjectedto processingsteps during formulation oftablets.

Prepared powder mixture in 1:1 ratio for bulk excipients and in 1:10 for lubricants orfor trace excipients.Ground excipients in mortar and screen through suitable screenfor through mixing. Fill in vial and seal. Keep samples at 55ºc for 10 days. Removesamples after every two days and analyze for drug content, TLC, UV spectra for drugcontent,$R_f$value andλmax.

Table9:Codesof mixturefordrugexcipientscompatibilitystudy

Name	Code
Nizatidine	N
Nizatidine+MCC	NM
Nizatidine+Lactose	NL
Nizatidine+crosspovidone	NC
Nizatidine+SSG	NS

Nizatidine+Mg.stearate	NM
Nizatidine+Talc	NT
Nizatidine+Aerosil	NA
Nizatidine+allexcipients	NAE
Nizatidine+croscarmellose sodium	NCS

Table10:DataforRfvalueofdrugexcipientscompatibilitystudy

Code	Rfvalue			
	0days	2Days	5Days	10Days
N	0.73	0.728	0.729	0.728
NM	0.73	0.731	0.73	0.729
NL	0.73	0.73	0.732	0.028
NC	0.73	0.73	0.73	0.73
NCS	0.73	0.725	0.729	0.729
NS	0.73	0.728	0.728	0.73
NM	0.73	0.73	0.731	0.728
NT	0.73	0.73	0.729	0.729
NA	0.73	0.734	0.73	0.728
NAE	0.73	0.732	0.727	0.728

Table 11: Data for max value in 01.N HCl of drug excipients compatibilitystudy

Code	max(nm)			
	0days	2Days	5Days	10Days
N	314	314	314	314
NM	314	314	315	315
NL	314	314	314	314
NC	315	314	315	314
NCS	314	314	314	314
NS	314	314	312	314
NM	315	314	314	314
NT	314	314	313	315

NA	314	313	315	314
NAE	315	314	314	313

Table12:Dataforassayvalueof drugindrug-excipientscompatibilitystudy

Code	Drugcontent (%) 0days	2Days	5Days	10Days
N	99.93	99.48	99.27	98.97
NM	99.76	99.18	99.12	98.86
NL	99.68	99.18	99.01	98.86
NC	99.46	99.16	98.86	98.74
NCS	99.18	99.10	98.58	98.48
NS	99.16	99.10	98.86	98.51
NM	99.28	99.20	98.89	98.68
NT	99.33	99.28	99.11	98.58
NA	99.18	99.11	98.72	98.18
NAE	99.28	99.18	98.91	98.58

2.1.1.1. FTIRStudies:

Drug excipients compatibility study was performed by mixing drug with polymer inequalproportionandthemixturewaskeptunderacceleratedstabilitycondition(i.e.40^{0}c and 75% R.H.) for a period of 21 days in a glass vial. It was hermeticallysealed with rubber stopper using carnauba wax. Same mixture under control condition(i.e.5%H_20)waskept.IR spectrumwas noted for mixtureafter 21 days.

The I.R. Spectrum of previously dried samples were recorded by KBr dispersiontechnique.2-3 mg of samples was mixed with previously dried IR grade potassiumbromideandkeptinsamplecell,thecellwasthenfittedonsample holderandspectrumwererecordedwith FTIR.

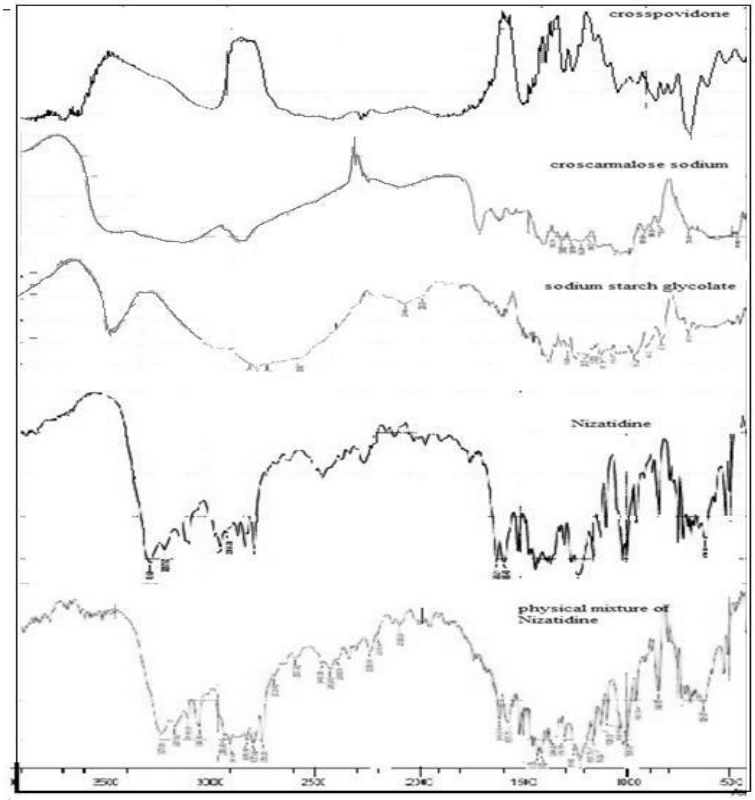


Figure31:IRspectraofpurecrosspovidone,crosscarmaolsesodium,sodiumstarchglycolate, pure Nizatidineand physicalmixtureofNizatidine

2.1.1.9DifferentialScanningCalorimetry

Differential Scanning Calorimetry (DSC) was performed using Shimadzu DSC 60instrument. The samples were hermetically sealed in aluminum pans and heated overthetemperaturerange35°Cto300 Cwithheatingrateof10 C/min.Inertatmosphere wasprovided bypurgingnitrogengas flowingat 10 ml/min.

