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FORMULATION AND IN VITRO EVALUATION OF CIPROFLOXACIN SUSTAIN RELEASE TABLETS

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Abstract:
Ciprofloxacin hasa shortbiologicalhalf-life of4–6 hours andhaving less bioavailability, whichnecessitatesmultipledaily dosing. Hence,thepresentstudy wasaimedto develop a SUSTAINrelease formulation ofCiprofloxacin to reduce the dose related side effects and to reduce the dosage regimen. The presentresearchprojectaimed to develop a Control releaseoralformulationofhypertension drugCiprofloxacin,thepresentresearchcomprising Ciprofloxacinused for thesymptomatic relief of pulmonary arterial hypertension.PolymerslikeXanthan Gum, Carbopol 940, and Ethyl Cellulose wereusedforcontrollingthedrug release,andthepolymersaremixed in a predetermined ratio. Totally 12 formulations were prepared and evaluated for pre-compression and post-compression parameters, and all the results were found to be within the limits. From the drug and excipients compatibility studies (FT-IR) it was confirmed that the drug and excipientsused weren't have any interactions. The in vitro dissolution studies revealed that the F8 formulation containing 250mg of Carbopol 940 controls the drug release upto 12 hours. So Carbopol 940 containing F8 formulation was considered to be suitable for the formulation of CiprofloxacinSUSTAIN release tablet and the drug release kinetics revealed that the F8 formulation shows zero order kinetics withsuper case- II transport mechanism.

Keywords:Ciprofloxacin,Carbopol 940, sustain release, FT-IR.

1.INTRODUCTION

Sustained release dosage forms are the substances which initially release drug sufficiently to provide therapeutic effect soon after administration and further a gradual release over an extended period of time3. Not all drug candidates are suitable for the preparation of sustained release dosage forms. The understanding of the certain parameters are very essential in the development of sustained release dosage forms, those are mainly drug physico-chemical characteristics such as, aqueous solubility, partition coefficient, ionization constant, drug stability4 and biological parameters viz., absorption, distribution, metabolism, excretion, biological half life, therapeutics of drug in vivo environment5 and also dose size and dosage frequency. It is always been a challenging task to the pharmaceutical scientist to prepare suitable sustained release dosage forms in pharmaceutical industry, because there is a possibility of dose dumping due to food, poor in vitro - in vivo correlation, decreased systemic availability in comparison with conventional dosage forms due to incomplete release or increased first pass metabolism6. Being several types of solid oral dosage forms, tablets offer more flexibility in the preparation to scientists when compare to other liquid and semi solid dosage forms. The various approaches to prepare essential solid oral sustained release drug delivery systems are given summarized below[1-4]

I. Diffusion-controlled DDS

- Hydrophobic matrix systems
- Hydrophilic matrix systems
- Inert matrix systems
- Reservoir matrix systems

II. Dissolution - controlled DDS

- Based on dissolution-controlled release of solid particles
- Based on dissolution-controlled release coated technologies
- Based on dissolution-controlled release matrix technologies
  III. Osmotic controlled DDS
  IV. Biodegradable polymeric DDS
- Microparticles
- Ion Exchange resins
- Nanoparticles
  V. Ligand-based targeting DDS
  VI. Stimulus responsive DDS
- Physically modulated: Temperature
- Chemically modulated: pH dependent

Although the above systems are commonly used for sustaining the drug delivery, there are some practical limitations of these techniques. The applicability of osmotic drug delivery technology for sustaining the drug release is very less due to the preparation aspects, quality control of these systems are more expensive when compare to other drug delivery systems and also getting the integrity and consistency of coating is very hard. The rate of production is the main limitation for microspheres and high dose is one of the major limitations for preparation of nanoparticles. Ligand based systems are especially used as target drug delivery systems to a specific site. Stimulus responsive drug delivery systems release the medicament depending up on the biological rhythms and this technology is not suitable to all categories of drugs. The drugs which are having high absorption window in the upper part of the gastric region are only suitable for gastric floating systems. Among all these drug delivery systems just mentioned, especially diffusion and dissolution controlled drug delivery systems such as hydrophilic and hydrophobic matrix systems are very interesting and suitable for most categories of drugs.

Matrix Systems: Matrix devices consist of drug dispersed homogenously throughout a continuous phase of polymer or lipid. The device can be prepared either by the compression of polymer/drug mixture. Preparation of matrix tablets are widely been used now a days due to least complicated approach for retarding the release rate of drugs over 10 an extended period of time[5-8]because their formulation is simpler, inexpensive, easy to produce13 and they have good in vitro-in vivo correlation. A matrix system is capable of accommodating both low and high drug loading active ingredients with a wide range of physical and chemical properties. Based up on types of release retardants the matrix systems are divided into two categories such a. Hydrophilic matrix systems b. Hydrophobic matrix systems

1.1. Extended-ReleaseDosage Forms

Dosageformswhichcanreduceatleastatwofoldreductionindosing frequency ascomparedtothedrug presentedinaconventionalform,suchassolutionora prompt-releasingconventionalsolid dosageformare termedasextendedrelease dosage forms.

These productsareformulatedtomake the containedmedicamentavailableover anextendedperiodof time after administrationwithinitstherapeutic rangeandhence reduction in dosingfrequencyas compared to theconventional dosageforms.[9-12]

Theyinclude:

- **Controlled Release(IdealZero-Order)**
- **Prolonged Release**

Comparisonofdifferenttypesofmodifiedreleasedosageformulationsasperplasma

concentration vs. time can beexplained bythefollowingfigure.

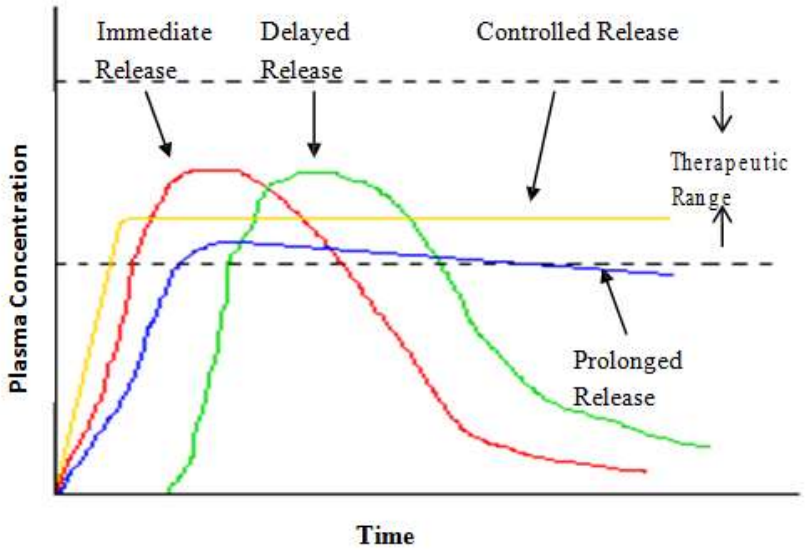

Fig1: Plasma concentration vs. Time curve fordifferent typeof dosage forms

Modified-releaseproductscanalsobeexplainedby otherdifferenttermssuchas extended-release, prolonged-release,controlled-release, controlled-delivery, slow- releaseandsustained-release,delayedrelease,timereleaseetc.Theseformulations, bydefinition,haveareducedrateofreleaseofactivesubstance.Ingeneral,these terms areinterchangeable [13].

A delayed-release product are modified-release, but by definition isnotextended- release.They canreleasediscreteamount(s)ofdrugsometimeafterdrug administration,e.g.enteric-coatedproductsexhibitalagtimeduring whichlittleorno absorptionoccurs. Whilea number of such modified-release productsareavailable as both prescription and over-the-counter drugs.Onlyalimited number havebeen shown to offer atherapeutic advantage [13-14].

Release RateandDoseConsideration[15]

Conventionaldosage formsinclude solutions,capsules,tablets,emulsions,etc. These dosage formscanbe consideredtorelease their active ingredientsintoan absorption poolimmediately.

K_r K_a K_e

Dosage form ⟶ Absorption pool ⟶ Target area

Drug ⟶ Absorption ⟶ Elimination

Release

Where,

K_r= First orderrateconstant fordrugrelease.

K_a = First orderrateconstant fordrugabsorption.

K_e = First orderrateconstant foroveralldrug elimination.

 ForimmediatereleasedosageformsK_r>>>K_a oralternatively absorptionofdrugacrossabiologicalmembraneistherate-limiting step in deliveryof thedrugto its target area.
 For non-immediaterelease dosage forms,K_r<<<K_a,thatis,release of drugfromthedosageformistheratelimitingstep. Thiscausethe abovekinetics scheme toreduceto

Thus,theefforttodevelopadelivery systemthatreleasedrugslowly mustbe directedprimarily atalteringthereleaserateby affectingthevalueofK_r. Theideal goalindesigning acontrolled-releasesystemistodeliverdrug tothedesiredsiteata rateaccordingtoneedsof the body,i.e.aself-regulated systembasedonfeedback control but this isadifficult assignment.

Terminology[16]:

Controlleddrugdeliveryormodifiedreleasedelivery systemsmay bedefined as follows: -

Controlled– Releaseformulation:

Thecontrolledreleasesystemistodeliveraconstantsupply oftheactive ingredient,usually atazero-orderrate,by continuouslyreleasing,foracertainperiod,anamountofthedrugequivalenttotheeliminatedby thebody. Anideal controlled drug delivery is the one, which delivers the drugs at a predetermined rate, locallyor systemically, for aspecific periodoftime.

Repeataction preparations:

Adoseofthedrug initiallyisreleasedimmediately afteradministration,which isusually equivalenttoasingledoseoftheconventionaldrugformulation. Aftera certainperiod, asecondsingle dose isreleased. Insome preparation,a third singledoseisreleasedafteracertaintimehaselapsed,followingtheseconddose. The mainadvantage*is*thatitprovidesthe convenience of supplying additional dose(s)withouttheneedofre-administration. Ithas*disadvantage*thattheblood levelsstillexhibitthe“Peakandvalley”characteristicofconventionalintermittent drugtherapy.

Extended-Releaseformulations:

Extended-Releaseformulationsareusually designedtoreducedosefrequency andmaintainrelatively constantorflatplasmadrugconcentration. Thishelpsavoid the side effects associated with high concentration.

Delayed releasepreparations:

Thedrug isreleasedlaterafteradministration. Thedelayedactionis achievedby theincorporationofaspecialcoat,suchasentericcoating,orothertime barrierssuchasthe formaldehyde treatmentofsoftandhardgelatincapsules. The purposesofsuchpreparationsaretopreventsideeffectsrelatedtothedrugpresence inthestomach,protectthedrug fromdegradationinthehighly acidicp^Hofthegastric fluid.

Sitespecific targeting:

Thesesystemsrefertotargetingofadrugdirectly toacertainbiological location. In this casethetarget is adjacent to or in thediseased organ ortissue.

Receptor targeting:

Thesesystemsrefertotargetingofadrugdirectly toacertainbiological location. Inthiscasethetargetistheparticularreceptorforadrug withinorganor tissue. Sitespecifictargetingandreceptortargetingsystemssatisfy thespatialaspect ofdrugdeliveryand arealso considered to becontrolled drugdeliverysystems.

1.2 ADVANTAGESAND DISADVANTAGESOFORAL EXTENDED-RELEASEDOSAGE FORMS

Allcontrolledreleasedosageformshaveacommongoalofimprovingthe drugtherapycompared to that achieved bytheir non sustained counterparts.

Advantages

- Avoid patient complianceproblems
- Employless quantitydrug.
- Minimizeor eliminate local side effects.
- Minimizeor eliminate systemicside effects.
- Reducedosingfrequencyand fluctuation of therapeuticplasma concentration
- Obtain less potentiation or reduction in drugactivitywith chronic use.
- Minimizedrug accumulation with chronic dosing.
- Improves efficiencyin treatment
- Cures or control conditions morepromptly.
- Improves control ofcondition i.e., reduces fluctuations in druglevel.
- Improves bioavailabilityofsomedrugs.
- Makes use ofspecial effects in sustained release aspirin formorning relief of

Arthritis bydosingbeforebedtime.

