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"FORMULATION DEVELOPMENT & EVALUATION OF ORAL SUSTAINED RELEASE SUSPENSION CONTAINING ANTIDIARRHEAL DRUG"

[1]Ashvini Arun Tukar, [2]Atul Bisen, [3]Dr. Manjeet Singh, [4] Dr. Rajesh Mujariya

[1,2,3,4]Institute of pharmaceuticalscience & Research (IPSR) , Balaghat, MP

Email id: ashvinipatle@gmail.com

Abstract: Antidiarrheal drug, combination of racecadotril & ofloxacin & theobjective to incorporate the fix dose combination of drug in the sustained release to check thesuitability of product. To reduce the dosing, frequency and improve the patient complianceparticularlyin pediatric classtominimizethetoxicityduetooverdosewhichofteninconventional dosage form. Chewable tablet are not ideal with pediatric & geriatric patient due toneedofchewingsustainedreleasesuspensionwillcertainlyhelpfulforthispatientanti-diarrhealtreatment should beeffectiveincombination, Ofloxacin-Indion complex was prepared for the sustain release action and by batch process in different ratiosas 1:1, 1:2, 1:3. Prepared complexes were evaluated for pH and % drug content. Highest drugcontentof88.45%was foundin 1:3 complexandhenceselectedforfurtherstudies.Rcecadotril - Eudragit EPO polymer complex was prepared for immediate action bykneading method in ratio of 1:1,1:2,1:3, were also evaluated for pH and drug content.Thestabilitystudieswheredoneat40ºC±2ºC&RH70%±5%for3monthandsuspension was evaluated for pH, drug content, viscosity, % drug leaching and drug releasepattern In case of1:3complex98.45%drugcontentwasfoundandhenceitwaschosenforfurtherstudies.

Key words: Racecadotril, Ofloxacin,Antidiarrheal drug, Eudragit, Indion resinatecomplex

INTRODUCTION

It is defined in absolute or relative terms base either the frequency of bowel moment orthe consistency of stools or condition in which feces are discharge from the bowel frequently inthe liquid form. Diarrhea may be acute or chronic type consequence of viral or bacterial infection and symptoms of an underlying, on-going disorder, such a small-absorption or acute inflammatory bowel disorder. Incubation period is about 10-14 days. Diarrhea is leading to cause of child mortality in developing countries accounting for 1.5-2 million deaths in children under five year. In consequence, the economic impact of the disease and its treatment are of considerable importance. Diarrhea results from various viral, bacterial, and parasitic infections and is most frequently of infectious origin. 40to 45 % pathogen responsible for this. The principle bacteria pathogen responsible for acute diarrhea, E.Coli, rotavirus, and shigella, which responsible to enhance amount of enkephalines receptor on site of intestine, due to that dehydration produced.

Mechanism Action

During incubation period bacteria invade into the lymphoid tissue of smallintestine.Thereafter, the microbes spread via the blood to the liver, spleen & gall bladder. A bacteria rimicperiod follows by malaise,headache, drowsiness & aching limbs.The intestinal lymphoid tissuebecomesacutelyinflamed &ulcerated.

Line of Treatment :-PrimaryTreatment:

a.Non-specificAnti-Diarrhealagents: Theagentwhichreducesdailyfecalvolumedecreasefluidand increasestools viscosityand bulk density.

1.Antisecretory:e.g.Racecadotril

2.Antimotility:e.g.Loperamide

a.Antimicrobialagent: TheagentwhichinhibitbacterialtopoisomeraseIVandDNAgyrasewhichresponsible for replication.

e.g.Metronidazole,Ornidazole,Ofloxacin.

Material and Method

Ofloxacin it belongs to category Floroquinoloneantibiotic, Antimicrobial, Eudragitand all the other reagent were analytical grade obtain from SPU chemical laboratory.