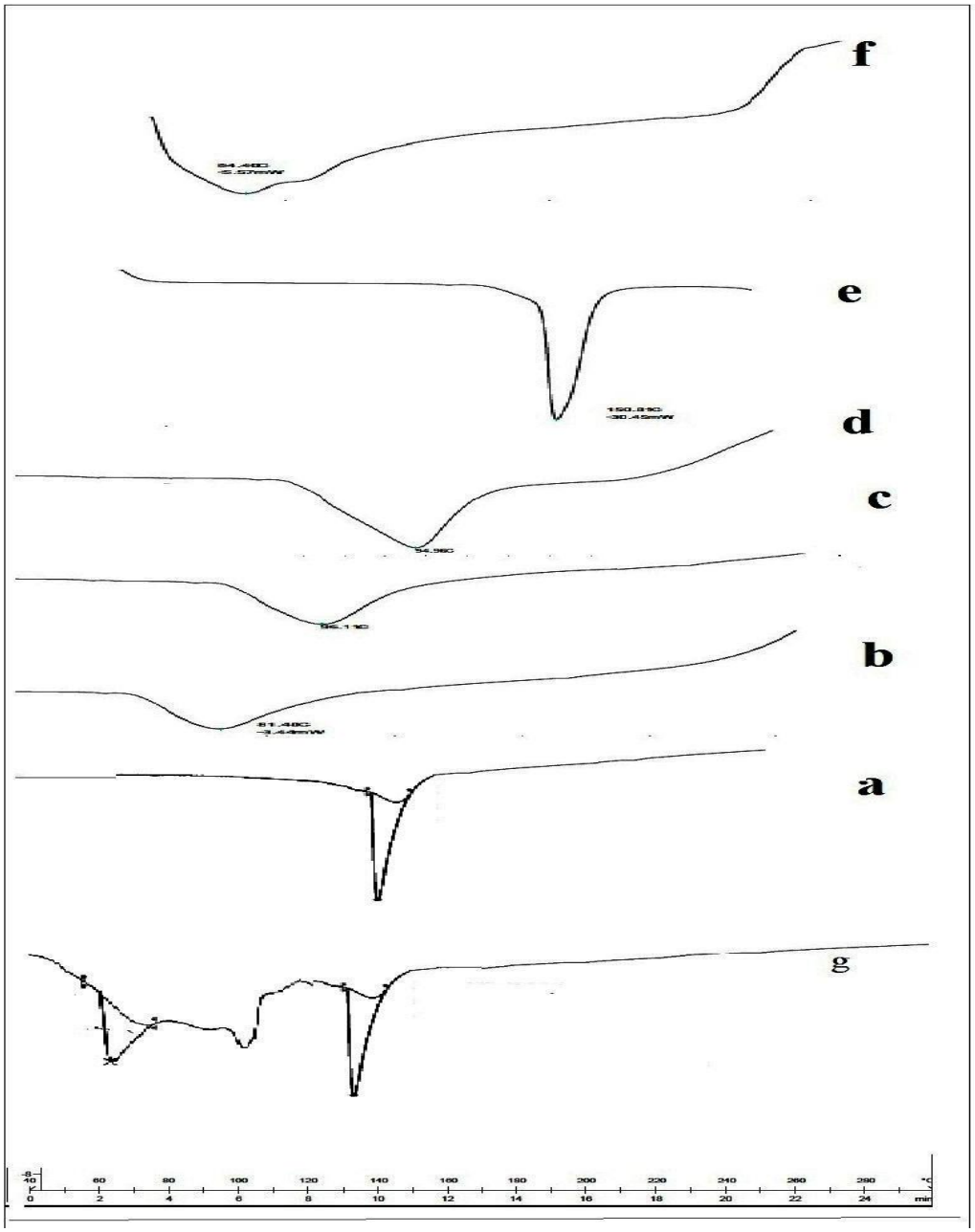


Figure 32: DSC thermogram of (a) pure Nizatidine, (b) pure microcrystallinecellulose,(c)purecroscarmellosesodium,(d)purecrosspovidone,(e)purelactose, (f) pure sodium starch glycolate, (g) physical mixture of Nizatidine withall excipients

2.2 Developmentofformulation

During the past several decades, conventional drug dosage forms have been widelyused for treatment of various conditions. Thesedrug dosage forms typically provideanimmediateorrapidmedicationrelease,andsupplyagivenconcentrationorquantityofthedrugtothebody'ssystemiccirculatory systemwithoutanyratecontrol. To maintain the effective plasma drug concentration, frequent administrationis required. Due to poor drug efficacy, the incidence of side effects, frequency ofadministration and patient compliance of these conventional drug preparations, manytraditional drug dosage forms are undergoing replacement by modified drug-releasedosage forms. Treatments of numerous diseases using traditional drug products areofteninconvenientandimpracticalifdiseasesymptomsoccurduringthenightorearly morning. During the early 1990s, modified-release drug preparations achievedcontinuous and constant-rate drug de- livery, in which constant or sustained drugoutputminimizedrugconcentration“peakandvalley”levelsintheblood,sopromotingdrugefficacyandreducingadverseeffects.Modified-releasedrugpreparations are expected to provide reduced dosing frequency and improved patientcompliance compared to conventional release preparations. Several controlled-

releasepreparationspresentnumerousproblemssuchasresistanceanddrugtolerance.Controlled-release medications deliver continuous treatment, rather than providingrelief of symptoms and protection from adverse events solely when necessary, thedevelopment of a advanced drug delivery systems (DDSs) i.e. pulsatile drug deliverysystem to optimize and create new innovative DDS which provide a defined dose, at achosenrate, ata selectedtime,to atargeted siteisnow agrowingchallenge.

2.2.1 Formulationof coretabletsofNizatidine

The core tablets containing Nizatidine (150 mg per tablet), lactose, microcrystallinecellulose (Avicel® PH101), polyvinyl pyrrolidone (PVP k30)and superdisintegrantlike crosspovidone, croscarmellose sodium (Ac-Di-Sol®) sodium starch glycolate,were prepared by direct compression. Initially, the core tablet excipients were dryblended in polybags for 10min, followed by the addition of Talc, magnesium stearateand Aerosil ® 200. The powder components were further blended for 5min. The coretablets (diameter, 9mm; biconvex; average tablet weight, 360mg) were compressedusingaEight stationtablet machine (karnavati,Ahmadabad,India).

Ingredients	CT1	CT2	CT3	CT4	CT5	CT6	CT7	CT8	CT9
Nizatidine	150	150	150	150	150	150	150	150	150
Lactose	86.8	83.2	79.6	86.8	83.2	79.6	86.8	83.2	79.6
Avicel	100	100	100	100	100	100	100	100	100
Ac-Di-Sol	7.2	10.8	14.4	-	-	-	-	-	-
Crosspovidone	-	-	-	7.2	10.8	14.4	-	-	-
SSG	-	-	-	-	-	-	7.2	10.8	14.4
PVPk 30	10	10	10	10	10	10	10	10	10
Mgst.	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Aerosil	2	2	2	2	2	2	2	2	2
Wt of coretabletsin(mg)	360	360	360	360	360	360	360	360	360

Table13:FormulationCodeforCoreTablets

Material	%weightratio								
Ethylcellulose	90	75	60	90	75	60	90	75	60
EudragitNE30D	10	25	40	-	-	-	-	-	-
Methocel	-	-	-	10	25	40	-	-	-
EudragitS100	-	-	-	-	-	-	10	25	40
Triethylcitrate	20	20	20	20	20	20	20	20	20

Talc	5	5	5	5	5	5	5	5	5

2.2.2 Time-Lagged Coating of CoreTabletsforPulsatileReleaseof Nizatidine

Coatingsolutionsofethylcellulose(rupturablepolymer)combinedwithhydroxypropylmethylcellulose(erodiblepolymer)wereprepare dinisopropylalcohol.Theweightratiosofethylcellulose(AqualonECN10)tohydroxypropylmethylcellulose(MethocelE15),Ethylcell ulosetoeudragits100(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 trals batches. The solution wasplasticized with triethyl citrate (20%, w/w, with respect to dry polymer), and then talcwas added as glidant (5%, w/w, related to dry polymer). The homogeneous dispersionwas gently stirred throughout the coating process. The polymer solution was sprayedonto the core tablets ina conventionalpancoating apparatus till the desired weightgain (5%, w/w). Coating conditions are listed in Table .At each stage the coated tabletswerefurtherdriedinthecoatingpanfor15minat40◦C.Thetabletswerethenplacedintheoven at 40ºC for2h to remove theresidual solvent.

Table14:Coatingsolution

***TriethylcitrateandTalc usedin%w/w withrespecttodrypolymerCoatingofthetablets**

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 coatingsolution through coating gun. The coating pan operated at fixed RPM (35) for allpolymeric solution. The coating solution was applied when the tablet bed in thecoatingpan reached up to 60ºc.

