FORMULATION AND EVALUATION OF FLOATIN GBEADSOF OF LOXACINUSINGELECTRONMICROSCOPY

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ABSTRACT: While in mid-air Pharmacological delivery systems aim to increase the amount of time a drug spends in the stomach after oral ingestion. Many doctors recommend the fluoroquinolone antibiotic ofloxacin for the treatment of stomach and duodenal ulcers. Its solubility varies with pH, being somewhat soluble at neutral and somewhat insoluble at acidic pH. Adverse effects on absorption in the lower parts of the gut arise due to drug precipitation in the intestine. Therefore, systems that remain in the stomach for an extended length of time and release the active ingredient gradually are required. The current research set out to find a way to distribute ofloxacin in a way that would allow it to be retained fordevelopingofloxacin-containing rice bran oil-entrapped zinc pectinate beads, which increases local activity in the stomach area against Helicobacter pylori. Different types of flocculent ofloxacin beads were created by combining Low Methoxy Pectin with other polymers that influence the rate of flocculation, such as Xanthan Gum, Gellan Gum, or Karaya Gum. The beads were made using the emulsion gelation technique. The beads were given buoyancy by using rice bran oil, which has a low density. The spherical beads exhibited the maximum drug content and drug trapping when made with a combination of Low Methoxy Pectin and Gellan Gum. To achieve the desired level of buoyancy, the beads had to be treated with at least 25% w/w rice bran oil, according to the buoyancy tests.

Keywords: Antibiotic, Absorptionwindow,Gastricresidencetime,Polymer mixture,Stomach

INTRODUCTION: Several physiological constraints are present in most oral dose forms. These include uneven drug release, shorter residence time in the stomach, and variable gastrointestinal transit due to varying gastric emptying.

Because only portion of the medicine is absorbed once it travels down the absorption site, this causes partial absorption of medications with an absorption window in the upper section of the small intestine. Thanks to floating drug delivery systems (FDDS), all of the aforementioned conditions may be satisfied, and the medications can be effectively delivered to the absorption window for local action for the treatment of gastrointestinal problems such gastro-esophageal reflux. The hydro-dynamically balanced systems (HBS) or floating drug delivery systems (FDDS) are able to float in the stomach for an extended length of time because their bulk density is lower than that of gastric fluids. time. The medication is released from the system at a controlled pace while the systems float on the stomach contents. Gastric residence time (GRT) increases and, in certain situations, variations in plasma drug concentrations are better controlled as a consequence of this. Efficacious against both Gram-positive and Gram-negative bacteria, ofloxacin is a broad-spectrum antibiotic. An efficient method for treating gastric and duodenal ulcers, as well as eliminating Helicobacter pylori from the stomach, is to formulate FDDS of H2 antagonists.

DATA AND PROCEDURES:

Apex Formulations Pvt. Ltd. of Ahmedabad, Gujarat, India provided the ofloxacin, Sigma Aldrich chemicals of Hyderabad, India provided the gellan gum, and Sigma Aldrich of the United States supplied the Xanthan gum. The rice bran oil and Karaya gum were sourced from Sri AnjanayaAgrotech Pvt. Ltd in Harihar and Mumbai, Karnataka, India, respectively. Analytical grade chemicals and reagents were used in every other case.

Methods:

DevelopmentofCalibrationCurve: Ofloxacinequivalentto100mgwasdissolvedin100mlof 0.1 N hydrochloric acid buffer (pH 1.2) to get astock solution A. 10 ml was pipetted out and thevolumewasmadeupto100mlwith0.1Nhydrochloricacidbuffertogetastocksolution B.

From the stock solution B, aliquots were dilutedto10ml with 0.1 N hydrochloric acid buffer to get 1to8µg/mlsolutionsandmeasuredat294.5nm.(SpectrophotometerUV-1601, Shimadzu,Japan)[1].