For the preparation of complex, formulation & evaluation of oral sustained releasesuspensionfollowingAPI&excipientswereused

Table no 1:

Ingredients	Grade	Supplier
Ofloxacin	Pharma	ZimLabs,Kalmeshwar
Racecadotril	Pharma	SymedLabLtd.Hydrabad
IndionResin254	Pharma	IonExchangeIndiaLtd. Mumbai
Eudragit Polymer	Pharma	Evonik IndiaPvt. Ltd., Mumbai
CMCSodium	EP	MerckspecialitiesPvt.Ltd.,Mumbai
Methyl paraben	EP	AltalaboratoryLtd.
Propyle paraben	EP	AltalaboratoryLtd.
Saccharin	EP	LOBAChemiePvt. Ltd.Mumbai
Citricacid	EP	ThermofisherIndiaPvt.Ltd.Mumbai
Sorbitol	EP	LOBAChemiePvt. Ltd.Mumbai
Ethanol	EP	PurtiDistilleries,Nagpur
Flavour	Food	DevanshwarehousingPvt.Ltd.Pune
Colour	Food	SuryaPvt. Ltd.,Mumbai

Calibrationcurveof Ofloxacin in0.1NHCl (pH1.2)

Accurately weighed ofloxacin (10mg) dissolved in 100 ml of 0.1 N Hcl& the volume madeup to 100 ml (100µg/ml).

Pipette out 1 ml and dilute upto 10 ml by using 0.1 N Hcl (10µg/ml).Aliquots of 0.2, 0.4, 0.6, 0.8 dilute upto 10 ml to make different concentration 2, 4, 6, 8 and10µg/mlrespectively. All sampleswere filter&measuredabsorbanceat294nm.

CalibrationcurveofOfloxacin inphosphatebufferpH7.4

Accurately weighed ofloxacin (10mg) dissolved in 100 ml phosphate buffer pH 7.4 & thevolumemade upto100ml(100µg/ml).Pipetteout1mlanddiluteupto10mlby usingphosphate buffer (10µg/ml) Aliquots of 0.2, 0.4, 0.6, 0.8 dilute up to 10 ml to make differentconcentration2,4,6,8and10µg/mlrespectively.Allsampleswerefilter&measuredabsorbanceat 294 nm.

Calibrationcurveof Racecadotril in 0.1NHCl(pH1.2)

Accurately weighed racecadotril (10mg) dissolved in 100 ml of 0.1 N HCl & the volumemade up to 100 ml (100µg/ml). Pipette out 1 ml and dilute upto 10 ml by using 0.1 N HCl(10µg/ml) Aliquots of 0.2, 0.4, 0.6, 0.8 dilute upto 10 ml to make different concentration 2, 4, 6,8and 10µg/mlrespectively. All sampleswerefiltered&measured absorbanceat 231 nm.

FTIR Study

FTIRtransmissionspectrawereobtainedbyusingaIRAffinitySShimadzu spectrophotometer. Sample were prepared by mixing with KBr. The scanning range was 500 to4,000cm^{-} peakwererecorded.Thisusedforcheckingdrug,polymerinteractionandcompatibility.

PreparationofOfloxacin-Indion resinatecomplex(Batchprocess)

Accurately weighed 100 mg activated resin (neutral) in 50 ml deionized water stir for 10minthen addweighedamount of Ofloxacininto it (100mg) itaccording todifferentratio 1:1, 1:2,1:3.Dispersion was keptforevaporation. Drycomplexwascollected &coded.

EvaluationofOfloxacin-Indion254 complexes

Drugcontent(%)determination

Accuratelyweighed10mgresinatein10mlvolumetricflaskanddissolvedwithphosphatebufferpH7.4makeupvolumeupto10ml(1000µg/ml).Withdraw0.1mlanddiluteupto10ml(10µg/ml).Aliquotsof0.2,0.3tomake20µg/ml,30µg/ml,filteredand takenabsorbanceat294nm.

pHdetermination

pH ofdrugresinatecomplexwasdeterminebyusingpH meter.

Evaluationof (1:3)Ofloxacin-Indion254complex(resinate)

1.Particlesizedetermination

2.FTIRStudy

3.*In –vitro*drugrelease

1.Particlesizedetermination

Particle size was determined by using Malvern zeta sizer. The samples were diluted withdistilled water adjusted to a conductivity of 50µS/cm. The pH was between 6 -7 the average ofparticlesizedistribution is given from 30 run.

***In-vitro*dissolutionstudies**

The *In-vitro* drug release study of ofloxacin-indion complex was conducted using the USPdissolution Apparatus-II (paddle type) and 900ml of 0.1N HCl (pH1.2) as dissolution medium.The study was conducted at temp.37±0.5ºC and paddle rotation of 50 rpm. The drug resinateplaced inside vessel. Withdraw 5ml sample and filter were predetermined time interval (15 min)withreplacing5mloffreshdissolutionmediumaftereachsampling.Thereleasestudyabsorbance at wavelength 294 nm. After 2 hr replace the medium with phosphate buffer pH 7.4andperformed studyforfurther6hr.