Table15:Theprocessconditionforcoating

Theprocesscondition forcoating	
Inlettemperature	50º-60ºc
Producttemperature	35-40ºc
Sprayrate	4-8ml min^{-1}
Spraynozzle diameter	1mm
Distanceinbetween tabletbed Spraygun	10-15cm
Panspeed	35 RPM
Thelevel of coating	5%

3.1 EvaluationofPowderBlend

Tablet powder blends of core were evaluated for various pre compression parameterssuch as Angle of repose, loose bulk density, Tapped bulk density, Compressibilityindex and Hausner's ratio.

- **Angleof repose**

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

Angleof reposeis calculatedbyformula:

$$r=(area/\pi)^{1/2}. \quad \text{(a)}$$

$$\theta=\tan^{-1}(h/r) \quad \text{(b)}$$

- **Bulkdensity**

Bulkdensityisdefinedasthemassofapowderdividedbythebulkvolume.Thebulk density of a powder depends primarily on particle size distribution, particleshape and the tendency of the particles to adhere to one another. Bothloosebulkdensityandtappedbulkdensitywere determined. A quantity of 10 g of powderfrom each formula, previously lightly shaken tobreakanyagglomeratesformed,wasintroduced intomeasuringcylinder.Aftertheinitialvolumewasobserved, the cylinder was allowed to fall under its own weight onto a hard surfacefrom the height of 2.5 cm at 2-second intervals. The tapping was continued until nofurtherchangeinvolumewasnoted.LBDandTBDwerecalculatedusingthefollowingformulas.

$$LBD = \frac{\text{Weight of the Powder}}{\text{Volume of the packing}}$$

$$TBD = \frac{\text{Weight of the Powder}}{\text{Tapped volume of the packing}}$$

- **CompressibilityIndex**

Thecompressibilityindexofthepowderorgranuleswasdeterminedby Carr'scompressibilityindex.

$$\text{Carr's Index } (\%) = \frac{(TBD - LBD)}{TBD} x100$$

Thisis asimpleindexthatcan bedeterminedon small quantitiesofpowder

- **Hausner'sRatio:**Hausner'ssratiocanbedefinedas'itistheratiooftappeddensitybythe looseDensity'

$$\text{Hausner Ratio} = \frac{\text{Tapped Density}}{\text{Loose density}}$$

3.2 EvaluationofCoreTablets

The result of evaluation of core tablets for thickness, weight variation, hardness, andfriability and drug content were shown in table from these tables it is concluded thatallcoretabletspreparedand passesthe officialevaluation test criteria.

- **Thickness**

The thickness of the individual tablets is measured by use of the Vernier Calipers,whichprovidesaccurateinformationonthevariationsofthicknessbetweenthetablets. Tablets thickness should be controlled with in a ±5% variation of the averagethickness.In addition thickness must be controlled to get uniform tablet weight in thelot. From six tablets from each batches of formulation of core tablets were used andmeanthicknessvalue and standarddeviationwerecalculated for eachformulation.

- **Hardness**

The hardness which is called the crushing strength for tablet is measured to determineitsstrengthandenduranceduringtransport.Thehardnessalsohasanindirecteffecton the disintegration ofthe tablets as more hardness delays the disintegration time.The hardness or the crushing strength of the tablets are determined by using Monsantohardness tester. For each formulation, the hardness of six tablets was measured usingMonsantohardnesstesterandmean valueand standarddeviation wascalculated.

- **Weightvariation**

Tostudyweightvariation,20tabletsofeachformulationwereweightusinganelectronic digital balance. The average weight of each tablet was calculated and fromthepercentagedeviation in weight was calculated.

- **Friability**

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence oflamination or breakage when subjected to mechanical shock or attrition. The friabilityof tablets was determined using Roche Friabilator. It is expressed in percentage (%).Twenty tablets were initially weighed (Initial Wt) and transferred into friabilator. Thefriabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. Thetabletswere weighedagain (FinalWt). The% friabilitywasthen calculated by,

$$\mathbf{F}\ (\%) = \frac{\text{Initial Wt} - \text{Final Wt}}{\text{Initial Wt}} \mathbf{x100}$$

- **Drugcontent**

Five tablets were weight accurately and powdered. The drug content was determinedbyfollowingprocedure.
Standardsolution: 10µg/ml ofNizatidine solutionin 0.1N HCl
Sample solution**:** an accurately weight amount of powder equivalent to 100 mg ofNizatidine was extracted with 100 ml0.1 N HClto get final concentration of 10µg/ml. measure the absorbance of standard and sample solution at 314 nm using o.1NHCl solution as blank.
The drug Nizatidine that belongs to the H_2 antagonist class has been reported in themonographstohave'Nizatidinecontainsnotlessthan97.0percentandnotmorethantheequivalent of 101.0 per cent ofstated amount of thedrug.

- **Disintegrationtest**

It is determined by using USP device which consist of 6 glass tubes that are 3 incheslong, openat one endand held against 10 meshscreenatthe bottom end of basketrack assembly. To test for disintegration time, one tablet is placed in each tube and thebasket arch is positioned in a 900 ml beaker of water at $37^0C \pm 2^0C$. A standard motordriven device is used to move the

basket assembly up and down. To be in compliancewith the USP standard, all tablets must disintegrate and all particles must pass throughthe10 mesh in the timespecified.

- **Dissolutionofcoretablets**

The test was carried out in USP dissolution basket assembly (Model TDL Electrolab,India) in 900ml medium at 37±0.5 ◦C at a rotation speed of 100rpm using pH 6.8phosphate buffer for 1 Hr .the aliquots of dissolution fluid were removed at specifictime intervals and assayed for the amount of Nizatidine released by spectrometer(modelshimadzu-UV1700, Japan)at wavelength314nm.

3.3 Evaluationof coatedtabletsforpulsatilereleaseof Nizatidine

Prepared pulsatile release tablet was evaluated for official parameters like, Thickness,Hardness,and weight variation, Lag time of coating tabletsand content uniformityandIn-vitrodissolutionstudies.

- **Thickness**

The thickness of the individual tablets is measured by use of the Vernier Calipers,whichprovidesaccurateinformationonthevariationsofthicknessbetweenthetablets. Tablets thickness should be controlled with in a ±5% variation of the averagethickness.In addition thickness must be controlled to get uniform tablet weight in thelot. From six tablets from each batches of formulation of core tablets were used andmeanthicknessvalue and standarddeviationwerecalculatedfor eachformulation.

- **Hardness**

The hardness which is called the crushing strength for tablet is measured to determineitsstrengthandenduranceduringtransport.Thehardnessalsohasanindirecteffecton 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 Monsantohardness tester. For each formulation, the hardness of six tablets was measured usingMonsantohardnesstesterandmean valueand standarddeviation wascalculated.

- **Weightvariation**

Tostudyweightvariation,20tabletsofeachformulationwereweightusinganelectronic digital balance. The average weight of each tablet was calculated and fromthepercentagedeviation in weight was calculated.

- **Lagtimeof coatingtablets:**

CoatingtabletswereplacedintoUSPdissolutionpaddleapparatusatrotationspeed50 rpm with phosphate buffer IP pH 6.8, 37±0.5ºc and observed visually. The lag timewasdefinedasthe point, whenthe outer coatingruptured dueto swelling.