Disadvantages

- Dosedumping, toxicitycan occurif system fails.
- Reduced potentina patient education.
- Does not permit theprompttermination ofdrugtherapy.
- Cannot exercise anycontrol oncethe dosage formis administered.

1.3 ORAL CONTROLLED– RELEASEPRODUCTS:

Based on the releasemechanismthese are classified asfollows[17]:-

1. Diffusion-controlled products.

2. Dissolution-controlled products.

3. Erosion products.

4. Osmotic pump systems.

5.Ionexchangeresins.

1. Diffusion– Controlled products:

Inthese systems,there iswater–insoluble polymer whichcontrolsthe flow ofwater andthe subsequent release ofdissolved drugfromthedosage form. Diffusionoccurswhenadrug passesthroughthepolymerthatformsthecontrolled release device.The diffusioncanoccur throughporesinthe polymermatrixor by passingbetween polymerchains. Thesearebroadlydivided into two categories:-

A. ReservoirDevices.
B. MatrixDevices.

Thebasicmechanismsofdrugreleasefromthesetwosystemsarefundamentally different.

A. Reservoir Devices

Inthissystema water insoluble polymeric materialencasesa core of drug.Drug willpartitionintothemembraneandexchangewiththefluidsurrounding the particles (or)tablet.

Theactiveagentisreleasedtothesurrounding environmentby diffusionprocessthroughtheratelimitingmembrane.Inthereservoirsystemsthe drugdeliveryrate remains fairlyconstant.

B. Matrix Devices

Inthematrixdevicesthedrug oractiveisdispersedinpolymermatrix toforma homogeneoussystemknownasa matrixsystem.Diffusionoccurswhenthe drugpassesfromthepolymer matrixintotheexternalenvironment.Asthe release continues,itsratenormally decreaseswiththistypeofsystem,sincetheactiveagent hasaprogressively longerdistancetotravelandthereforerequiresalongerdiffusion time to release.

2. Dissolution-controlled products:

Intheseproducts,therateofdissolutionofthedrug iscontrolledby slowly solublepolymersorby microencapsulation.Oncethecoatingisdissolved,the drug becomesavailablefordissolution.By varyingthethicknessesofthecoatandits composition,the rateofdrugreleasecanbecontrolled. Some preparationscontaina fractionof thetotaldoseasanimmediate-releasecomponenttoprovideapulsedose soon after administration. Thepellet

dosageformsofdiffusion-ordissolution-controlledproductscanbeencapsulatedor prepared as a tablet.

Dissolution-controlled products can besub-divided into two types:-

A. Encapsulation Dissolution controls.
B. MatrixDissolution control.

A. EncapsulationDissolution control

Thesesystemsmethodinvolvescoating ofindividualparticles(or)granules ofdrug withaslowdissolvingmaterial.Thecoatedparticlescanbecompressed directly intotablets(or)placedincapsules.Therateofdissolutionofthedrug(and therebyavailabilityforabsorption)iscontrolledby microencapsulation.Oncethe coating is dissolved, the drug becomes available for dissolution. Byvarying the thicknesses ofthe coat and its composition, the rate ofdrugrelease can becontrolled.

Theseproductsshouldnotbechewedasthecoatingmay bedamaged. Oneof the advantages ofencapsulated pelleted products is that theonset ofabsorption is less sensitive to stomach emptying.

Theentranceofthepelletsintothesmallintestine (wherethemajority of drug absorption occurs) is usuallymore uniform than with non-disintegrating sustained-releasetabletformulations.

B. Matrix Dissolution control

Inthissystemanalternative approachistocompressthe drugwitha slowdissolvingcarrier.Heretherateofdrugreleaseiscontrolledby therateof penetration ofthe dissolution fluidinto the matrix, porosity, presenceof hydrophobic additives and the wet abilityof system and surfaceof particle.

3. Erosion products:

Inthis systemdrug oractive agentsare mixedwithbiodegradable polymers.Thesematerialsdegradewithinthebody asaresultofnaturalbiological processesand drugreleaseoccursat constant rate.

Mostbiodegradablepolymersare designedtodegradeasa result of hydrolysis of the polymer chains into biologically acceptable and progressively smallercompounds.Thereleaseifdrugfromtheseproductsiscontrolledby the erosionrateofacarriermatrix.Therateofreleaseisdeterminedbytherateof erosion.

4. Osmoticpumpsystems:

Theosmoticpump issimilartoareservoirdevicebutcontainsan osmotic agent(e.g.,theactive agentinsaltform)whichactstoimbibe water from the surroundingmediumvia asemi-permeable membrane.

Pressureisgeneratedwithinthedevicewhichforcestheactiveagent outof thedevice viaanorifice (of a size designedtominimize solute diffusion,whilst preventing thebuild-upofahydrostaticpressureheadwhichhastheeffectof decreasingthe osmotic pressureand changing

thedimensions{volume} ofthe device). Theadvantageofthis typeofproductisthattheconstantreleaseisunaltered by the environmentofthegastrointestinaltractandreliessimplyonthepassageofwaterinto the dosage form.

Therateofrelease can bemodified by altering theosmoticagentand the sizeof thehole.

5. Ionexchange resins:

Drug-resincomplexes("resonates")forextendedreleaseareknown andhavebeensuccessfully usedcommercially.Thedrugisboundtotheresinand releasedby exchangingwithappropriatelychargedionsincontactwiththeion exchangegroups. Thistechnique isapplicable tocertaindrugswhichhave particular characteristics in terms of their relativelyaffinityforthe polymers beingused.

1.4 Drug Properties Relevant To Controlled- Release Formulations

Theextentoffluctuationindrug concentrationatsteadystateisdetermined by therelativemagnitudeoftheeliminationhalf–lifeandthedosinginterval.Ifadrug isgiven atanintervalequaltothe eliminationhalf-life,there isa two-folddifference between the maximum and minimum concentrations at steadystate.

Somedrugsthosehaverelatively highsolubility atthelowpHwithshort biological half-life, are not suitable for conventional oral dosage formulations, becausethehighacidsolubilitypropertyofdrugresultsinrapiddrugabsorptionand clearance,causinglargeand undesirablefluctuations in plasma concentration.

For drugswithshorthalf-livesandwithaclear relationshipbetween concentrationandresponse,itwillbenecessarytodoseatregular,frequentintervals inordertomaintaintheconcentrationwithinthetherapeuticrange.Higherdosesat lessfrequentintervalswillresultinhigherpeakconcentrationswiththepossibility of toxicity.Forsomedrugswithwidemarginsofsafety,thisapproachmay be satisfactory,e.g.amoxicillinhasahalf-lifeofapproximately onehour,butadosage frequencyof 8hours. Judicious choiceofthedrug substanceisthemostimportantdecisioninthe successfuldevelopmentofcontrolledreleaseproduct.Severalcategoriesofdrug have potentialfortheirtherapeuticsimprovementofefficacy viacontrolled-releaseoral routes e.g. antianginal,Anti-inflammatory, Antihistaminic, Antigastric resistant agents,Antipsychoticagents,Antidiabetic drugsofagents.The commongoalfor increaseddurationistwice a day,or whenfeasible,once a day. Severalpropertiesof thedrug itselfcanlead totheachievementofa 12to24hoursoralprolongedrelease dosage form. Some of the characteristics mitigating against success are the following:-

1. Veryshort half-lifeand/or arelativelylargesingledose.
2. Longhalf-life.
3. Potent drugwith a low margin safety.
4. Poorlysoluble and/or poorlyabsorbed.
5. Biological activitynot a function of corein blend.
6. Absorption primarilyactivethrough a„window".
7. Large first-pass metabolism.

Theselectionofboththedrugandretardantpolymersalong withthefiller excipientswill impactonthemechanismandratesofdrugreleasefromthedosage formulation.variousphysicochemical,biologicalpropertiesofa drugandits biopharmaceutical characteristics influencingin product design and performance.

A. Physicochemical properties

1. Aqueous solubility

Adruggoodaqueoussolubility servesasagoodcandidateforcontrolled releaseddosageformse.g.,pentoxifylline.Compoundswithvery lowaqueous solubility usuallysufferoralbioavailabilityproblemsbecauseoflimited gastrointestinaltransittimeoftheundissolveddrugparticlesandlimitedsolubility at the absorption site.

2. Partitioncoefficient

Between thetime that adrug isadministeredandthe time itiseliminated from thebody,itmustdiffusethroughavarietyofbiologicalmembraneswithactprimarily aslipid-likebarriers. Amajorcriterionin evaluationoftheabilityofadrugto penetrated these lipid membranes is its apparent oil/water partition coefficient, defined as

$K=C_o/ C_w$

Where

C_o= totalconcentrationof allformsof the drug,e.g.ionizedandunionized,in some organic phased at equilibrium, and

C_w=total concentration of allforms in an aqueous phase at equilibrium.

Drugswithapartitioncoefficientthateitherisextremely higherorlowerthat the optimumsare,ingeneral,poorer candidates for formulationintomodified- release dosage forms.

3. Drug Stability

Stabilityisanotherphysicochemicalproperty tobeconsideredinthedesignof sustained-releasesystems.Drugsthose are unstableinthestomachthatreleasesits contents onlyin theintestine. So itcan beplaced in aslowlysoluble from.

Stabilitystudiesareextremelyimportantthatthepharmaceuticalmanufacturer accurately predict the shelf-stability of a new product from accelerated storage stabilitydata.drugswithsignificantstabilityproblemsinanyparticulararеaofthe gastrointestinal tract areless suitable for formulation into controlled releasesystems.

4. Protein binding

The drug-Proteincomplexcanserveasa depotfor producinga prolonged releaseprofile,drugsthatexhibitahighdegreeofbinding toplasma.Themainforces ofattractionresponsibleforbinding arevanderwaalsforces, hydrogenbonding,and electrostaticforces.Drugsboundtomucinmay increaseabsorption.**e.g.:**Quaternary ammoniumcompounds bound to mucin in the gastro intestinal tract.

5. Molecular Sizeand diffusivity

Inadditiontodiffusionthroughthesebiologicalmembranes,inmany sustained- release systemsmustdiffusethroughapolymericmembraneormatrixthat isusedto controltheirreleasekinetics.Theabilityofadrugtodiffusethrough polymeric membrane or matrixthatisused tocontroltheir releasekineticsmembranesisa function ofits diffusivity(diffusion

coefficient).

Animportantinfluenceuponthevalueofthediffusivity(D)inpolymersisthe molecularsize(ormolecularweight) ofthediffusing species.Inmostpolymers,itis possibletorelatelogDempiricallytosomefunctionofmolecularsize.Thevalueof Dthusisrelatedtothesizeandshapeofthecavitiesaswellassizeandshapeof drugs.

Generally,thevaluesofthediffusioncoefficientfor intermediatemolecular weightdrugs,i.e. 150-400,throughflexible polymersrange from$10^{-6}$to$10^{-9}$$cm^2$/sec, with values on theorderof10^{-8}beingmostcommon.

B. Biological Factors

1. Absorption

Therate,extent,anduniformity ofabsorptionofadrugareimportantfactors whenconsidering itsformulationintoacontrolledreleasesystem.Sincetherate limitingstepindrugdeliveryfromacontrolledreleasesystemitsreleasefroma dosagefrom,ratherthanabsorptionarapidrateofabsorptionofthedrugrelativeto itsreleaseisessentialifthesystemistobesuccessful.Tomaintainconstantblood

(or)tissuelevelofdrugitmustbeuniformly releasedfromthecontrolledrelease system,andthenuniformly absorbed.Designofcontrolledreleaseproductwouldbe moredifficultwithrespecttotheoralroute.e.g.:Quaternary ammoniumcompounds; amino glycosides suchasGentamycin.

2. Distribution

Distributionofadrugintovascularandextravascularspacesinthebody isan importantfactorinit‟stheoveralldrugeliminationkinetics.Twoparametersthatare usedtodescribe thedistributioncharacteristics.The termapparentvolumeof distributionofadrugisfrequently usedtodescribethemagnitudeofdistribution.In thecaseoftwocompartmentmodelthetotalapartmentvolumeofdistributionfora drug at steadystatecan be calculated from thefollowingequation.