Formulationofsuspension

Optimize ratio of Ofloxacin-Indion & Racecadotril-Eudragit EPO polymer complexes wereselected for the formulation & development on the basis of various parameter like, drug content,pH,particlesize, threshold bitterness &% drugrelease.

ExcipientusedfortheformulationofSRsuspension

1.SodiumCMC-suspendingagent

2.Methylparaben- preservative

3.Propylparaben- preservative

4.Sorbitol-sweeteningagent, viscositymodifier

5.Citricacid –bufferingagent

6.Water-as vehicle

7.Saccharin-sweeteningagent

TableNo.2:Formulationofsuspension.

Sr. No.	**Ingredientuse**	**Batches**		
		F1	**F2**	**F3**
1.	Ofloxacin-indioncomplex	5.160gm	5.160gm	5.160gm
2.	Racecadotril-Eudragitcomplex	3.060gm	3.060gm	3.060gm
3.	SodiumCMC	0.533gm	0.433gm	0.333gm
4.	Methylparaben	0.067gm	0.067gm	0.067gm
5.	Propyleparaben	0.006gm	0.006gm	0.006gm
6.	Sorbitol	3.33 ml	3.33 ml	3.33 ml
7.	Citricacid	0.026gm	0.026gm	0.026
8.	Saccharin	1.66gm	1.66gm	1.66gm
9.	Water	Upto50 ml	Upto50 ml	Upto50 ml

Methodof manufacturing

10 ml dematerialize water was taken in a beaker, add carboxy methyl cellulose sodiumwith different concentration (1%,0.8%,0.6%) suspended slowly with constant stirring consider it1st solution.Methylparabensodiumandpropylparabensodiumwasdissolvedin5mldemineralized water and added in solution 1, kept overnight. Sorbitol and saccharin was addedinto the bulk with constant stirring, followed by citric acid & ofloxacin-Indion 254 complex,mixedfor30minandaddracecadotril-Eudragitcomplexwithconstantstirring.Finally flavor wasaddedandthoroughlymixedfor4hrsandkeptovernight.Finalvolumewasmadeupwithconstant stirringwhich wasthen subdividedand packedin amber colour glassbottles.

Evaluationofsuspension

1.Appearance

Suspensionwas evaluatedforcolour, odour &taste

2.pH

The pH determination study was carried out by using digital pH meter. The pH meter wascalibrated by using buffer solution of pH-4 and pH-7 the sample of sustained release suspensionwastaken andpH was measuredat roomtemperature.

3.Viscosity

Viscosity of suspension was measured by using Brookfield viscometer having rotation perminute was 50 Rpm &spindle no.61

4.% Drugcontentdetermination

For thedetermination of drug contenta suspension containing 50mg and 30mg equivalentof Ofloxacin and Racecadotril was filtered & the drug content was determined as mentionedpreviously.

5.Particlesize,distribuation&zetapotential

Allparameter waschecked byusingMalvernzeta sizermethod given as previous.

6.Redispersability

Ease of redispersability was determined by allowing the suspension to settle in a measuringcylinder. The mouth of the cylinder was closed and was inverted through 1800 and the numberofinversions necessarytorestorea homogeneous suspension was determined.

7.Sedimentationvolume&Sedimentationrate

Sedimentation volume was determined by properly shaking and storing the suspensions in100 ml measuring cylinder. The suspensions were allowed to settle down for 24hourandsedimentation time (rate) as well as sedimentation volumes were determined. The sedimentationvolumewas calculated usingthe official formulaas follow:

Sedimentationvolume(Vs)=Hu/Ho

RESULT&DISCUSSION

TableNo.3: Preformulationstudyofdrug

Sr.No.	DrugName	Color	Meltingpoint	Solubility	Taste
1.	Ofloxacin	Whitebuff	255°C	Ethanol	Bitter
2.	Racecadotril	White	75ºC	Ethanol	Bitter

TableNo.4: Preformulationstudyofresin

Sr.No.	Parameter	Std.Value	Observedvalue
1.	Moisturecontent	0.50 %	0.35%
2.	Waterabsorption time	10 min	10 min
3.	Particlesize	≥ 0.15mm	2µm