- **Drugcontent**

Twenty coated tablets were weight accurately and powdered. The drug content wasdeterminedbyfollowingprocedure.
Standardsolution: 10µg/ml ofNizatidine solutionin 0.1NHCl
Sample solution: an accurately weight amount of powder equivalent to 100 mg ofNizatidine was extracted with 100 ml0.1 N HClto get final concentration of 10µg/ml. measure the absorbance of standard and sample solution at 314 nm using o.1NHClsolution as blank

- **DissolutionmethodologyforcoatedtabletsforpulsatilereleaseofNizatidine**

To verify how the composition of the core and the barriers interferes with the drugrelease profile from the cores, in vitro dissolution studies were carried out using USPtype I dissolution apparatus I (basket method; Electrolab India Pvt. Ltd., Mumbai,India) in 900ml medium at 37±0.5 ◦C at a rotation speed of 100rpm. To mimic gastricpH conditions, test was carried out in 0.1N hydrochloric acid (pH 1.2) for2 hr.simulated intestinal fluid pH 6.8 for 3 hr and simulated colonic fluid pH 7.4. ThebuffersystemhavingpH6.8andpH7.4wasselectedtosimulatetheconditioninsmall intestine and colon. 5ml sample was withdrawn every 1h, filtered through andimmediately replaced by the fresh dissolution medium. All the dissolution sampleswere filtered through filter paper and analyzed immediately after the completion ofdissolutiontestbyUV–Visiblespectrophotometer(ShimadzuUV-1700,UV–visscanning spectrophotometer, Japan). Nizatidine released in 0.1N HCl was estimated atmax 314 nm.In this dissolution studies the USP type I dissolution apparatus I wasquitesuitableforcarryingthesamplesinthenextmediumanddissolutioniscontinuedwithout disturbingand touchingthe surfaceof coated tablets

- **DrugReleasekinetics**

Inmodeldependentapproachesreleasedatawerefittedtofivekineticsmodelincluding zero order , first order, Higuchi equation, Korsemeyer- Peppas equationand hixon-Crowell release equation to find the higher correlation (r^2>0.98), releaseexponent (n)and rateconstant (k_1)

StabilityTestingof theBestFormulation

Stability studies are an integral part of the drug development program and are one ofthemostimportantareasintheregistrationofPharmaproducts.Thepurposeof
Stability testing is to provide evidence on how the quality of a drug substance or drugproductvarieswithtimeunder theinfluence ofa variety of environmentalfactorssuch as temperature, humidity and light and enables recommended storage conditions,retestperiodsandshelflivestobeestablished.Stability assessmentstartedwithstudies on the substance to determine degradation products and degradation pathway.Temperature dependent stability studies were carried out on the best batches. Theywere packed in Low Density Polyethylene (LDPE) bags enclose in High DensityPolyethylene (HDPE) container.And stored under the following conditions for aperiodas prescribed byICH guidelines for accelerated studies.

(I)40±2ºcandRH75%±5%

Tablets were withdrawn after a period of initial, 1, 2, 3 months and analyzed for,Hardness,Drugcontent (%),Lagtime andDissolution study.

Table16:Physicalparametersof powderblend

Batch no	Parameters				
	Angle ofRepose (θ)	**BulkDensitygm/cm^3**	**Tapped Density gm/cm^3**	**Hausner's Ratio(H_R)**	**Carr's index(%)**
CT1	25.54	0.539	0.668	1.24	19.33
CT2	26.59	0.585	0.675	1.22	13.33
CT3	24.70	0.537	0.662	1.23	18.88
CT4	25.65	0.541	0.668	1.24	19.01
CT5	27.73	0.539	0.663	1.23	18.70
CT6	26.28	0.521	0.645	1.24	19.22
CT7	29.66	0.537	0.660	1.23	18.63
CT8	27.40	0.518	0.645	1.24	19.69
CT9	28.20	0.535	0.660	1.23	18.94

Table17:Evaluationparameters of coretablets

Batchno	**Thickness(mm)**	**Friability (%)**	**Hardness(Kg/cm^2)**	**WeightVariation(mg)**	**Drugcontent %**	**Disintegrationtime(Sec)**
CT1	3.43±0.05	0.60	4.8±0.4	0.362±0.7	98.28	140
CT2	3.46±0.03	0.48	4.9±0.5	0.358±0.5	98.48	128
CT3	3.55±0.02	0.57	5.1±0.8	0354±0.4	99.20	108
CT4	3.61±0.02	0.51	4.8±0.2	0.364±0.3	98.22	134
CT5	3.42±0.05	0.61	5.2±0.12	0.359±0.5	98.97	114
CT6	3.51±0.04	0.26	5.4±0.3	0.359±0.7	99.86	101
CT7	3.42±0.05	0.39	5.1±0.8	0.362±0.4	98.15	135
CT8	3.45±0.03	0.42	4.9±0.5	0.357±0.6	98.89	121
CT9	3.45±0.04	0.58	4.7±0.3	0.356±0.6	98.98	110

Table18:Dissolutiontestdataforcoretablets

Time (min)	CT1	CT2	CT3	CT4	CT5	CT6	CT7	CT8	CT9
0	0	0	0	0	0	0	0	0	0
5	22.48 ±0.04	25.18 ±0.12	30.45 ±0.05	43.59 ±0.11	47.73 ±0.02	49.97 ±0.21	23.48 ±0.8	24.18 ±0.05	29.45 ±0.04
10	45.3 ±0.08	46.53 ±0.13	51.51 ±0.04	63.3 ±0.24	65.69 ±0.06	67.48 ±0.03	39.3 ±0.22	40.53 ±0.05	49.51 ±0.11
15	66.24 ±0.25	67.47 ±0.08	68.29 ±0.01	71.95 ±0.08	78.25 ±0.04	79.25 ±0.18	61.24 ±0.14	65.47 ±0.09	66.29 ±0.07
20	78.08 ±0.07	78.09 ±0.17	83.54 ±0.05	78.16 ±0.01	88.25 ±0.10	89.28 ±0.06	72.08 ±0.04	77.09 ±0.13	80.54 ±0.23
25	81.15 ±0.12	87.24 ±0.04	95.54 ±0.8	87.16 ±0.21	92.25 ±0.02	93.54 ±0.11	84.77 ±0.05	85.24 ±0.12	91.54 ±0.04
30	85.75 ±0.05	91.51 ±0.23	97.51 ±0.13	94.87 ±0.04	96.75 ±0.03	97.11 ±0.10	85.26 ±0.09	90.51 ±0.21	96.51 ±0.18
45	94.94 ±0.14	96.02 ±0.12	97.85 ±0.04	97.45 ±0.16	97.48 ±0.23	98.48 ±0.14	94.04 ±0.15	97.02 ±0.13	96.85 ±0.01
60	95.02 ±0.03	96.6 ±0.05	98.66 ±0.1	97.45 ±0.09	98.42 ±0..06	99.68 ±0.02	95.02 ±0.12	97.56 ±0.05	98.98 ±0.08

Table19:Evaluationparametersof pulsatilereleaseNizatidinetablets:

Batch no.	Thickness (mm)	Hardness(Kg/cm^2)	WeightVariation(mg)	Lag time(Hr)	Drugcontent%
F1	3.63±0.04	5.1±0.4	0.382±1.6	5.39±0.03	98.28
F2	3.66±0.02	5.3±0.5	0.378±1.4	6.18±0.06	98.48
F3	3.75±0.03	5.2±0.8	0374±0.4	7.17±0.07	99.20
F4	3.81±0.06	5.0±0.2	0.382±3.5	2.27±0.07	98.22
F5	3.62±0.07	5.5±0.12	0.377±1.6	3.12±0.02	98.97
F6	3.71±0.06	5.6±0.3	0.377±2.8	3.28±0.04	99.86
F7	3.62±0.05	5.3±0.8	0.380±0.3	3.38±0.06	98.15
F8	3.55±0.03	5.2±0.5	0.375±1.5	4.24±0.04	98.89
F9	3.65±0.04	5.1±0.3	0.376±2.4	4.35±0.05	98.98