Where,

$Vd_{ss}=[(K_{12}+K_{21}) / K_{21}]V_p$

Vd_{ss}=Apparent volumeofdistribution at studystate.
K_{12} =Constant for central to peripheral compartment.
K_{21}=Constant from peripheral to central compartment.
V_p= Volume of centralcompartment

3. Metabolism

TheMetabolicconversionofadrugtoanotherchemicalfromusually canbe consideredinthedesignofacontrolled-releasesystemforthatdrug.There are two factorsassociatedwith metabolismofsomedrugs.Oneisability ofthedrug toinduce (or)inhibitenzymesynthesisandtheotherisfluctuatingdrugbloodleveldueto hepaticfirstpasseffect.Forexampletheorganmostresponsibleformetabolismisthe liver. Metabolism of adrugwillbereflecte3d in the elimination constant of adrug.

4. Eliminationandbiological half-life

Therateofeliminationofadrugisdescribedquantitatively by itsbiological half-lifeofadrug isrelatedtoitsapparentvolumeofdistribution(V)anditssystemic clearance.

$t_{1/2}$=0.693 V/Cl_s=0.693 V AUC/dose

Where,

Cl_s=systemic clearance.

Adrug withashorthalf-liferequiresfrequentdosing,andthismakesita desirablecandidateforacontrolled-releaseformulation.Onotherhand,adrug witha long half-life isdosedatgreatertimeintervals,andthusthereis needfor acontrolled- releasesystem.

5. Side effects

Mostof the drugswillproduce side effects.For some drugs,the incidence of Sideeffectsisbelieved tobeafunctionofplasmaconcentration,and itcan be minimizedby controllingtheconcentrationatwhichthedrugexistinplasma,and hencecontrolled releaseformulations appear to offer asolution to this problem.

6. Marginofsafety

TheMarginofsafetyofadrugmostlyusedtomeasureitstherapeuticindex. Insignofcontrolledreleaseonecanconsidertobetherapeuticallysafeandeffective indrugtherapy monitoring.Especiallyforpotentdrugs,whosetherapeutic concentrationrange is narrow,the valueof therapeutic indexissmall.**e.g.:**Cardiac glycosides, Anti-arrythmic drugs etc.

7. Total clearance

Clearanceisdefinedasthetheoreticalofbody fluidcontainingdrug,from whichthedrug iscompletely removedinagivenperiodoftime,itisexpressedin ml/min (or) liters / hour.Clearance is given by,

$$\text{Total Clearance} = \frac{\text{Rate of elimination}}{\text{Plasmadrug concentration}}$$

8. Meanresidencetime(MRT)

Meanresidencetimeisdefinedastimeofdrugmoleculeresidenceinthe body.Itisthetimecorresponding to63.2%eliminationfromthebody.Itiscalculated from AUC and AUMC.

MRT = AUMC/AUC

Where,

MRT =Mean residencetime.

AUMC=Areaunder thefirst-moment curve. AUC =Areaunder thezero-moment curve.

1.5. Matrix Technology

Matrixtechnologiesarepopularly usedbecauseofthesimplicity ofthe manufacturingprocessesrequired,levelofreproducibility,stabilityof theraw materialsanddosage formaswellaseaseofscaleupoperation,validationand favorable in-vitro in-vivocorrelation (IVIVC). Classically,simple matrix delivery systems exhibit first order orsquare root of time releasekinetics.

Thesesystemsimprove patientcomplianceanddecreasedincidenceofadverse drugreactions. Under idealconditions,a controlled-release formulationmaintains therapeuticbloodlevelofadrugforaspecificperiodoftime.Anumberof oral controlled-release dosage formshave beendeveloped andstudiedto restrictthese systemstospecific regionsof thegastrointestinaltractaswellastoimprove the pharmacologicalactivity andtoreducetoxiceffects.Inordertoovercomeallthose problemmentionedabove,thematrixtabletshasadditionaladvantagelike,Matrix tabletsareresistanttodosedumping.Theyaresimpleinnatureoftheformulations, and dueto robustness theyareunaffected byvariations iningredients [12,18].

Matrixtabletscontaining hydrophilicpolymersare acommonandcommercially successfulmeansofprolonging oraldrug delivery.Acommonproblemobservedwith hydrophilicmatrixsystemscontaining watersolubledrugsisaninitialbursteffectof the drug release [12,18].

Process ofManufacturing Matrix Tablets

Oneofthe commonlyemployed processes forthemanufactureof extended release dosage formsinvolvesthedirectcompressionofblendsofdrug,retardant material,andadditivestoformatabletinwhichthedrug isembeddedinthematrix core of retardant.Alternately,the retardant-drugblendscanbe granulatedpriorto compression.

Matrix devices are of two types: Matrix dissolution controlled and matrix diffusion controlled drug deliverydevices[18].

Matrix DiffusionControlledDrug Delivery Devices.

Matrixdiffusiondevicesareprepared by dispersingasoliddruginaninsoluble polymermatrixcarriersystem,i.e.adrugreservoirisformedby homogenous

dispersionofsoliddrug particlesthroughoutalipophilicorhydrophilicpolymer matrix.Therateofdrugreleaseisdependentontherateofdrug diffusionbutnoton the rate of solid dissolution. The equation describing drug from this system T. Hugichi has derived thissystem [18].

$$Q = \frac{Cs}{\tau}\sqrt{D\varepsilon\,(2A-\varepsilon\,Cs)\,t}$$

Where,

Q =Weight ingrams ofdrugs in theunitsurfacearea.

D =Diffusion coefficient ofdrugin the releasemedium.

ε=Porosityof thematrix.

τ =Tortuosityof thematrix.

Cs =Solubilityof thedrugin releasemediumand,

A =Concentration ofdrugin thetabletexpressed as g/ml.

The following assumptions weremadein deriving the above equation: A pseudo-steadystateis maintained during release.
A>>Cs i.e. excess soluteis present.

C =0 in solution at alltimes (perfect sink condition) Drugparticlesaremuchsmaller than thosein thematrix. Thediffusion coefficientremains constant.
No interactions betweenthe drug and the matrixoccur.

Onemanycontroldrugreleasefromahomogenousmatrixbyvaryingthefollowing parameters.
Initial concentration ofdrugin thematrix.
Drugsolubility.
Porosity

Tortuosity

Leachingsolvent composition.
Polymer system making up matrix.

Matrix Dissolution ControlledDrug Delivery Devices

Matrixdissolution devicescanalso beformulated bycompressing thedrug with aslowly dissolvingpolymercarrierintoatabletform.Therearetwogeneralmethods ofpreparingdrug-waxparticles:congealingmethodandaqueousdispersionmethod. Incongealing methodthedrug ismixedwithwaxmaterialandeitherspray congealed orcongealedandscreened. Intheaqueousdispersionmethod,thedrug-waxmixture is sprayed or placed in water and theresultant particles arecollected.

Matrixtabletsaremadeby directcompressionofmixtureofdrug,polymerand excipients.Theratelimiting stepincontrollingrelease fromtheseformulationsis liquidpenetrationintothematrix. Somechanneling agents(wetting agents)canbe incorporatedwiththeblend of mixture topromotepermeationof polymer matrixby water,whichallowsdrug dissolutionanddiffusionfromthechannelscreatedinthe matrix.Formulationsshouldbe designed,sothatporediffusionbecomestherate- controllingstep.

Drugbioavailability,whichiscritically dependentonthedrug:polymerratio, maybemodifiedby inclusionofdiluentssuchaslactoseinplaceofpolymerinlow- milligram-potencyformulations.

Drug releaseiscontrolled by penetrationofwaterthroughagellayerproduced by hydrationofpolymeranddiffusionofdrugthroughswollen,hydratedmatrix,in additiontoerosionofthegelledlayer.Thepolymerselectedforformulationaswell asthedrug polymer ratiocontrolstheextenttowhichdiffusionorerosionwhich controls releaseof thedrugfrom theformulation [18].

→ Optimizationofformulationparametersanddrug-carriersystemusing appropriate methods.
→ Percentageofdrugcontent.
→ Study ofDissolution
→ Release kinetic studies
→ Druginteraction studies byFTIR.

METHODOLOGY

Materials used:

S. No.	GREDIENTSAND AGENTS	ANUFACTURER / SUPPLIERS
1.	Ciprofloxacin	A. R. Life Sciences, Hyderabad
2.	Xanthan Gum	Strides arcolab,Bangalore.
3.	Carbopol 940	Strides arcolab,Bangalore.
4.	Ethyl Cellulose	Lobachemiepvt.ltd, Mumbai
5.	MCC	Lobachemiepvt.ltd, Mumbai
6.	Lactose	Lobachemiepvt.ltd, Mumbai
7.	PVP K 30	Lobachemiepvt.ltd, Mumbai
8.	Magnesium Stearate	Lobachemiepvt.ltd, Mumbai
9.	Talc	Lobachemiepvt.ltd, Mumbai

Instrumentsused:

Sr. No.	Instruments	Manufacturer
1	UV-Vis Spectrophotometer	T-60 UV-Visible Spectrophotometer.
2	FTIR 1700S Spectrophotometer	Shimadzu,Japan.
3	ElectronicWeighingBalance	Sartorious Ltd.
	Dissolution test apparatus TDT-08T Dissolution Tester (USP)	LAB India DS-8000
5	Digital Vernier Caliper	Dgisun Electronics Hyderabad.
6	Digital pH meter 7007	Dgisun Electronics Hyderabad.
7	Test Sieve (No. 40, 60)	ScientificEngineeringCorp. Delhi.
8	Hot AirOven	ServewellInstrument PVTLTD, Bangalore.
9	StabilityChamber	Lab Control EquipmentCo. Mumbai.
11	Friabilator USPEF-2	Eleectrolab, Mumbai
12	Tablet punchingmachine(Rimek mini press-1)(10 stations 9.25 mm concavepunches)	KarnavatiEngineering Ltd, Mehsana, Gujarat.
13	Monsanto Hardness Tester	Ketan engineering Ltd,Mumbai

Pre formulationstudies[42-43]

Pre formulationtestingisaninvestigationofphysicalandchemicalproperties ofdrugsubstances aloneand whencombined with pharmaceutical excipients. It is the first step in the ratio development of dosage form.

Solubility

Solubility ofCiprofloxacinwasdeterminedinpH1.2andpH7.4 and 6.8 phosphatebuffers.
Solubility studieswereperformedby takingexcessamountofCiprofloxacininbeakerscontainingthe solvents.The mixtures were shakenfor24hrsatregularintervals.Thesolutionswere filteredby usingwhattmann'sfilterpapergradeno.41.Thefilteredsolutionsare analyzed by spectrophotometrically.

Melting point:
Melting point of the drug was determined by taking small amount of druginacapillarytubeclosedatoneend.The capillarytubewasplacedinan electricallyoperatedmelting pointapparatusandthetemperatureatwhichthedrug melts was recorded. This was performed thrice and average value was noted.

Compatibility Studies

CompatibilitystudywithexcipientswascarriedoutbyFTIR.Thepuredrugand itsformulationsalong withexcipientswere subjectedtoFTIRstudies.Inthepresent study, the potassium bromidedisc (pellet) method was employed.

IdentificationofCiprofloxacin[44]
PREPARATION OF BUFFERS

A. 0.1 N HCL
Dilute 8.50 ml of HCL with distilled water to make up the volume to 1000 ml

B. 6.8 pH Phosphatebuffer
Dissolve 13.872 g of potassium dihydrogen phosphate and 35.084 g of disodium hydrogen phosphate in sufficient water to produce 1000 ml.

C. 7.4 pH Phosphate buffer
Dissolve 0.6 g of potassium dihydrogen phosphate and 6.4 g of disodium hydrogen phosphate and 5.85 g of sodium chloride in distilled water and dilute upto 1000.0 ml .