Drug Polymer Compatibility Studies:Differential Scanning Calorimetry

Using Differential Scanning Calorimetry (DSC-60, Shimadzu, Japan), we tested the compatibility of Ofloxacin with various polymers in a physical combination. When the temperature reached 350 °C, it was maintained at 10 °C/min. Purging was done using nitrogen gas at a rate of 30 ml/min.2. Fourier Transform Infrared Spectroscopy (FTIR): An IR spectrophotometer (Shimadzu, model 840, Japan) was used to capture the spectra of the drug and polymers. Any significant interactions between the two were then investigated. For the aim of comparing things and evaluating the peak pattern, this were done qualitatively.

The flotation zinc pectinate beads were prepared by passing Ofloxacin, LMP, GG, XG, and KG through filter no. 80 in isolation. The ofloxacin was dissolved in distilled water at a concentration of 20% by weight of the dry polymer. The aforesaid dispersion was used to dissolve LMP (3% w/v) on its own, as well as polymer mixes (3% w/v) including LMP and GG, LMP and XG, and LMP and KG in three different ratios. One formulation was specifically made using polymer mixtures (3% w/v) containing GG, XG, KG, and LMP.

TABLE1:FORMULATIONVARIABLESOFVARIOUSOFLOXACINBEADFORMULATIONS

Formulation code	LMP:GG (3%W/V)	LMP:XG (3%W/V)	LMP:KG (3%W/V)	LMP:GG:XG:KG (3%W/V)	RICE BRANOIL(3 %W/V)
F	10:0	10:0	10:0	-	15
	10:0	10:0	10:0	-	20
	10:0	10:0	10:0	-	25
F1	9:1	-	-	-	25
F2	8:2	-	-	-	25
F3	7:3	-	-	-	25
F4	-	9:1	-	-	25
F5	-	8:2	-	-	25
F6	-	7:3	-	-	25
F7	-	-	9:1	-	25
F8	-	-	8:2	-	25
F9	-	-	-	8:0.66:0.66:0.66	25

To the above mixture rice bran oil (25% w/w) wasadded and stirred to form a homogeneous emulsion.The drug-loaded emulsion was extruded through a23 G syringe needle into zinc chloride solution (5%w/v)maintained undergentleagitation.

Thebeadswereallowedtoremaininthesamesolution for 30 min to improve their mechanicalstrength. The formed beads were separated, washedwith water and allowed to dry at room temperatureovernight.

Table 1 lists the formulation variables for differentformulationsofOfloxacinloadedfloatingbeads.Blank beads without Ofloxacin were also preparedusingthe same technique[3,4].

EvaluationofPhysicochemicalParametersofFloatingBeads ofZincPectinate:

DeterminationofBead Diameter: The diameterofasampleofgelbeads(25beads)ofeachformulation was determined using a dial thicknessmeter.

Drug Content: An accurately weighed sample ofbeads (100mg) was crushed in a mortar and addedto100ml of 0.1N hydrochloric acid buffer (pH 1.2)and kept overnight under stirring to elute completedrug from the polymer matrix. It was filtered andanalyzedatof294.5nm(UVspectrophotometer,1601,Shimadzu,Japan)againstblankbeadmixture,whichwastreatedsimilarly.Thedrugcontentofeachformulationwasrecordedasmg/100mgofgel beads [5].

DrugEntrapmentEfficiency: Thepercentagedrug entrapment efficiency (% EE) of each beadformulationwascalculatedusingthefollowingequation: [5]

$$EE(\%) = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

Determination of Swelling Index: The swellingbehaviorofthezincpectinatebeadswasstudiedin

0.1 N HCl (pH 1.2) buffer. Approximately 100mgofbeadsweretakeninadissolutionbasketandweighed(W_1);thebasketsalongwiththebeadswereimmersedin0.1N HClbuffer.Theweight(W_2)ofthebasketalongwiththebeadswasdetermined for 8 h: every 30 minutes for the first 2h, and then every h after that. The swelling index(SI) of each formulation was calculated using thefollowingequation:

$$\%SI=\frac{W2 - W1}{W1} X\ 100$$

BuoyancyStudies: Thetimebetweentheintroduction of the FDDS into the medium and itsbuoyancy to the upper one third of the dissolutionvessel (floating lag time) and the time for which theformulation constantly floated on the surface of themedium(floatingduration)weremeasuredsimultaneously as a part of dissolution studies byvisualobservation [6].