Table20:DissolutiontestdataforpulsatilereleaseNizatidinetablets

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	0.87 ±0.02	0.53 ±0.07	0.48 ±0.07	0.69 ±0.07	0.45 ±0.09	0.15 ±0.08	0.87 ±0.01	0.53 ±0.12	0.48 ±0.02
2	1.47 ±0.02	1.12 ±0.04	0.64 ±0.06	1.20 ±0.13	0.97 ±0.04	1.58 ±0.10	1.47 ±0.03	1.12 ±0.07	0.64 ±0.07
3	1.96 ±0.11	0.34 ±0.01	1.00 ±0.01	84.59 ±0.02	2.72 ±0.10	8.16 ±0.03	8.16 ±0.10	2.99 ±0.02	0.99 ±0.13
4	2.71 ±0.03	0.77 ±0.06	1.14 ±0.06	87.14 ±0.01	58.69 ±0.13	83.00 ±0.11	84.26 ±0.09	6.15 ±0.08	7.16 ±0.10
5	9.31 ±0.10	1.40 ±0.07	2.42 ±0.01	88.78 ±0.03	96.13 ±0.06	97.13 ±0.02	93.26 ±0.12	85.16 ±0.03	70.13 ±0.08
6	79.61 ±0.02	10.07 ±0.10	3.94 ±0.03	90.35 ±0.11	96.66 ±0.08	98.92 ±0.10	94.21 ±0.06	93.48 ±0.01	82.13 ±0.04
7	85.78 ±0.08	91.13 ±013	14.74 ±0.08	96.58 ±0.06	97.16 ±0.09	98.95 ±0.11	95.15 ±0.08	95.87 ±0.07	90.15 ±0.07
8	93.80 ±0.13	92.72 ±0.08	87.87 ±0.06	96.58 ±0.03	97.16 ±0.02	98.95 ±0.08	98.13 ±0.07	96.26 ±0.09	95.75 ±0.09
9	93.80 ±0.04	94.72 ±0.04	92.51 ±0.07	96.58 ±0.10	97.16 ±0.12	99.58 ±013	98.13 ±0.04	97.13 ±0.07	96.13 ±0.11
10	93.80 ±0.07	94.72 ±0.09	92.50 ±0.13	96.58 ±0.51	97.16 ±0.03	99.62 ±0.10	98.13 ±0.02	97.18 ±0.01	96.14 ±0.13

Table21:KineticReleaseData forpulsatilereleaseNizatidinetablets

Batch	Zero order	First order	Hixon	Higuchi	Korsemeyer-Peppas	
	r^2	r^2	r^2	r^2	r^2	n value
F1	0.819	0.837	0.835	0.750	0.818	0.328
F2	0.719	0.713	0.713	0.621	0.636	0.338
F3	0.613	0.568	0.581	0.503	0.722	0.767
F4	0.627	0.876	0.788	0.725	0.762	0.253
F5	0.862	0.803	0.845	0.828	0.877	0.259
F6	0.751	0.810	0.852	0.803	0.928	0.243
F7	0.753	0.824	0.862	0.804	0.868	0.288
F8	0.806	0.888	0.858	0.748	0.892	0.279

F9	0.863	0.815	0.914	0.835	0.856	0.249

Table22:Evaluationparametersofthebestbatch F6afterstability

Parameter	Initial	1Month	2Month	3Month
Hardness(kg/cm^2)	5.6	5.4	54	5.6
Drugcontent(%)	99.86	99.12	99.15	99.54
LagTime(h)	3.28	3.21	3.30	3.25
% DrugRelease	99.62	99.05	98.90	98.81

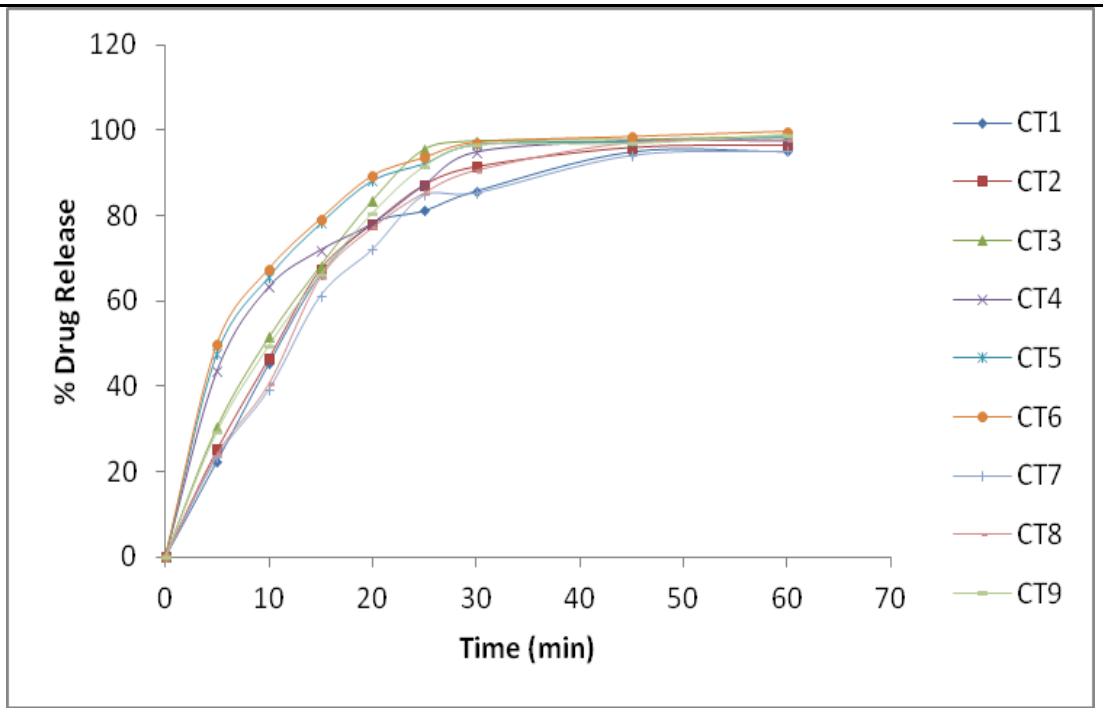


Figure33:Drugrelease profileof coretablets.