Verification or Ofloxacinλmax

Wavelengthofmaximumabsorbance(λmax)forthesolutionof ofoxacininethanolwasperformed&thespectrumobtained as shownin figure:-

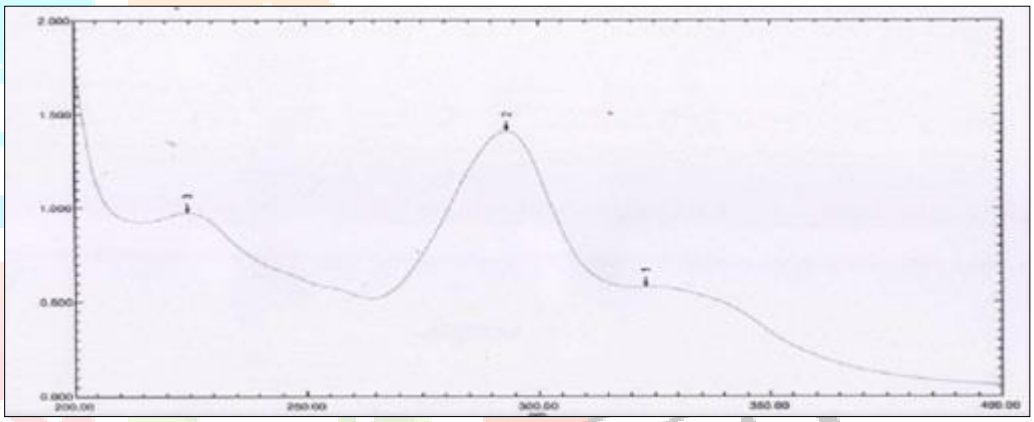

Fig.1:UVspectrumof ofloxacin

Fromtheabovespectrumabsorption maxima(λmax)was foundto beat 294 nm.

Racecadotril

Wavelengthofmaximumabsorbance(λmax)forthesolutionofracecadotrilinethanolwasperformedthespectrumobtained as shownin figure:-

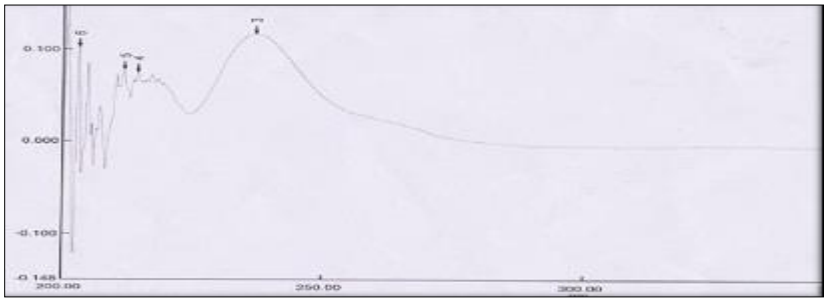

Fig.2:UVspectrumofracecadotrilFromtheabovespectrumabsorption maximawas foundto beat 231nm.

Calibrationcurve

TableNo.5:Graded absorbanceofofloxacin in0.1NHCl

Sr.No	Conc.(µg/ml)	Absorbance
1	0	0
2	2	0.202
3	4	0.389
4	6	0.589
5	8	0.789
6	10	1.05

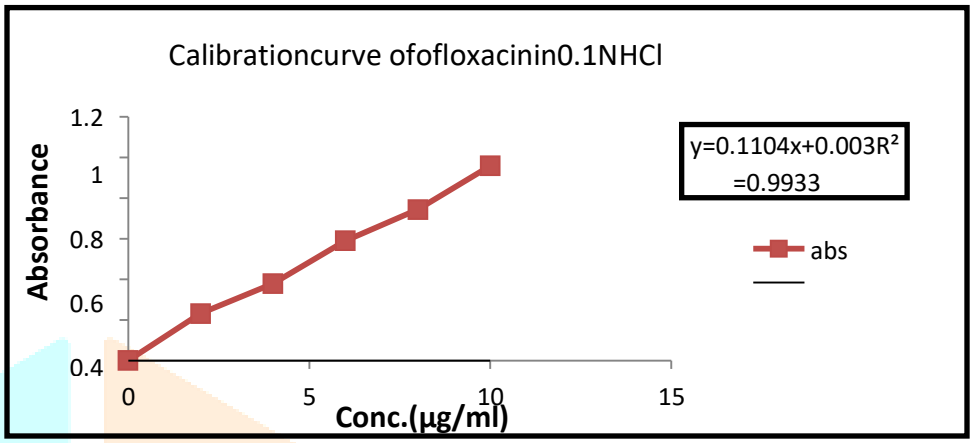

Fig.3:Calibrationcurveofofloxacinin 0.1NHCl

From the above calibration curve it was concluded that, the ofloxacin in 0.1NHCl followsBeer-Lambert law within the concentration range of 2-10µg/ml. Having regression value (R^2)0.993