Invitro*DrugReleaseStudies:Invitro*releasecharacteristics of ofloxacin floating gel beads (n =3) were evaluated employing USP XIV dissolutiontestingapparatus2(paddlemethod)using500mlof 0.1 N HCl buffer as dissolution medium maintainedat 37 ± 0.5 °C. The contents were stirred at 50 rpm.A 5mlaliquotof the solutionwaswithdrawn atpredetermined time intervals for 8 h and fresh 5mldissolutionmediawasreplacedtomaintainsinkcondition. The sample aliquots were analyzed at awavelengthof 294.5 nm[7].

Stability Studies: Stability studies were carried outaccordingtoICHguidelinesbystoringtheformulationF1at40±2°Candrelativehumidity 75±5%foraperiodoftwomonthsinaprogrammable environmental test chamber (CHM-10S, Remi Instruments Ltd., Mumbai, India). Thesampleswere withdrawnat30and60daysandanalyzed for the drug content, floating behavior and*in vitro* drugrelease[8].

ScanningElectronMicroscopy(SEM): Morphologicalexaminationofthesurfaceandexternal structure of the dried beads of formulationF1, F4 and F7 (Both drug loaded and blank beads)wasperformedusingascanningelectronmicroscope (SEM) (model JEOL, JSM-840A). Thesampleswere goldcoatedpriorto thescanning[9].

RESULTSANDDISCUSSION:

Development of Calibration Curve: Concentrationandabsorbanceobtainedforstandardplotof Ofloxacin in 0.1 N hydrochloric acid buffer (pH1.2)areshown in **Fig. 1.**

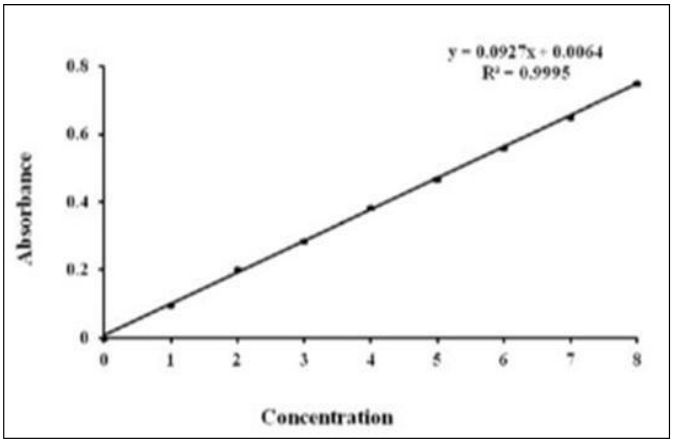

FIG.1:CALIBRATIONCURVEOFOFLOXACIN

Drug Polymer Compatibility Studies:DifferentialScanningCalorimetry(DSC): TheDSCthemogramsofphysicalmixtureofOfloxacinandthepolymersshowedthatcharacteristicpeaksofpolymersandOfloxacinpeakswerestillpresentinthe physicalmixture butslightly shifted fromtheiroriginalpositionsasshowninFig.2.Thefindingsindicate thatthe drug andpolymersarecompatiblewitheach other.