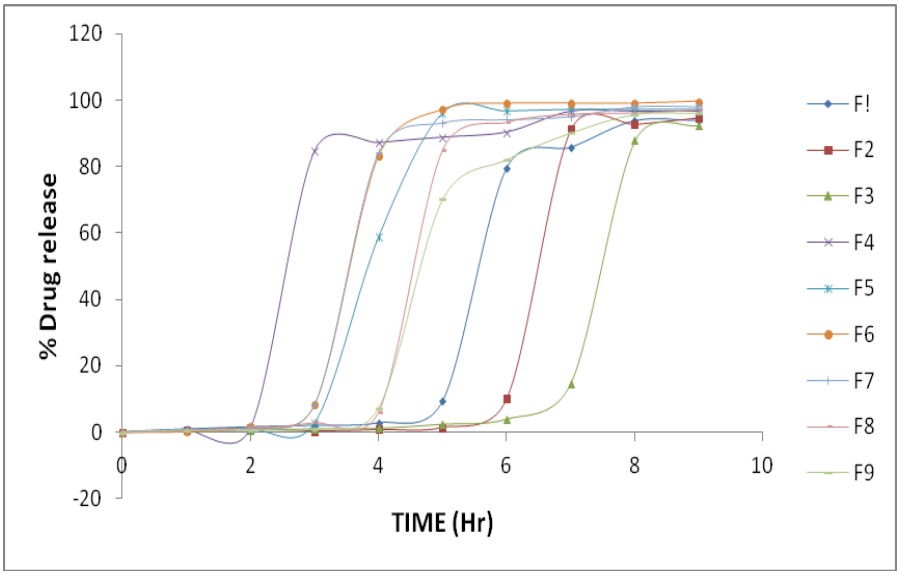


Figure34:DrugreleaseprofileofpulsatilereleaseNizatidinetablets.

4.1 PreformulationstudiesforNizatidine

- Nizatidinewasobservedtobealmostwhitebuffcrystallinepowder,sulphermercaptonodourwithmetallicbittertest.Theresultsareshown inTable 2.
- Themeltingpoint was found to be 131-134ºC.
- Thesolubilitystudies of Nizatidine wereperformedin 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. ThesolubilitystudiesofNizatidinewereperformedinvarioussolventsissummarizedin Table3
- The UV spectrum was recorded in the range of200-400 nmas shown inFigure24, 25, 26.
- Maximum absorption of wavelength was determined in 0.1 N HCl, pH 6.8phosphatebuffer, pH7.4Phosphate buffer.Theresults is shown inTable 4
- IRspectrumof Nizatidine isshownin Figure27.The principalpeaksofmaximumabsorbancealongwith interpretation areshownin Table 5
- A linear relationship was obtained in Beer-lamberts plot of Nizatidine. Theabsorbance valueare shown in Table 6,7,8 using absorbance concentrationdatabeer-lamberts plot was plotted in Figure28,29,30
- Drug excipients compatibility studies show no interaction between Nizatidineand selected excipients as there was no significant shift of λ max and R_f value.Thedrugcontent was also good. Theresults areshownin Table 10, 11, 12

FTIRSpectroscopyStudy:

TheIR spectrameasurements were performed shown in Figure 31. TheInfraredSpectra of pure Nizatidine exhibited IR signals showscharacteristic peaks on at 3280cm^{-1}(N-H stretching), 3107 cm^{-1}(C-H stretching in NO_2CH),3094 cm^{-1}(CH stretch inthiazolering),1521cm^{-1}(Thiazolering),2945cm^{-1},2860cm^{-1}(C-HstretchinginNCH$_3$,CH$_2$CH$_2$),1377cm^{-1},1359cm^{-1}(ThiazoleringforonefrequencyissymNO$_2$,H-bonded ,conjugated)

The Infrared Spectra ofphysical mixture ofNizatidine exhibited IR signals showscharacteristic peaks on at 1359 cm^{-1}(Thiazole ring for one frequency is sym NO$_2$,H-bonded ,conjugated), 2860 cm^{-1}(C-H stretching in NCH$_3$,CH$_2$ CH$_2$), 3094 cm^{-1}(CHstretchin thiazole ring),3280 cm^{-1}(N-H stretching).

DifferentialScanningCalorimetrystudy

The DSC thermogram obtained of pure drug and excipients are shown in Figure 32.TheDSCcurveofpureNizatidineexhibitedasingleendothermiccurvecorresponding to the melting of drug. Onset of melting was obtainedat 135ºc.shownin Figure 30a. The superdisintegrant croscarmellose sodium, crosspovidone ,sodiumstarch glycolate shows broad endothermic fusion peaks at 96.11ºc,94.96ºc and 84.48ºcrespectively shown in Figure 30c,30d,30e which is due to glass transition state. TheDSC spectrum of physical mixture of Nizatidine and mixture of other excipients hasalsoshownsameendothermicpeakslikepuredrugshowninFigure30.Theseobservations of DSC study indicate absence of significant interactions between drugandexcipients used intablet formulations and coatingmaterials.

Evaluationof PowderBlend

Powdercharacteristicsforallbatcheswereevaluatedforvariousprecompressionparameterssuchas Angleofrepose,loosebulkdensity(LBD),Tappedbulkdensity(TBD), Compressibility index and Hausner's ratio. The results are shown in Table 16.Allpreparedbatchesexhibitedgoodflowpropertiesandcompressioncharacteristicsascomparedtopure drug.TheangleofreposeforbatchesCT1 toCT8exhibitedangleof repose between24.70to29.66indicatinggoodflow propertiesfor the powderblendreadytocompress.Carr'sindexforallthepreparedbatchesvariedfrom13.33to 19.69indicatinggoodcompressioncharacteristicsforthegranulesreadyforcompression.Hausner'sRatioforallthebatcheswasfoundtobebetween1.22to 18.63indicatinggoodcompressioncharacteristics.

4.2 Evaluation ofCoreTablets

Routine pharmacopoeial physical evaluation tests for uncoated tablets were performedlike tablet thickness, weight variation, tablet hardness, friability and drug content.Results obtained for these tests are summarized in Table17. Thickness of all uncoatedtablets varied from 3.42±0.05 mm to 3.61±0.02 mm. Friability for all batches rangedbetween 0.26 % to 0.61 %.Tablets hardness varied from 4.7±0.3 Kg/cm^2 to 5.4±0.3Kg/cm^2. Weight Variation for all batches was between 0354±0.4mg to 0.364±0.3mg.Drug content from all batches was 98.28 % to 99.86%. While the disintegration timefor uncoated tablets varied from 101 seconds to 140 seconds. All the prepared batchespassedtheroutinephysical evaluation testsas per limits of pharmacopoeia.

From these results it is observed that all core tablets prepared and passes the officialevaluationtestcriteria.Thethicknessoftheindividualtabletsismeasuredbyuseof

theVernierCalipers,whichprovidesaccurateinformationonthevariationsofthicknessbetweenthetablets.(Tabletsthicknessshouldnotl essandnotmorethanina±5% variation oftheaveragethickness.)
Batch CT6 contained Concentration 4% of crosspovidone giving lowest disintegrationtime.Resultsfordisintegrationtimeobtainedforvariousbatchesaregivenintable17.

Dissolutionofcoretablets:

Dissolution data of core tablet of Nizatidine tablets are reported in Table 18. Drugdissolved at specific time periods was plotted as percent drug release versus time(min). Release profile of core tablet of Nizatidine with different concentration ofsuperdisintegrantareshown in Figure33
All the core tablets batches showed complete drug release within 60 min. The percentof the drug release versustime plotshows thatthe dissolutionrate wasdirectlyproportional 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 differentconcentrationof superdisintegrant in coretablet.