Determination of UV spectrum of Ciprofloxacin:
10 mg of Ciprofloxacin was dissolved in 10 ml of buffer. so as to get a stock solution of 1000 µg/ml concentration. From the above stock solution pipette out 1ml of the solution and makeup the volume to 10ml using buffer to get the concentration of 100 µg/ml concentration. From this stock solution pipette out 1ml of the solution and makeup the volume to 10ml using buffer to get the concentration of 10 µg/ml concentration, this solution was scanned under UV Spectroscopy using 200-400nm.

Preparation of Standard Calibration Curve of Ciprofloxacin in pH 1.2:
A. Preparation of Stock Solution
10mg of Ciprofloxacin was dissolved in 10ml of pH 1.2 buffers so as to get a stock solution of 1000 µg/ml concentration.

B. preparation Standard Solution
1ml of stock solution was diluted to 10ml with pH 1.2 buffer in 10ml volumetric flask this gives a concentration of 10µg/ml. Aliquot of standard drug solutions were prepared by withdrawing 0.2, 0.4, 0.6, 0.8,1.0 and 1.2ml and transferred in to 10ml volumetric flask and were diluted up to the mark with pH 1.2 buffer. This gives the final concentration of 2, 4, 6, 8, 10 and 12µg/ml of Ciprofloxacin respectively. The absorbances of the solution were measured against pH 1.2 as blank at 279 nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Preparation of Standard Calibration Curve of Ciprofloxacin in pH 6.8:

A. Preparation of Stock Solution

10mg of Ciprofloxacin was dissolved in 10ml of pH 6.8 phosphate buffer so as to get a stock solution of 1000µg/ml concentration.

B. preparation Standard Solution

1ml of stock solution was diluted to 10ml with pH 6.8 buffer in 10ml volumetric flask this gives a concentration of 10µg/ml. Aliquot of standard drug solutions were prepared by withdrawing 0.2, 0.4, 0.6, 0.8,1.0 and 1.2ml and transferred in to 10ml volumetric flask and were diluted up to the mark with pH 6.8 buffer. This gives the final concentration of 2, 4, 6, 8, 10and 12µg/ml of Ciprofloxacin respectively. The absorbances of the solution were measured against pH 6.8 as blank at279 nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Preparation ofCiprofloxacin Controlled Release Tablets:[44-48]

Controlled releasetablets ofCiprofloxacin werepreprepared byDirect compression method usingvariable concentrations of different polymers likeXanthan Gum, Carbopol 940, Guar Gum. Direct compression method is widely employed method forproduction of compressed tablets.

Direct Compression:

In this process the tablets are compressed directly from powder blends of active ingredient and suitable excipients, which will flow uniformly in to the die cavity and forms a firm compact.

Brief manufacturing procedure for the preparation of tablets:

Step 1- Weighed all the ingredients separately.

Step 2- The l drug and the other excipients were passed through 40# sieve together and blended for 10 minutes.

Step 3- The magnesium stearate was passed through 60# sieve and added to the blend of step2 and blended for 5 minutes.

Step 4- Compressed the blend of step 3 in to tablets by using 8.5mm, round punches.

Tablet compositionof different formulations ofCiprofloxacinControlled Release tablets

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ciprofloxacin	250	250	250	250	250	250	250	250	250	250	250	250
MCC	216	166	116	66	216	166	116	66	216	166	116	66
Xanthan Gum	100	150	200	250	-_	-	-	-	-	-	-	-
Carbopol 940	-	-	-	-	100	150	200	250	-	-	-	-
Ethyl cellulose	-	-	-	-	-	-	-	-	100	150	200	250
Lactose	10	10	10	10	10	10	10	10	10	10	10	10
PVP K30	20	20	20	20	20	20	20	20	20	20	20	20
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Mg. stearate	2	2	2	2	2	2	2	2	2	2	2	2
Total (mg)	600	600	600	600	600	600	600	600	600	600	600	600

EvaluationParameters [49-52]

PreCompressionParameters

A. Bulk density (D_b)

Itistheratioofpowdertobulkvolume.Thebulkdensity dependsonparticlesize distribution,shapeand cohesiveness ofparticles.Accuratelyweighed quantityof powderwascarefully pouredintograduatedmeasuringcylinderthroughlargefunnel andvolumewasmeasuredwhichiscalledinitialbulkvolume.Bulkdensity is expressed in gm/ccand is given by,

$D_b = M / V_o$

Where, D_b=Bulk density(gm/cc) M is the mass ofpowder (g)
V_o is thebulk volume ofpowder(cc)

B. Tappeddensity (D_t)

Tengramsofpowderwasintroducedintoaclean,dry100mlmeasuringcylinder.The cylinder wasthen tapped100times fromaconstantheightandtappedvolume was read.It is expressed ingm/cc and is given by,

$D_t = M / V_t$

Where,
D_t=Tapped density(gm/cc)
M is the mass ofpowder (g)
$V_t$isthe tapped volumeof powder(cc)

C. **Compressibilityindex:**Thecompressibilityofthepowderwas determined bythe

Carr's compressibilityindex.

$$\mathrm{CI} = \frac{\rho_{\mathrm{tap}} - \rho_{\mathrm{bulk}}}{\rho_{\mathrm{tap}}} \times 100$$

where ρ_{tap} is the tap density and ρ_{bulk} is the bulk density.

Table 4.4: Relation between the Carr's index of powder and its flow characteristics:

Sr.No.	Carr's index	Typeofflow
1.	5-15	Excellent
2.	12-15	Good
3.	18-21	Fair
4.	23-30	Poor
5.	33-38	Verypoor
6.	>40	Extremelypoor

D. Hausner ratio:

Hausnerratio =tapped density/ bulk density

Values ofHausnerratio; <1.25: goodflow

>1.25: poorflow

IfHausnerratioisbetween1.25-1.5,flowcanbeimprovedbyadditionof glidants.

E. Angleofrepose (θ)

Itisdefinedasthe maximumangle possiblebetweenthesurfaceof pileofthepowder and the horizontal plane.Fixed funnelmethodwas used.A funnelwasfixed withits tipatagivenheight(h),aboveaflathorizontal surfaceonwhichagraphpaperwas placed.Powderwascarefully pouredthroughafunneltilltheapexoftheconicalpile justtouchesthetipof funnel.Theangleof reposewasthencalculatedusing the formula,

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

where,
θ= angle ofrepose
h =height of pile, r=radius of thebaseof thepile.

Table 4.5: Comparison betweenangles ofreposes and flowproperty:

AngleofRepose	**Flow**
<25	Excellent
25 – 30	Good
30 – 40	Moderate (addition of 0.2% glidant required)
>40	Poor

Post CompressionParameters[53]

A. Thickness and diameter

Controlof physicaldimensionofthe tabletsuch asthicknessanddiameterisessential for consumer acceptance andtabletuniformity.The thicknessanddiameter of the tablet was measured usingVerniercalipers.It is measured in mm.

B. Hardness

The Mansantohardnesstester wasused todetermine thetablethardness.The tablet washeldbetweenafixedandmoving jaw.Scalewasadjustedtozero;loadwas graduallyincreaseduntilthetabletfractured.Thevalueoftheloadatthatpointgives ameasureof hardness ofthe tablet. Hardness wasexpressed in Kg/cm^2.

C. Friability (F)

Tabletstrengthwastestedby FriabilatorUSPEF-2.Preweighedtabletswereallowed for100revolutions(4min),takenoutandwere dedusted.Thepercentageweightloss was calculated byrewritingthe tablets. The%friabilitywas then calculated by,

$$F = \frac{(W_{initial}) - (W_{final})}{(W_{intial})} \times 100$$

D. Weight variationtest

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. First the total weight of 20 tablets from each formulation is determined and the average is calculated. The individual weight of the each tablet is also determined to find out the weight variation

E. Uniformity of drug content.

Fivetabletsofvariousformulationswereweighedindividually andpowdered. Thepowderequivalenttoaverageweightoftabletswasweighedanddrug was extractedindifferent buffers,thedrug contentwasdeterminedusing aUV/VisibleSpectrophotometer (Single beam spectrophotometer).

In-vitro releasestudy:

Apparatus	**USP XXIV dissolution testing apparatus II (Paddle method)**
Dissolution medium	0.1N HCL, 6.8 pH phosphate buffer,
Temperature	37± 0.5^0 C
RPM	50
Vol. withdrawn and replaced	5ml every 1 hour
λ max	279 nm in pH 1.2 buffer and 279 nm in pH 6.8
Blank solution	Buffers used
Duration of study	12 hours
Volume of dissolution media	900ml

Procedure:

The release rate of Ciprofloxacin from tablets was determined using The United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle type). The dissolution test was performed using 900 ml of pH 1.2, for first 2 hours and followed by phosphate buffer (pH 6.8; 900 mL) for remaining hours at 37.5±0.5^0C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hours, and the samples were replaced with fresh dissolution medium. The samples diluted to a suitable concentration with respected dissolution medium. Absorbanceofthese solutionswasmeasuredusing aUV-VisibleSpectrophotometer(Single beam spectrophotometer). Cumulativepercentageof drugreleasewas calculated.

KineticAnalysisofIn-Vitro ReleaseRates ofControlledReleaseTablets

The resultsof invitro releaseprofileobtainedfor alltheformulationswere plotted in modes ofdata treatment as follows:-

1. Zero – order kineticmodel– Cumulative% drug released versus time.
2. First–orderkineticmodel–Logcumulativepercentdrugremainingversus time.
3. Higuchi'smodel–Cumulativepercentdrugreleasedversussquarerootof time.
4. Korsmeyerequation/Peppa'smodel–Logcumulativepercentdrugreleased

versus logtime.

- **Zero OrderKinetic**

It describes the system in which the drugreleaserate isindependentofits concentration.

Qt = Qo + Ko t

Where

Qt=Amount of drugdissolved in time t

Qo =Initial amount of drugin thesolution,which is often zero and

Ko =zero order release constant.

Ifthe zero order drugreleasekinetic is obeyed, then aplotofQt versus t will give a straight line with a slopeofKoand an intercept at zero.

- **FirstOrderKinetic**

It describes the drug release from the systems in which the release rate is

concentrationdependent.

Log Qt = log Qo + kt/ 2.303

Where

Qt = amountof drugreleased in timet.

Qo =initial amount of drugin thesolution k = first order release constant

Ifthe first order drugreleasekinetic is obeyed, then aplotoflog (Qo-Qt)

versus t willbestraight line with a slopeof kt/ 2.303and an intercept att=0 oflog Qo

- **Higuchi Model**

It describes thefraction ofdrugreleasefrom amatrixis proportional to square root oftime.

$Mt / M\infty = kHt^{1/2}$

Where
Mt and$M\infty$arecumulative amounts of drugrelease at timet and infinite time,

And
kH=Higuchi dissolution constant reflectionformulation characteristics.

Ifthe Higuchi model of drugrelease (i.e.Fickian diffusion) is obeyed, thenaplot ofMt / M∞ versus$t^{1/2}$willbestraight line with slopeof kH.

- **Korsmeyer-Peppasmodel (PowerLaw)**

Thepower law describesthe drugreleasefrom thepolymeric system in which release deviates from Fickian diffusion, as expressed in following equation.

$Mt / M\infty = ktn$

$\log [Mt / M\infty] = \log k + n \log t$

Where

Mt and$M\infty$arecumulative amounts of drugrelease at timet and infinite time

(i.e. fraction ofdrugrelease at timet),

device,**k=**constant incorporatingstructural and geometrical characteristics of CR

n=diffusional release exponent indicativeof themechanismof drug release fordrugdissolution.

To characterizethe releasemechanism, the dissolution data {Mt / M∞ <0.6} are evaluated.

A plot of log {Mt / M∞}versus log twillbelinear withslopeofnandintercept gives thevalueoflog k.

Antilogof logkgives thevalue ofk.