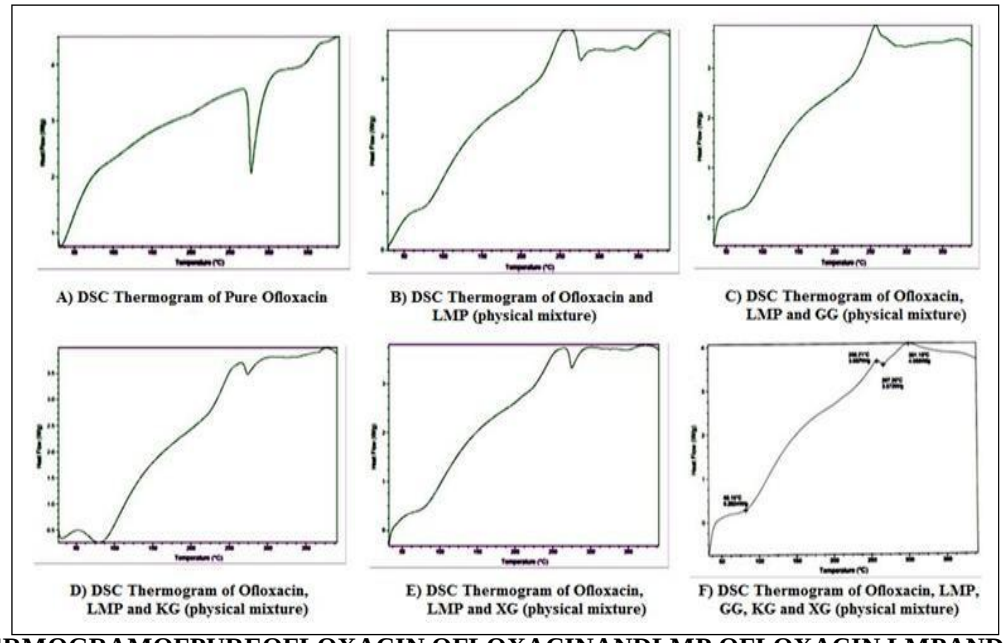

FIG.2:DSCTHERMOGRAMOFPUREOFLOXACIN,OFLOXACINANDLMP,OFLOXACIN,LMPANDGG, OFLOXACIN,LMPANDKG,OFLOXACIN,LMPANDXG,OFLOXACIN,LMP,GG,KGANDXG

Fourier Transform Infrared Radiation (FTIR): All the above bands associated with the pure drugarepresentintheFTIRspectraofdrugincombinationwithgellangum,karayagumandxanthangumasseeninFig.3.Thisshowsthatthereisnochemicalinteractiontakingplacebetweendrugand excipients.