TableNo.6: Gradedabsorbanceofofloxacin inphosphatebufferpH 7.4

Sr.No	Conc.(µg/ml)	Absorbance
1	0	0
2	2	0.260
3	4	0.498
4	6	0.728
5	8	0.973
6	10	1.09

Fig.4:Calibrationcurveofofloxacin in phosphatebufferpH7.4

From the above calibration curve it was concluded that, the ofloxacin in 7.4 Phosphate bufferfollows Beer-Lambert law within the concentration range of 2-10µg/ml. Having regression value (R^2)0.997.

TableNo.7: Gradedabsorbanceof racecadotrilin 0.1NHCl

Sr.No.	Conc.(µg/ml)	Absorbance
1	0	0
2	2	0.225
3	4	0.398
4	6	0.703
5	8	0.915
6	10	1.07

TableNo.8: Gradedabsorbanceof racecadotril inphosphatebufferpH6.4

Sr.No	Conc.(µg/ml)	Absorbance
1	0	0
2	2	0.239
3	4	0.387
4	6	0.589
5	8	0.776
6	10	0.978

Fig.:Calibrationcurveofracecadotril in0.1NHCl

Characterizationofdrug&complexes

FTIRStudyofofloxacin,physicalmixture,complex

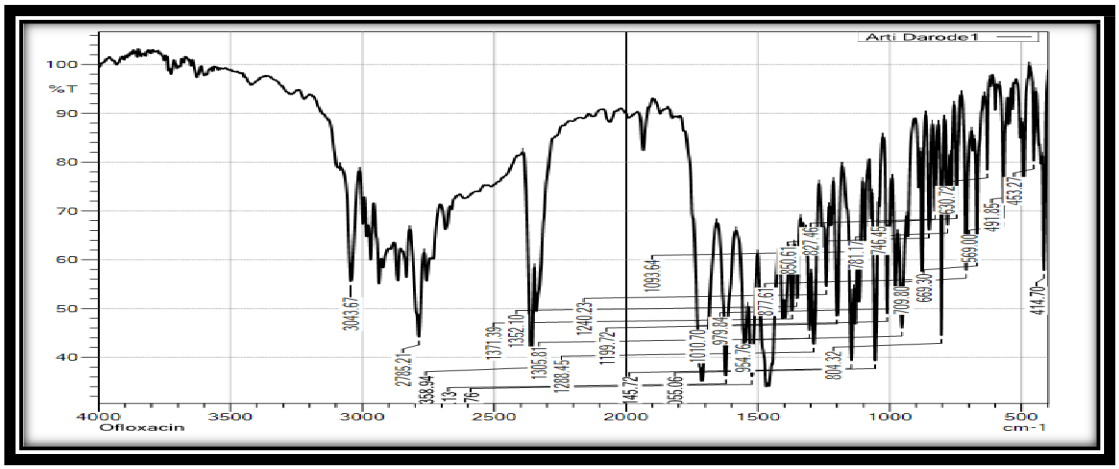

Fig.5: FTIRspectrumofofloxacin

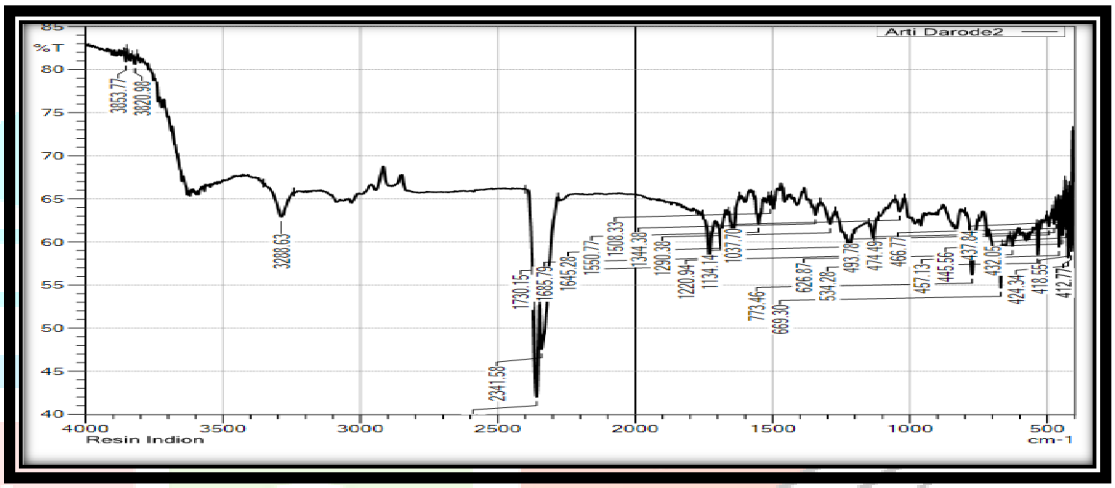

Fig.6: FTIRspectrumofresinIndion254

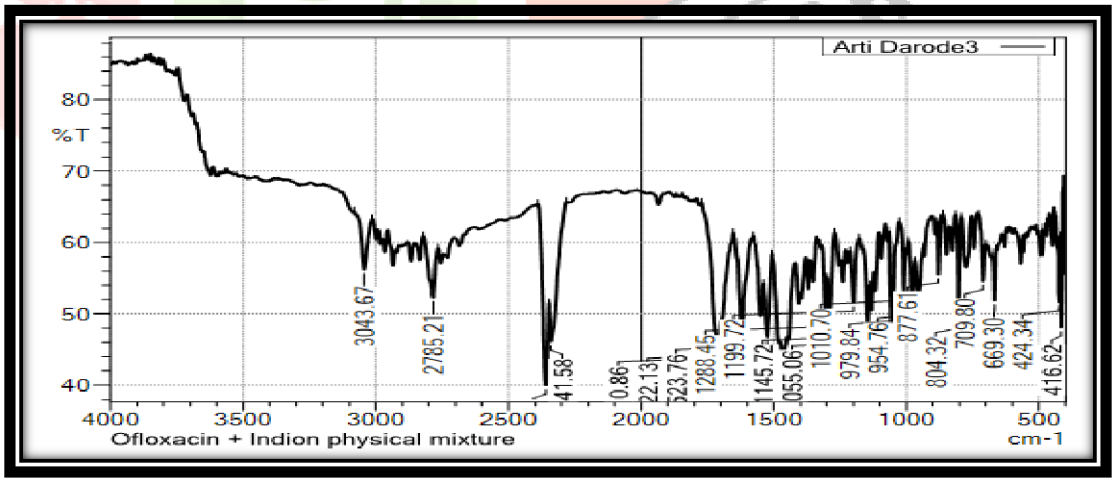

Fig.7: FTIRspectrum ofOfloxacin- Indion254physicalmixture

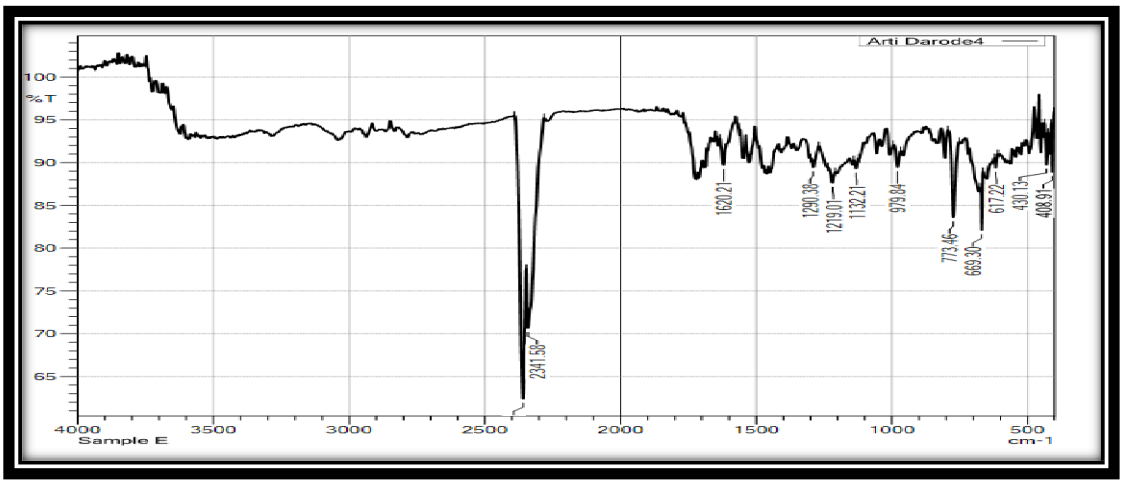

Fig.8:FTIRspectrum ofOfloxacin-Indion254complex.TableNo.9:FTIRInterpretationofofloxacin,physicalmixtureandcomplex

Peakassignment	Pure drugOfloxacin	Resin Indion254	Physical mixture ofOfloxacin & Indion254	Ofloxacin-Indion254 Complex(1:3)
OHstretchingvibration	3043.47	-	3043.67	-