Peppas used the nvaluein order to characterize different releasemechanisms as shown in thetablebelow

Table 4.8: Mechanism ofDrug Releaseas perKorsmeyerEquation/Peppa's

Model:

S. No	Release exponent	Drug transport mechanism	Rate as a function of time
1	0.5	**Fickian diffusion**	$t^{-0.5}$
2	0.45 < n = 0.89	**Non -Fickian transport**	t^{n-1}
3	0.89	**Case II transport**	Zero order release
4	Higher than 0.89	**Super case II transport**	t^{n-1}

RESULTS AND DISCUSSIONS

PREFORMULATION STUDIES

Determination of melting point

The melting point of Ciprofloxacin was found to be 312°C whichcompiledwith BPstandards, indicating purityof thedrugsample**.** which was determinedbycapillarymethod

Solubility studies:

Table: Solubility studies of Ciprofloxacin

Solvent	% Solubility
1.2 pH buffer (0.N HCL)	0.245±0.045
7.4 pH Phosphate buffer	0.586±0.071
6.8 pH Phosphate buffer	0.683±0.065

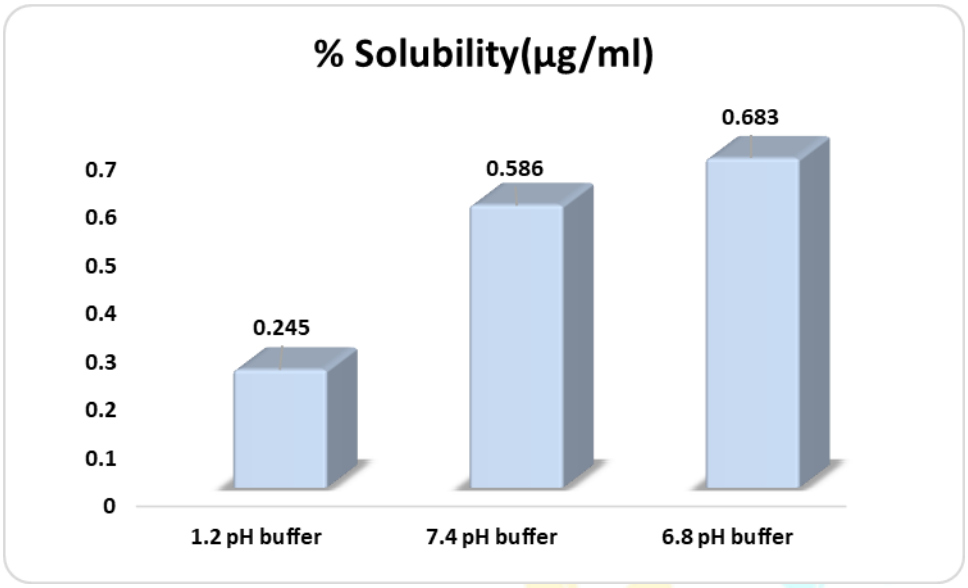

Fig5.1: Solubility studies of Ciprofloxacin

Discussion: From the above solubility studies, it was observed that among that 3 buffer solutions (0.1N HCL i.e pH 1.2, 7.4 pH Phosphate buffer and 6.8 pH phosphate buffer) the drug was soluble freely in 6.8 pH buffer.

FTIR studies:

Drug-Excipient compatibility studies:

TheIRspectrumofpuredrugwasfoundtobe similartothestandardspectrumof Ciprofloxacin.

Fromthespectraof Ciprofloxacin,combinationofCiprofloxacinwithpolymers,it was observed that all characteristic peaks of Ciprofloxacin were not altered and present without alteration in the combination spectrum, thus indicating compatibility of the drug and polymers. FTIRspectra of Ciprofloxacin, and Optimized formulationareshowninFigure respectively.

FTIR Spectra of Pure drug:

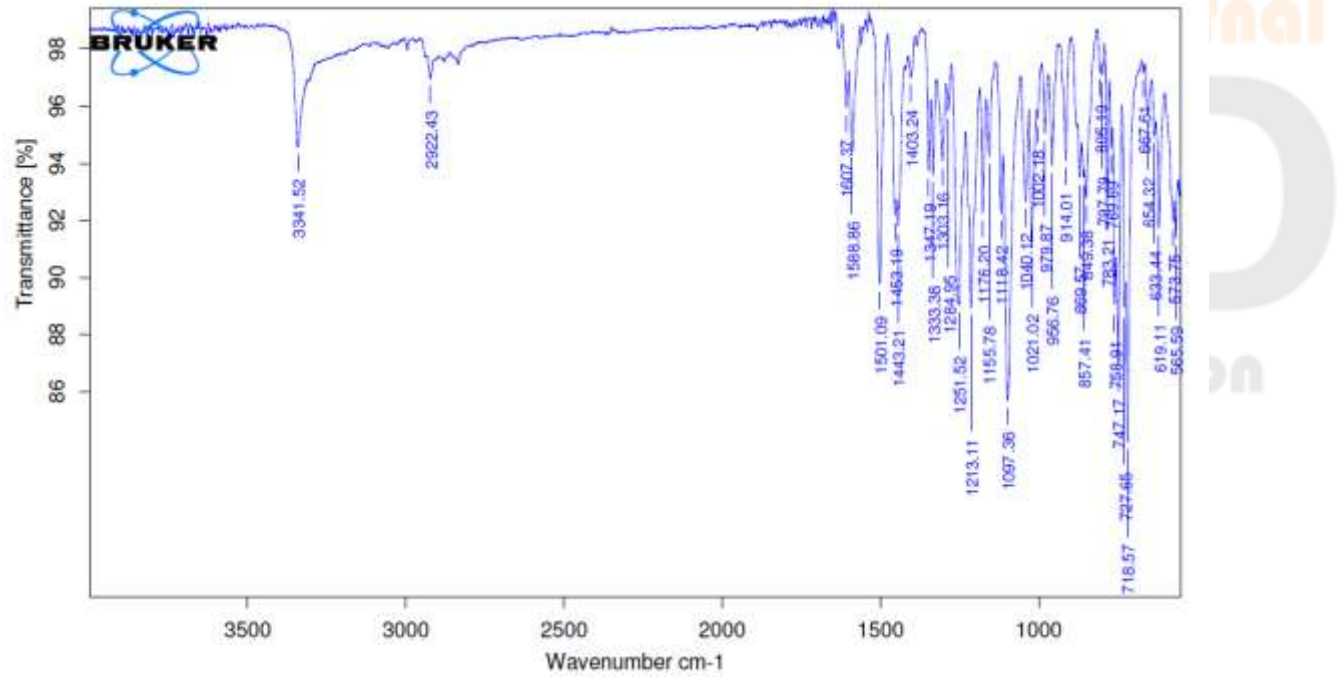

Fig.5.7FTIR Spectra of Pure drug

FTIR Spectra of Drug and Excipients:

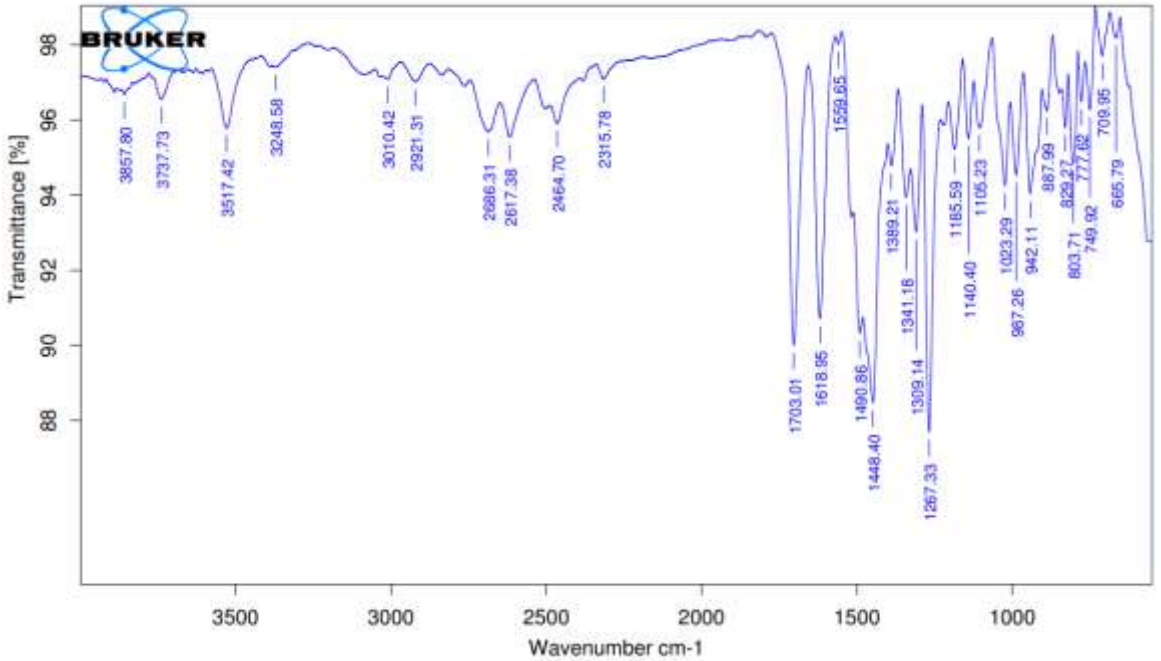

Fig.5.7.1FTIR Spectra of Drug and Excipients

Discussion: From the drug excipients compatibility studies we observe that there are no interactions between the pure drug and (drug+ excipients) which indicates there are no physical changes.

UV Determination:

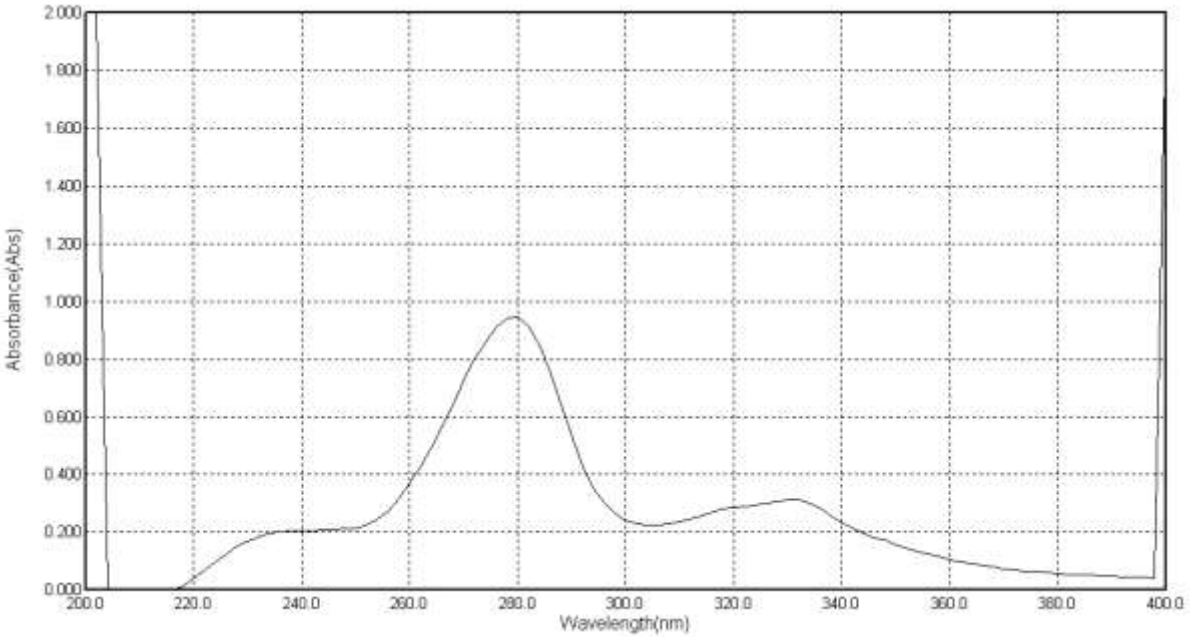

Fig.5.6.Uv spectrum of Ciprofloxacin

Discussion: A solution of Ciprofloxacin containingthe con 8µg/ mlwas prepared in 6.8pH buffer and UV spectrum was taken using Single Beam Spectrophotometer (YIS-294).Thesolutionwasscannedintherangeof200–400nm.The maximum absorbance was foundto be at 279 nm.