4.2 Evaluation of pulsatilereleasetabletsofNizatidine

Pharmacopoeialphysicalevaluationtestsforcoatedtabletswereperformedliketabletthickness,weightvariation,tablethardness,drugco ntentandcontentuniformity
.ResultsareshowninTable19fromthesetablesitisconcludedthatallcoretabletspreparedandpassestheofficialevaluationtestcriteria.The tablethardnessofallthecore tablet formulation was determined and it was found in the range 5.1-5.6 kg/cm^2.**Evaluationparametersofpulsatilerelease**
Routine pharmacopoeial physical evaluation tests for coated tablets were performedliketabletthickness,weightvariation,tablethardnessanddrugcontent.Resultsobtained for these tests are summarized in Table 19. Thickness of all coated tabletsvaried from 3.63±0.04mm to 3.81±0.06mm. Tablets Hardness varied from 5.1±0.3Kg/cm^2 to 5.6±0.3.Weight Variation for all batches was between 0.374±0.4 mg to0.382±3.5 mg. Drug content from all batches was 98.22% to 99.86%. While the lagtimeforcoated tablets varied from 2.27±0.07hrto7.17±0.07hr.
All the prepared batches passed the routine physical evaluation tests as per limits ofpharmacopoeia.From these results it is observed that all core tablets prepared andpasses the official evaluation test criteria. The thickness of the individual tablets ismeasuredbyuseoftheVernierCalipers,whichprovidesaccurateinformationonthe
variations of thickness between the tablets. (Tablets thickness should not less and notmore than in a ±5% variation of the average thickness.)The weight variation test
wascarriedoutasperofficialmethodandaveragepercentagedeviationofalltheformulation were found to be within limit as per pharmacopeia standardthe deviationshould not less than 5%. Drug content study of all formulation was carried out as perofficial method and the results are shown in Table 19. The content uniformity test wasalso carried out as per official method and it was found that all batches showed goodcontentuniformity.

Lagtime forcoatedtablets

The lag time for all prepared batches was found to be dependent onthe ratio ofcoating component. Ethyl cellulose and Eudragit NE 30D was used in the ratio of60:40%, 75:25% and 90:10% (w/w). The lag time of all batches of was found to be inbetween 5.39±0.03 to7.17±0.07. Ethyl cellulose and Methocel was used in the ratio of60:40%, 75:25% and 90:10% (w/w). The lag time of all batches of was found to be inbetween 2.27±0.07 to 3.28±0.04. Ethyl cellulose and Eudragit S100 was used in theratio of 60:40%, 75:25% and 90:10% (w/w). The lag time of all batches of was foundto be in between 3.38±0.06 to 4.35±0.05. As the concentration of rupturable polymerincreased proportionally increases the lag time. In this study formulation having F6contained (60:40) w/w amount of coating ratio shows the lag time having a 3.28±0.04

Dissolutionstudies:

Dissolution data of pulsatile release Nizatidine tablet are reported in Table 20 drugdissolved at specific time periods was plotted as percent drug release versus time (hr)curve.ReleaseprofileofNizatidinewithdifferentpolymercoatisshowninFigure34.
All polymers shows no drug or small amount of drug release in the first two hoursafter words a different drug release profile was evident for each polymer in differentratio. The time at which rupture of the polymer layer in the dissolution medium wastaken as indication for the beginning of the drug release into the medium.the lag timeand drug release was directly related to concentration ratio to the polymer in coatingsolution andthe coating level. Percent drug release Vs time plotshows that thedissolution rate was inversely proportional to the combination of polymer in coatingsolutionshown in Figure34.
A significant difference was observed in the percent of the drug release for differentcombinationofpolymerincoatingsolution.Allthecoatedtabletwithvariablecoatingcombination showed anearlycomplete drugreleasein 6h-8h
The percent of the drug release versus time plot shows that the dissolution rate wasinversely proportional to the amount of film forming (erodible) polymer in the coatingsolutionThe lag time and in vitro drug release profile for all three polymers combinations withethylcellulose in different ratio is different

Kineticmodellingofdrugrelease

To analyze the *in vitro* release data various kinetic models were used to describe therelease kinetics. Data obtained from the in-vitro release studies were subjected toKinetic treatment to know the order of release. The 'r' values for zero order, firstorder, higuchi and Peppas are given in table 21. From these tables it is observed thatthereleaseprofileswerenon-linearsuggestingthatthedrugreleasefromtheformulations was not zero order that was confirmed by low 'r^2' values of 0.613 – 0.8163. Higuchi plots of all the formulations were non linear because 'r^2' values arenot near about 1 in all the cases. The formulations were subjected to Peppas plots bytaking log cumulative % drug released versus log time. The plots are found fairlylinear and slope value was calculated (n value) which was ranges of 0.243 to 0.767 orF1 – F9 indicatingthe drugwas released byFickian diffusion mechanism.[84]
Thezeroorderratesdescribethesystemswherethedrugreleaserateisindependentof its concentration. The first order describes the

release from system where releaserate is concentration dependent. According to Higuchi release of drugs from insolublematrix as a square root of time dependent process based on Fickian diffusion. TheHixson-Crowell cube root law describes the release from systems where there is achange in surface area and diameter of particles or tablets [85]. Korsemeyer et al deriveda simple relationship which described drug release from a polymeric system. To findoutthemechanismofdrugrelease,first60%drugreleasedatawasfittedinKorsemeyer–Peppasmodel[86]

$$Q_t/Q_\infty = K_k t^n$$

Where Mt / M∞ is fraction of drug released at time t, k is the rate constant and n is therelease exponent. The n value is used to characterize different release mechanisms asgiventable23 for cylindrical shaped matrices.

Table23:Diffusionexponentandsolutereleasemechanismforcylindricalshape[88]

Exponent(n)	Overallsolutediffusionmechanism
0.5	Fickiandiffusion
0.5 <n <0.89	Anomalous(non-Fickian)diffusion
1.0	Case-IItransport
Higherthan1.0	Supercase-IItransport

According to Korsemeyer where n is the release exponent, indicative of mechanism ofdrug release. Fickian diffusional release and a case-II relaxational release, are thelimits of this phenomenon. Fickian diffusional release occurs by the usual moleculardiffusion of the drug due to a chemical potential gradient. Case-II relaxational releaseisthedrugtransportmechanismassociatedwithstressesandstate-transitioninhydrophilic glassy polymers which swell in water or biological fluids. This term alsoincludes polymer disentanglement and erosion.[87] Table 23 describes the limits of thisanalysis for cylindrical shape, e.g. a tablet. The value of the release exponent in tabletformulationis.0.243 indicating Fickian diffusion.

StabilityStudy

The best batch F6 was stored at 40^{0}C (±5ºc) and 75% RH (±5%) for 3 months toanalyze various physical parameters, results were showed inTable 22. No majordifferences were found between evaluated parameters before and after and all are inacceptablelimits.[89]

SUMMARYANDCONCLUSION

Nizatidine was to be freely soluble in chloroform, in methanol; soluble in water andbuffered solution slightly soluble in ethyl acetate and isopropanol. The melting wasobservedat 131-134ºc.

TheDSCcurveofpureNizatidineexhibitedasingleendothermicresponsescorresponding to the melting of drug. Onset of melting was obtained at 135ºc.Thesuperdisintegrantcroscarmellosesodium,crosspovidone,sodiumstarchglycolateshows broad endothermic fusion peaks at 96.11ºc, 94.96ºc and 84.48ºc respectivelywhichisduetoglasstransitionstate.TheDSCspectraofphysicalmixtureofNizatidineandmixtureofotherexcipientshasalsoshownsameendothermicpeaklikepuredrug.TheseobservationsofDSCstudy indicateabsenceofsignificantinteractionbetween drugandexcipients used intablets formulation.