C-Hstretching	-	3288.63	669.30	669.30
CH3,CH2	2785	-	2785.21	-
CONH	-	2341.58	2341.58	2341.58
C=Cstretching	-	-	-	1620.21
C=O stretchingvibration	1358	-	-	-
S-Ostretching	-	1134	-	-
C-Fstretching	979	-	-	
$COCH_3$	-	-	-	773.46
=C-Hout of plane bendingvibration	746	-	-	-

Evaluationofcomplexes

Ofloxacin-Indion254complex

Drugcontent&pHdeterminationofOfloxacin –Indion254complex

TableNo.10: Drugcontent&pHdeterminationofOfloxacin-Indion254complex

Sr.No.	Complexratio	DrugContent	pH
1.	1:1	82%	5.9
2.	1:2	85%	5.8
3.	1:3	88.45%	6

TableNo.11: Particlesize&particlesizedistribution ofOfloxacin-Indion 2541:3complex

Complex	**Particlesize**	**Polydispersityin dex(PDI)**	**Entrapment Efficiency(%)**
Ofloxacin-Indion254complex	0.9258µm	0.694	89.1

TableNo. 12: Evaluation parameter before&afterstabilityofsuspension

Parameters	**Beforestability**	**Poststability(3month)** **F3formulation**
Appearance	Uniform	Uniform
Taste	Sweetpalatable	Sweetpalatable
Color	yellow	yellow
pH	7.2	7.1
Viscosity(cps)	54	56
Sedimentationvolume	0.98	0.98
Sedimentationrate	0.69 ml/min	0.69 ml/min
Redispersability	+++	+++
Drugcontent	89%(ofloxacin) 97%(racecadotril)	89%(ofloxacin) 97%(racecadotril)
Drugleachinginto container	0.34(ofloxacin) 0.37(racecadotril)	0.34(ofloxacin) 0.37(racecadotril)
Wt/ml(mg/ml)	1.4	1.4
Particlesize	0.838µm	0.612µm
Zetapotential	-9.73µm	-8.06