StandardCalibrationCurveofCiprofloxacinin pH 1.2 Buffer:

Table: StandardCalibrationCurveofCiprofloxacinin pH 1.2 Buffer

Concentration(µg/ml)	Absorbance
0	0
2	0.176
4	0.297
6	0.458
8	0.624
10	0.792
12	0.932

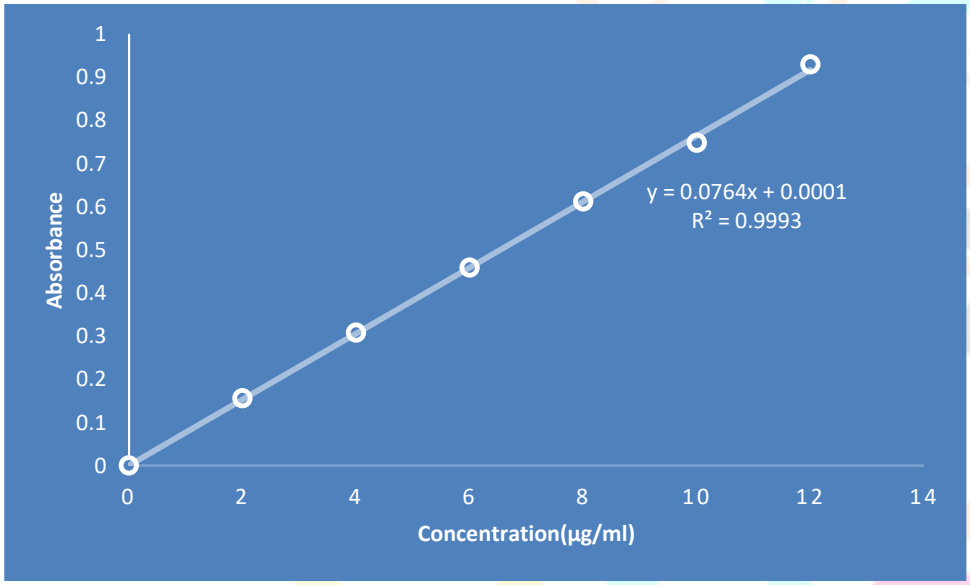

Fig : Standard calibrationcurveof Ciprofloxacinin pH 1.2

Discussion:

Thestandardcalibrationcurveshown0.998,throughthatthedrug obeysBeersandLamberts lawintheconcentrationrangeof0to 12 µg/mL.Astandardgraphwasplottedby keepingthe knownconcentrationonX–axisandobtainedabsorbanceonY–axis.

5.3.3.StandardCalibration CurveofCiprofloxacinin pH 6.8:

Table:7.4: StandardCalibration CurveofCiprofloxacinin pH 6.8

Concentration(µg/ml)	Absorbance
0	0
2	0.155
4	0.307
6	0.458
8	0.612
10	0.747
12	0.929

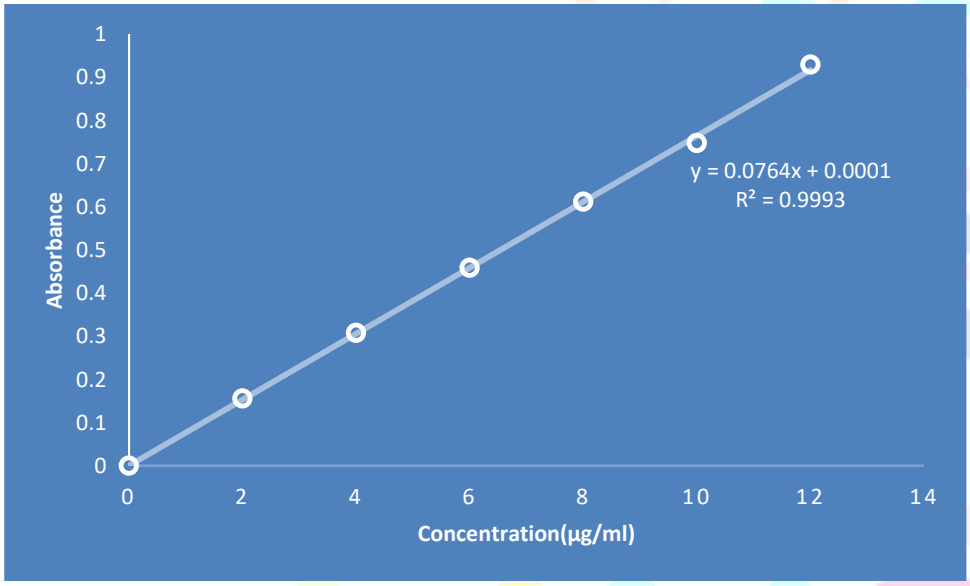

Fig : standardcalibrationcurveCiprofloxacinin pH 6.8 Phosphate Buffer

Discussion:

Thestandardcalibrationcurveshown R^2 value0.999 which ie near to 1 shows the linearity,throughthatthedrug obeysBeersandLamberts lawintheconcentrationrangeof0to 12 µg/mL.Astandardgraphwasplottedby keepingthe knownconcentrationonX–axisandobtainedabsorbanceonY–axis.

Evaluation of Ciprofloxacin controlled release matrix Tablets

Table:5.5. Pre CompressionParameters ofCiprofloxacin controlled release Tablets:

FC	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of Repose
F1	0.485±0.004	0.535±0.006	18.45±1.25	1.21±0.12	25.25±0.54
F2	0.454±0.006	0.526±0.004	17.29±1.29	1.24±0.16	28.48±0.26

F3	0.467±0.004	0.529±0.001	16.46±1.37	1.28±0.28	27.26±0.36
F4	0.476±0.006	0.534±0.002	15.12±1.23	1.21±0.34	29.16±0.18
F5	0.468±0.002	0.529±0.008	17.26±1.19	1.16±0.16	26.48±0.24
F6	0.474±0.004	0.542±0.004	16.48±1.15	1.18±0.28	27.02±0.23
F7	0.485±0.002	0.581±0.006	14.26±1.28	1.17±0.19	28.39±0.29
F8	0.497±0.007	0.598±0.004	12.77±1.24	1.11±0.25	24.12±0.24
F9	0.456±0.004	0.587±0.002	19.26±1.16	1.19±0.24	28.48±0.56
F10	0.474±0.001	0.585±0.007	18.29±1.12	1.18±0.18	27.58±0.18
F11	0.479±0.001	0.557±0.002	17.47±1.24	1.15±0.47	26.74±0.45
F12	0.487±0.005	0.575±0.001	15.64±1.18	1.14±0.51	27.03±0.89

Discussions:

- The angle of repose of different formulations (F1-F12) was found to be in the range of 24.12±0.24 to 29.16±0.18. But the formulation F9 having the excellent flow property with 24.12±0.24. So, it was confirmed that the flow property of blends was free flowing.
- The bulk density of blend was found between 0.454±0.006 to 0.497±0.007.
- The Tapped density was found between 0.529±0.001 to 0.598±0.004. These values indicate that the blends had good flow property.
- Carr's index for all the formulations was found to be between 18.45±1.25 to 12.77±1.24 and Hausner's ratio from 1.28±0.28 to 1.11±0.25 which reveals that the blends have good flow character.

5.7 PostCompressionParameters ofCiprofloxacin controlled release tablets:

Table 5.6: Physical properties oftabletformulation(F1 toF12):

FC	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight Variation (mg)	Drug Content (%)
F1	5.16±1.66	7.58±0.74	0.72±0.18	602.29±1.54	96.43±0.42
F2	5.72±0.78	7.47±0.62	0.66±0.82	601.02±0.26	95.25±0.26
F3	5.32±0.88	8.45±0.95	0.54±0.66	599.56±0.54	93.63±0.39
F4	5.58±0.74	8.67±0.76	0.56±0.38	598.28±0.11	95.18±0.25
F5	5.37±0.82	8.28±0.88	0.69±0.65	600.64±0.78	93.25±0.26
F6	5.69±0.79	8.56±0.94	0.56±0.26	601.51±0.86	95.43±0.38
F7	5.57±072	8.62±0.37	0.48±0.72	598.24±0.24	97.67±0.45
F8	5.68±0.36	8.98±0.72	0.45±0.58	600.47±0.54	98.35±0.26

F9	5.85±0.84	8.89±0.49	0.94±0.45	601.12±0.18	94.74±0.38
F10	5.87±0.84	7.48±0.84	0.87±0.84	602.14±0.84	96.47±0.84
F11	5.12±0.84	8.25±0.84	0.68±0.84	598.15±0.84	95.47±0.84
F12	5.29±0.84	8.79±0.84	0.59±0.84	599.52±0.84	97.68±0.84

Discussion:

- Thickness of the Ciprofloxacin tablets were found to be in the range of 5.12±0.84 mm to 5.85±0.84 mm.
- Hardness of the Ciprofloxacin tablets were found to be in the range of 7.47±0.62 to 8.98±0.72 kg/cm2.
- Friability of the Ciprofloxacin tablets were found to be in the range of 0.45±0.58 to 0.94±0.45 %.
- The Weight Variation of the Ciprofloxacin tablets were found to be in the range of 598.15±0.84 to 602.29±1.54 mg.
- Drug content of the Ciprofloxacin tablets were found to be in the range of 93.63±0.39% to 98.35±0.26%.

5.8 In-vitro drug releasestudies:

*In-vitro*drugreleasestudieswerecarriedoutusingUSPXXIIdissolutionapparatus typeII(Lab India DS 8000)at50rpm.Thedissolutionmediumconsistedof 900mlofbuffer,maintainedat37±0.5 ^{0}C.Thedrugreleaseat differenttimeintervalswasmeasuredusinganultravioletvisiblespectrophotometer (PG Instruments). Thestudywas performed in triplicate

Table.5.7: In vitro dissolution studies with formulation F1 to F4

Time (hrs)	**F1**	**F2**	**F3**	**F4**
0	0	0	0	0
1	25.47 ±1.48	29.47 ±1.45	17.45 ±1.36	12.47 ±1.24
2	34.47 ±1.19	43.77 ±1.22	25.46 ±1.36	26.45 ±1.21
3	48.47 ±1.45	55.42 ±1.16	35.14 ±1.36	34.19 ±1.25
4	59.87 ±1.47	67.41 ±1.01	49.87 ±1.46	45.48 ±1.17
5	74.58 ±1.65	75.92 ±1.24	57.82 ±1.22	57.15 ±1.28
6	88.47 ±1.25	83.72 ±1.36	64.46 ±1.14	66.41 ±1.15
7	96.48 ±1.62	89.35 ±1.87	72.84 ±1.22	72.16 ±1.42
8		92.08 ±1.11	79.48 ±1.54	81.45 ±1.21
9		98.47 ±1.24	87.25 ±1.28	88.68 ±1.10
10			98.36 ±1.26	92.14 ±1.48
11				98.58 ±1.44
12				

Table.5.7: In vitro dissolution studies with formulation F5 to F8

Time (hrs)	F5	F6	F7	F8
0	0	0	0	**0**
1	31.82 ±1.13	24.48 ±1.14	16.72 ±1.21	**14.57 ±1.48**
2	47.26 ±1.22	33.78 ±1.26	28.42 ±1.67	**28.24 ±1.47**
3	59.24 ±1.38	42.14 ±1.42	31.46 ±1.22	**37.48 ±1.54**
4	66.84 ±1.42	54.81 ±1.19	39.58 ±1.44	**45.24 ±1.29**
5	75.86 ±1.19	66.46 ±1.04	48.82 ±1.51	**56.34 ±1.61**
6	83.92 ±1.58	75.98 ±1.54	57.77 ±1.13	**63.48 ±1.24**
7	91.64 ±1.22	81.89 ±1.12	68.21 ±1.27	**70.19 ±1.37**
8	98.86 ±1.04	89.21 ±1.36	76.48 ±1.25	**79.18 ±1.45**
9		93.15 ±1.28	82.46 ±1.57	**85.29 ±1.36**
10		98.26 ±1.36	91.49 ±1.64	**91.42 ±1.28**
11			98.16 ±1.95	**95.43 ±1.28**
12				**99.41 ±1.25**