The Infrared Spectra of pure Nizatidine exhibited IR signals showscharacteristicpeaks on at 3280 cm^{-1}(N-H stretching), 3107 cm^{-1}(C-H stretching in NO_2CH),3094cm^{-1}(CH stretch in thiazole ring), 1521 cm^{-1}(Thiazole ring), 2945 cm^{-1},2860 cm^{-1}(C-HstretchinginNCH_3,CH_2CH_2),1377cm^{-1},1359cm^{-1}(Thiazoleringforonefrequencyis sym NO_2,H- bonded ,conjugated).The Infrared Spectra ofphysical mixture ofNizatidine exhibited IR signals showscharacteristic peaks on at 1359 cm^{-1}(Thiazolering for one frequency is sym NO_2,H- bonded ,conjugated), 2860 cm^{-1}(C-H stretchinginNCH_3,CH_2CH_2),3094cm^{-1}(CHstretchinthiazolering),3280cm^{-1}(N-Hstretching). The IR spectrum of physical mixture shows the major peaks of Nizatidine.These observations of IR spectra indicate that's there was no chemical interaction inbetweenNizatidine and otherexcipients.

Powder blends for all batches of core tablet were evaluated for various precompressionparameterssuchasAngleofrepose,loosebulkdensity,Tappedbulkdensity,Compressibility index and Hausner's ratio so these observations concluded that, thecoretablets powder blend showsgood flowpropertyandgood compressibilityindex.The core tablets of Nizatidine were complied the official tests for thickness, weightvariation, hardness, friability, drug content and dissolution studies. It was observedthatthereleasefromCT1toCT9wasrangingbetween95.02 to 99.08% ofthedrugreleasewithin60min.Theformulationcontained2-4%w/wofcrosscarmaolsesodium(CT1-CT3)showsthedisintegrationtimefrom108to140secanddrugrelease in the ranging between 95.02-98.66%. The formulation batches contained 2-4% crosspovidone (CT4-CT6) shows the disintegration time time from 101to 134 secanddrugreleaseintherangingbetween97.45-99.08%.Theformulationbatchescontained 2-4% sodium starch glycolate (CT7-CT9) shows the disintegration timefrom110 to 135 secanddrugreleasein therangingbetween 95.02-98.98%.

From results obtained from dissolution and disintegration time the best batch wasfound to be CT6. Core tablets prepared with4% crosspovidone start disintegratingwithinfewmin.itshows50%drugreleasein5minand90%drugreleasein20min.as the amount of superdisintegrant decrease the release was decreased. Pulsatile drugdeliverysystemrequiredfastdrugreleaseafterinitiallagphase.Formulationcontaining 4% crosspovidone showsfastdisintegration and dissolutionandhenceusedas corefor furtherlagged time coatingformulation.The coated tablets of Nizatidine were evaluated for Thickness, Hardness, Weightvariation,disintegrationtest, andcontent uniformityandIn-vitrodissolutionstudies

It was observed that the release from F1 toF9 was ranging between 92.50 to 99.62%ofthe drugreleaseupto 10 hr.The formulation coated with ethyl cellulose with the Eudragit NE30D in the ratio of90:10%,75:25%,60:40%(w/w)(F1-

F3)showsthelagtime5.39±0.03,6.18±0.06and 7.17±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)showsthelagtime2.27±0.07,3.12±0.02and3.28±0.04hrrespectively 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)showsthelagtime3.38±0.06,4.24±0.04and4.35±0.05hrrespectivelyanddrugrelease intherangingbetween96.14-99.13%.Thebestbatchselectedonthebasisofdrugreleaseafteralagtime.FormulationF6couldnotreleasethedrugininitialhoursbutgivesth eimmediatelyburstreleaseattime ofmidnight hours.To analyze the *in vitro* release data various kinetic models were used to describe therelease kinetics. The zero order rates describe the systems where the drug release rateis independent of its concentration. The first order describes the release from systemwhere release rate is concentration dependent. According to Higuchi release of drugsfrom insoluble matrix as a square root of time dependent process based on Fickiandiffusion.TheHixson-Crowellcuberootlawdescribesthereleasefromsystemswherethereis achangeinsurfaceareaand diameter ofparticles or tablets.

$C = K_o t$

Where,K_0iszero-orderrateconstantexpressedinunitsofconcentration/timeandtisthe time.

$LogC = LogCo - Kt/2.303$

Where,C_0 is theinitialconcentration ofdrugandKisfirst orderconstant.

$Q = Kt^{1/2}$

Where,Kistheconstantreflectingthedesignvariablesofthe system.$Q0^{1/3} - Qt^{1/3} = K_{HC}t$

Where, Qt is the amount of drug released in time t, Q_0 is the initial amount of the drugintablet and $K_{HC}$is therate constantforHixson-Crowell rateequation.

The following plotswere made:cumulative%drugreleasevs.time(zero orderkinetic model);log cumulative of %drug remaining vs.time (first order kineticmodel);cumulative%drugreleasevs.squarerootoftime(higuchimodel)logcumulative % drug release vs. log time (Korsemeyer model) and cube root of drug %remaininginmatrixvs. time (Hixon-crowell cuberoot law).

Mechanismofdrugrelease

Korsemeyer et al derived a simple relationship which described drug release from apolymeric system. To find out the mechanism of drug release, data was fitted inKorsemeyer–Peppasmodel:

$Mt/M\infty = Kt^n$

Where Mt / M∞ are fraction of drug released at time t, k is the rate constant and n isthe release exponent. The n value is used to characterize different release mechanismsasgiven in table21 for cylindrical shaped matrices.

According to various kinetic models, were giving linear relationship. In Zero orderplot the r2 value obtained is 0.751and first order gave 0.810 describing the drugrelease rate relationship with concentration of drug. The dissolution data was alsoplottedinaccordancewithHixsonCrowellcuberootlaw.Applicabilityofdata(r2=0.852) indicates a change in surface area and diameter of tablets with the progressivedissolution of matrix as a function of time. According to Korsemeyer where n is therelease exponent, indicative of mechanism of drug release. Fickian diffusional releaseandacase-IIrelaxationalrelease,arethelimitsofthisphenomenon.Fickiandiffusionalreleaseoccursby theusualmoleculardiffusionofthedrug duetoachemicalpotentialgradient.Case-IIrelaxationreleaseisthedrugtransportmechanismassociatedwithstressesandstate-transitioninhydrophilicglassypolymers which swell in water or biological fluids. This term also includes polymerdisentanglementanderosion.Table21describesthelimitsofthisanalysisforcylindricalshape,e.g.atablet.Thevalueofthe releaseexponentinNizatidineobtained as 0.243 which as per Table 23 is beyond the limits of Korsemeyer modelso-called power law. The power law can only give limited insight into the exactrelease mechanism of the drug. Even if values of the exponent n are found that wouldindicateadiffusion controlled drugreleasemechanism.

The best batch F6 was stored at 40^0C (±5°c) and 75%RH (±5%) for 3 months toanalyzevariousphysicalparameters.Nomajordifferenceswerefoundbetweenevaluated parameters before andafter,and all are in acceptable limits. From thestability data for pulsatile release Nizatidine tablet it can be concluded that there wereno change inany parameter tested in formulation so best batch F6are said to bestable.

Conclusively the present study demonstrates the Nizatidine could be successfully deliveredtoprovidenighttimereliefofgastricacidity bydesigningtimelaggedcoatingchronopharmaceutical formulation (F6). It provided the delivery of drug at midnight hours.The formulation is to betakenafter meal itgives burst releaseat midnight activity.Thiswillprovide anideal therapeuticregimenwith enhancedpatient compliance.

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