From the observation shown in table, it was concluded that, after 3 month stability of suspension,significant changes was not observed with respect to the stability affecting parameters likepH,viscosity, particle size,zeta potential, sedimentation rate, sedimentation volume. Also, drugcontent,drugleachinginsuspensionwasfoundtobesatisfactorywhichindicatesstableformulation.

Vs=sedimentation volume,

Hu=Ultimateheight of suspension,

Ho=Originalheightof thesuspensionbeforesettling

Summary & Conclusion

On the basis of all evaluation, racecadotril - Eudragit EPO complex (1:3) & ofloxacin-indion complex (1:3) was selected for formulation & development of suspension. Suspensionwere prepared by general dispensing method using Carboxy methyl sodium as dispersive mediabyusingwater vehicleotheringredient whichrequireto formulate stableflocculatedsuspension.

The rheology of suspension results confirmed that the suspensions are pseudoplastic innature i.e. shear thinning in nature. The viscosity also found to be optimum to withdraw theformulationfrom container.From the dissolution profile of the prepared suspension % drug release of ofloxacin fromthe suspension was found to be 86% over the period of 8hr & % drug release ofracecadotril98% over the periodof2 hr. Hence, itwas concluded that the suspension containing drugresinatecomplexshows thegoodcombinationofimmediateandsustain releaseeffect.

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