Table.5.7: In vitro dissolution studies with formulation F9 to F12

Time (hrs)	F9	F10	F11	F12
0	0	0	0	0
1	29.82 ±1.48	22.86 ±1.14	17.48 ±1.14	13.58 ±0.14
2	35.26 ±1.27	31.78 ±1.26	26.78 ±1.26	26.47 ±1.24
3	48.24 ±1.34	39.14 ±1.42	34.14 ±1.42	34.45 ±1.21
4	55.84 ±1.54	47.81 ±1.19	58.81 ±1.19	48.19 ±1.25
5	68.88 ±1.42	56.46 ±1.04	62.46 ±1.04	53.48 ±1.17
6	75.95 ±1.14	65.98 ±1.54	68.98 ±1.54	64.15 ±1.28
7	87.47 ±1.25	78.89 ±1.12	75.89 ±1.12	72.41 ±1.15
8	98.24 ±1.15	84.21 ±1.36	80.21 ±1.36	78.16 ±1.42
9		91.15 ±1.45	88.15 ±1.28	83.45 ±1.21
10		97.26 ±1.26	93.26 ±1.36	87.68 ±1.10
11			98.74 ±1.36	93.14 ±1.48
12				97.58 ±1.44

In Vitro Drug Release Studies:

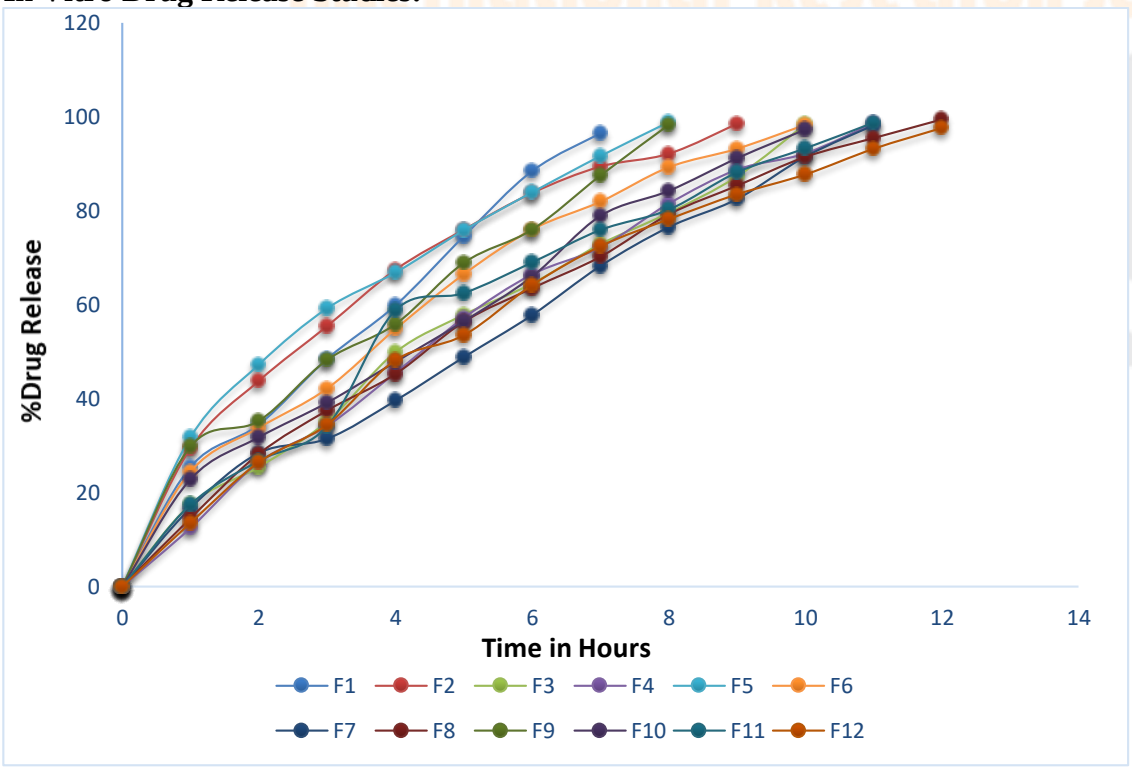

Fig5.8:In Vitro Drug Release Studies Of F1-F12 Formulations

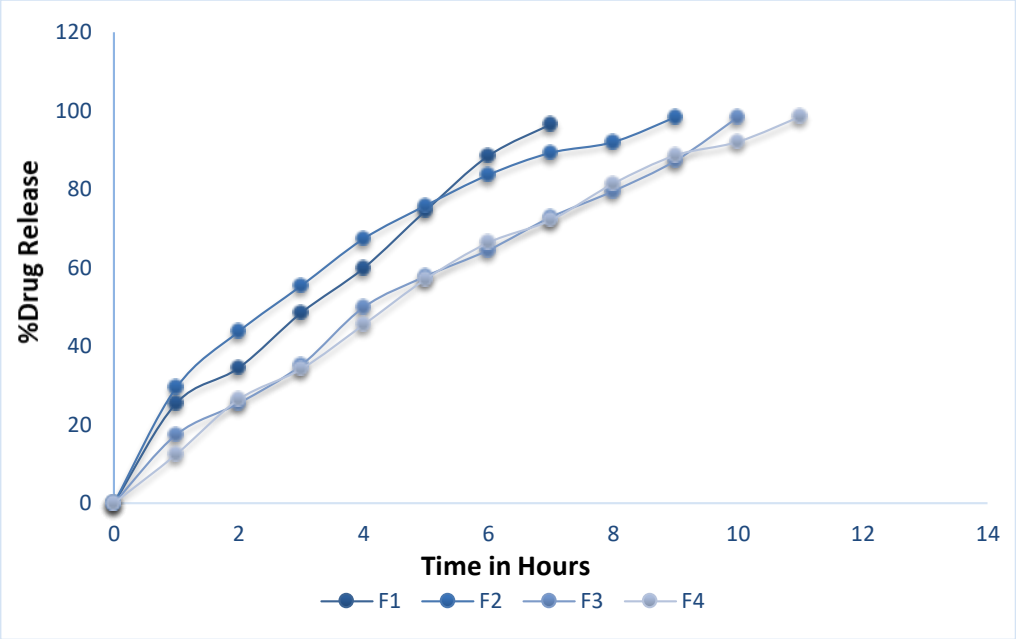

Fig:5.9:In Vitro Drug Release Studies Of F1-F4 Formulations

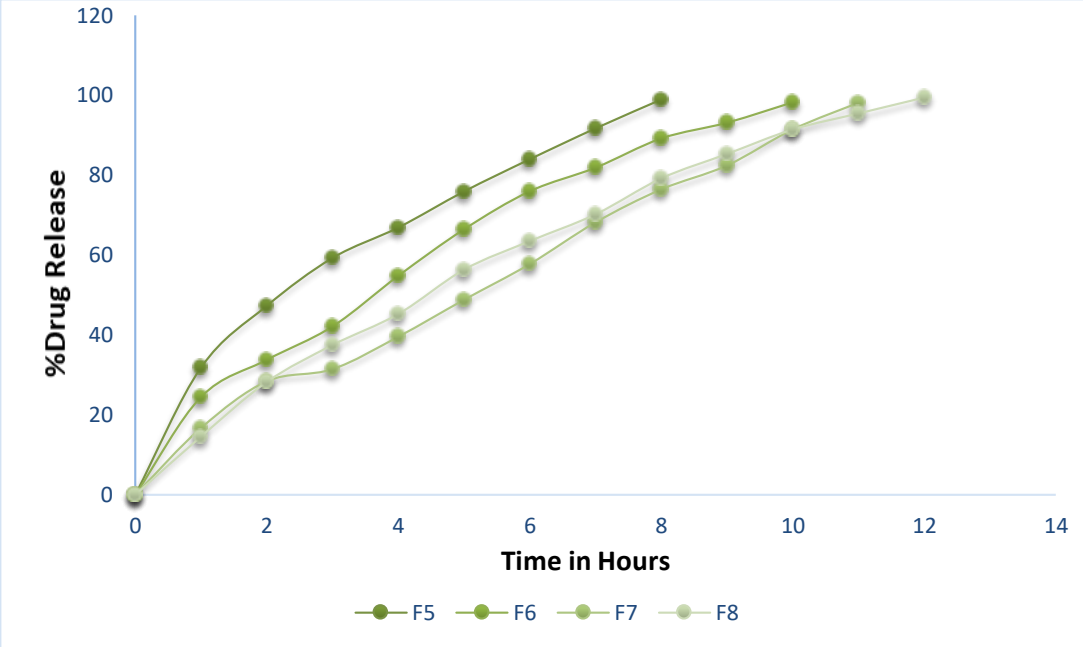

Fig:5.10:In Vitro Drug Release Studies Of F5-F8 Formulations

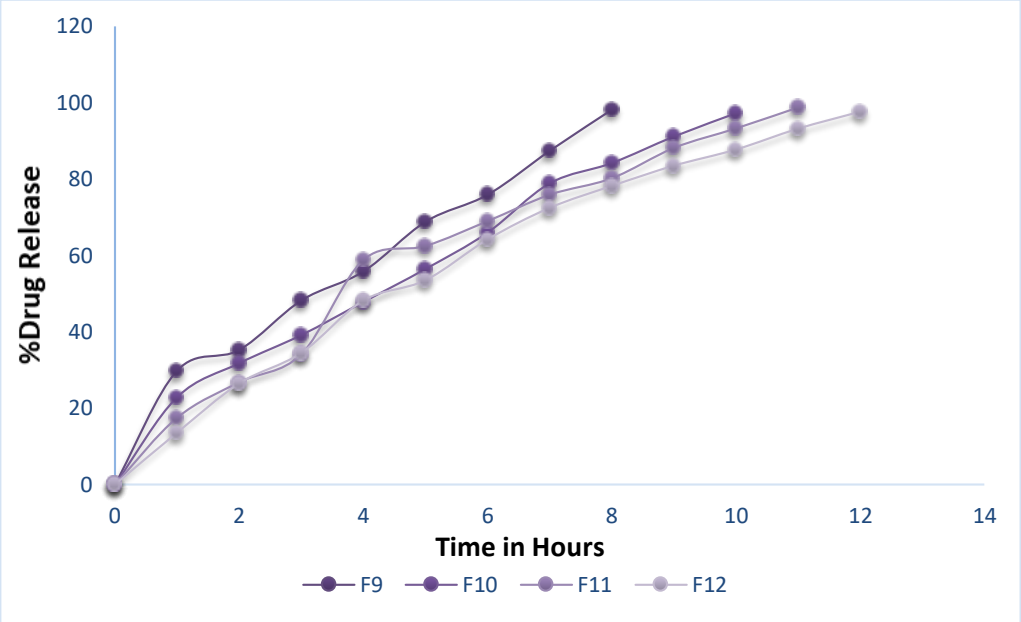

Fig:5.10:In Vitro Drug Release Studies Of F9-F12 Formulations

Discussion:

From the in vitro drug release studies of Ciprofloxacin controlled release tablets using Xanthan Gum, Carbopol 940 and Ethyl cellulose in three different polymer ratios using lactose as a diluent, MCC as a binder and PVP K30 as filler.

From Formulations, the F1-F4 were formulated using xanthan gum in four different ratios like 100mg, 150mg, 200mg and 250mg the drug release of F1 was 96.48±1.62 at the end of 7th hour, F2 was 98.47±1.24 at the end of 9th hour and F3 was 98.36±1.26 at the end of 10th hour and F4 releases 98.58±1.44% at the end of 11th hour.

So, when the polymer concentration increases the drug release time was increased but F4 showing the highest release at the end of 11th hour only. So further dissolution was takes on the polymer Carbopol 940.

The formulation F5-F8 were formulated by using Carbopol 940 in four different ratios like 100mg, 150mg, 200mg and 250mg, the drug release of F5 was 98.86±1.04 at the end of 8th hour, F6 was 98.26±1.36% at the end of 10th hour and F7 was 98.16±1.95 at the end of 11th hour and F8 releases 99.41±1.25% at the end of 12th hour

While the formulation done with the Carbopol 940 shows the higher amount of drug released at the end of 12th hour. So further studies were done with Ethyl cellulose.

The formulations from F9-F12 were formulated by using Ethyl cellulose in four different ratios like 100mg, 150mg, 200mg and 250mg, so the drug release of F9 was 98.24±1.15 at the end of 8th hour, F10 was 97.26±1.26% at the end of 10th hour and F11 was 98.74±1.36 at the end of 12th hour and F12 releases 97.58±1.44 % at the end of 12th hour

In this turn, with the polymer Carbopol 940 the formulation F8 shows the better results up to 12th hour. Hence the formulation F8 was identified as the Optimized formulation. So further Release kinetics was done to this formulation.

5.9.Drug Release Kinetics:

Zero Order:

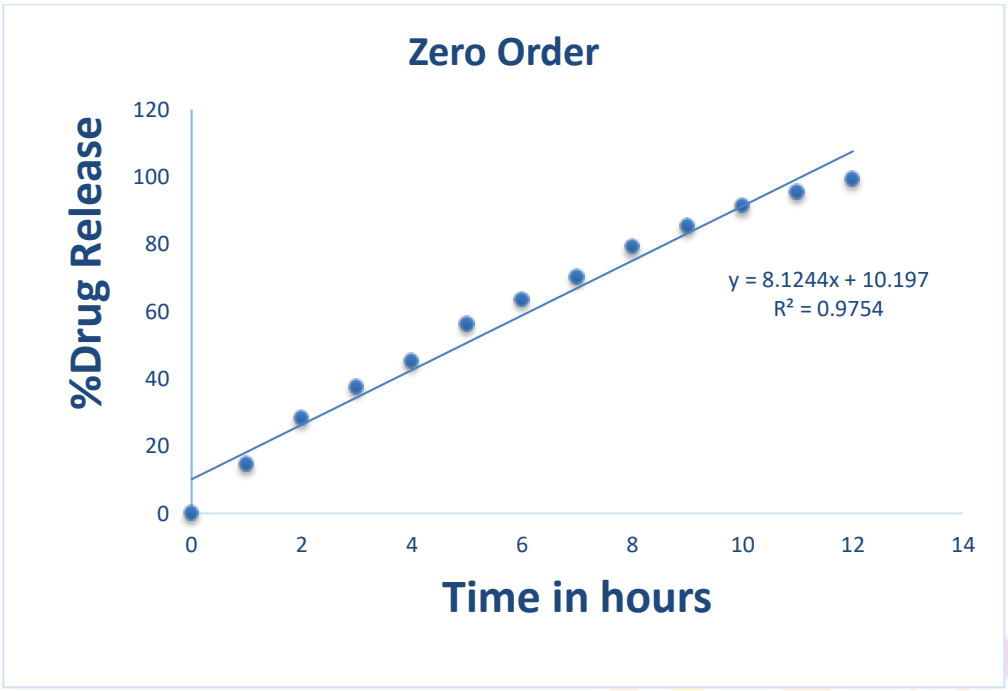

Fig: 5.12. Zero order graph of optimized formulation(F8)

First Order:

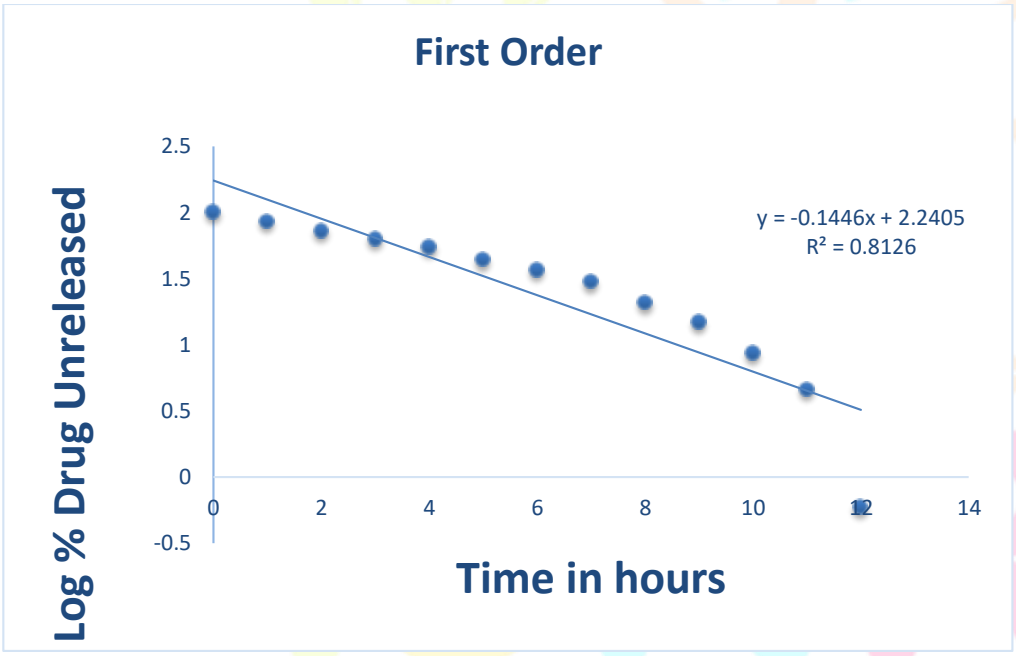

Fig:5.13.First order graph of optimized formulation(F8)

Higuchi Plot:

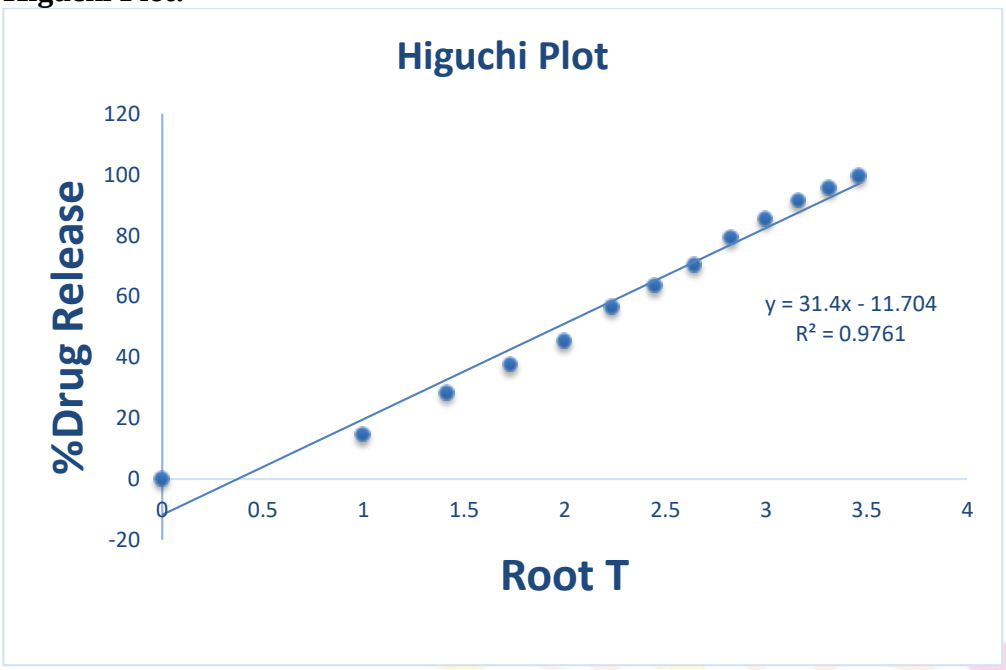

Fig:5.14.Higuchi graph of optimized formulation(F8)

Peppas Plot:

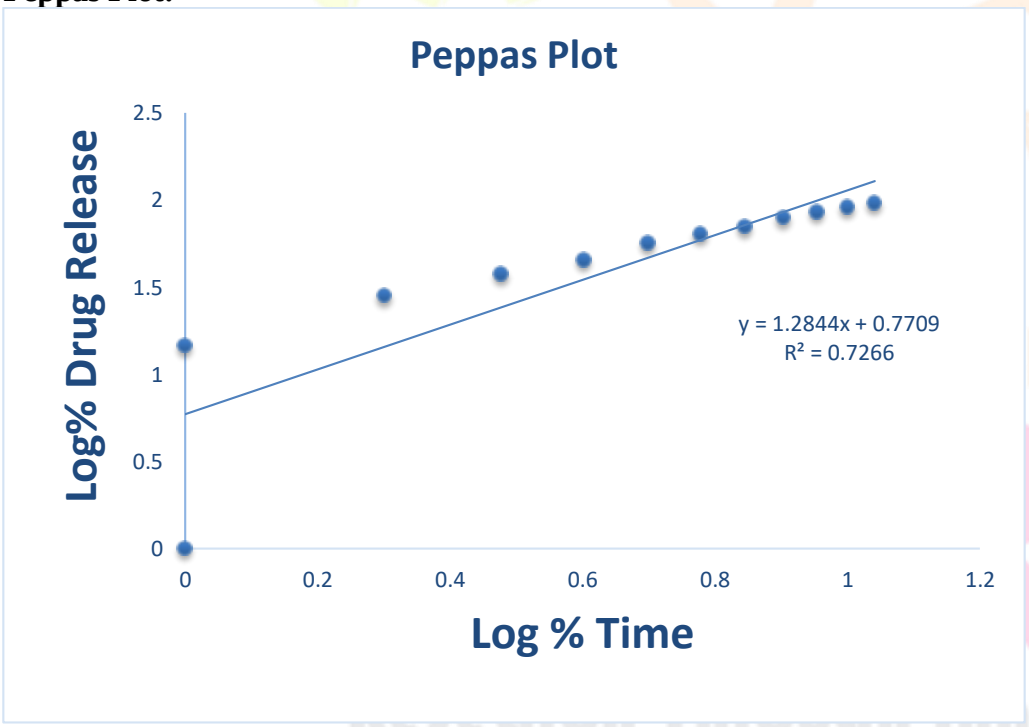

Fig:5.15.Peppas graph of optimized formulation(F8)

Table:5.8.Drug release kinetics

R^2 values					n values
Formulation	**Zero order**	**First order**	**Higuchi**	**Korsmeyer - Peppas**	**Korsmeyer-Peppas (n)**
F8	0.975	0.812	0.972	0.726	1.284

Discussions:

The invitro dissolution data for the optimized formulation F9were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation F9 shows R^2 value 0.975. As its value nearer to the '1' it is conformed as it follows the Zero order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot, if n = 0.45 it is called Case I or Fickian diffusion, 0.45 < n < 0.89 is for anomalous behavior or non-Fickian transport, n = 0.89 for case II transport and n > 0.89 for Super case II transport.

The 'n' value is 1.284 for the optimized formulation (F8) i.e., n value was > 0.89 this indicates super case transport. The release kinetics for the optimized formula are shown in table.

SUMMARY

Inthisstudy, controlled release tabletsofCiprofloxacinwerepreparedby Direct compression method,using Xanthan Gum, Carbopol 940 and Ethyl cellulose polymers. The pre compression and post compression parameters show that the values were found to be acceptable within the range. FT-IR studies revealed that the drug and excipients used weren't have any interactions. The drug-polymer ratiowasfoundtoinfluencethereleaseofdrug fromtheformulations.

Different parameterslikehardness,friability,weightvariation,drug contentuniformity,*in-vitro* drugreleasewereevaluated in all the parameters the optimized formulation F9 yields best results and among in all 12 formulations F8 formulation containing 250mg of Carbapol 940 controls the drug release up to 12 hours. So Carbapol 940 was considered to be suitable for the formulation of Ciprofloxacin controlled release tablets. BasedontheseresultsformulationF8 wasfoundtobe themostpromisingformulations.Theregressioncoefficient(R^2)of Zero order of Optimized formulation F8 shows R^2 value 0.975.The 'n' value is 1.284 for the optimized formulation (F8) i.e., n value was > 0.89 this indicates super case transport

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