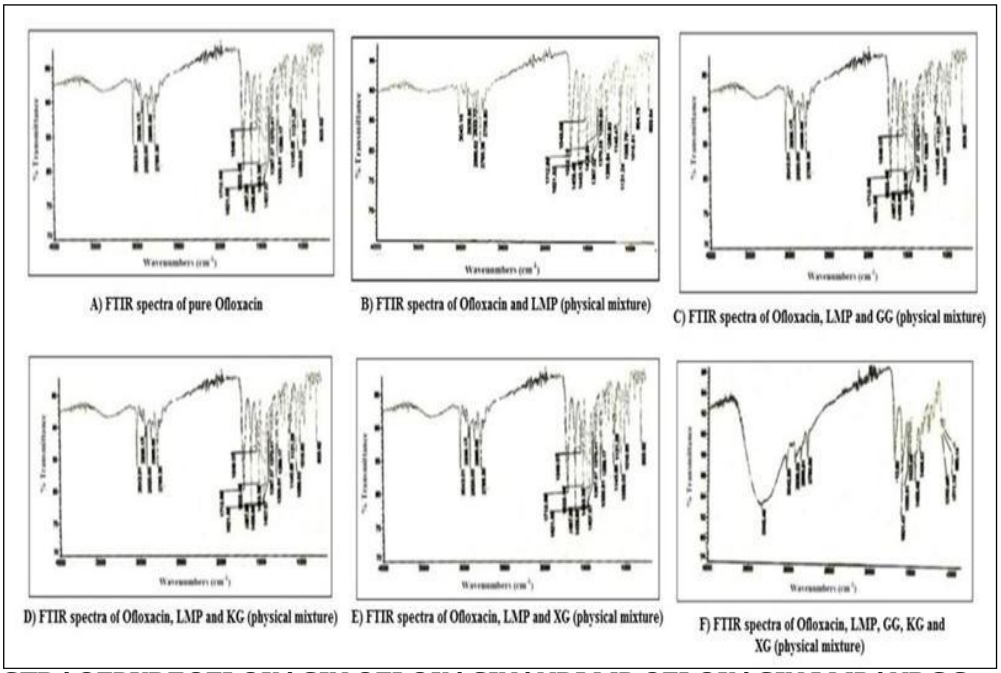

FIG.3:FTIRSPECTRAOFPUREOFLOXACIN,OFLOXACINANDLMP,OFLOXACIN,LMPANDGG, OFLOXACIN,LMPANDKG,OFLOXACIN,LMPANDXG,OFLOXACIN,LMP,GG,KGANDXG

EvaluationofPhysicochemicalParametersofFloatingBeads ofZincPectinate:

Determination of Bead Diameter: The preparedbeads were almost spherical and translucent. Themeansurfacediameterof10formulationswasbetween1.691±0.022(mean±SD)and2.099± 0.041(mean±SD).

Drug Content, Drug Entrapment Efficiency andSwellingIndex: Thepercentdrugcontent,entrapmentefficiencyandswellingindexforvariousOfloxacinfloatingbeadformulationsisshown in **Table 2.**

TABLE2:CHARACTERIZATIONOFFLOATING ZINCPECTINATEBEADS

FormulationCode	Meandiameter±SD(mm)	Drugcontent(mg)	%EE	%SwellingIndex
Fblank	1.691±0.022	-	-	-
F	1.693±0.015	2.437±0.037	57.49	0.74
F1	1.751±0.023	1.236±0.017	78.81	2.42
F2	1.841±0.022	1.620±0.054	69.16	1.79
F3	1.898±0.018	1.551±0.114	72.13	2.21
F4	2.193±0.017	1.681±0.023	76.20	1.01
F5	1.836±0.018	1.621±0.063	60.61	3.75
F6	2.057±0.069	1.362±0.035	74.28	1.22
F7	2.009±0.027	1.713±0.111	65.40	2.10
F8	2.099±0.041	1.417±0.027	62.98	1.74
F9	2.008±0.063	1.434±0.240	58.95	0.72

Buoyancy Studies: The floating ability of preparedbeads was evaluated along with dissolution studies.The beads without oil sank immediately in 0.1 NHCl(pH1.2),whilebeadscontainingsufficientamountofricebranoil(25%)demonstratedinstantaneousandexcellentfloatingproperties**(Table3).**

TABLE3:BUOYANCYCHARACTERISTICSOFFLOATINGBEADS

FormulationCode	Amountofoil(%w/w)	FLT(min)	FloatingDuration(h)
FBlank	-	NF	NF
F	10	NF	NF
F	15	NF	NF
F	25	0	24
F1	25	0	24
F2	25	0	24
F3	25	0	24
F4	25	0	24
F5	25	0	24
F6	25	0	24
F7	25	0	24
F8	25	0	24
F9	25	0	24

Invitro*DrugReleaseStudies:Invitro*drugreleasestudyofOfloxacinfloatingbeadswascarried in 0.1N HCl (pH 1.2), for a period of 8 h. Inthe0.1NHCl,thebeadsexhibitedabiphasicreleaseprofileasaninitialrapiddrugreleasephase(bursteffect)followedbyasustained,graduallyincreasing drug release phase after 1 h extending upto8h. FormulationF containedonly LMPcouldnotsustaintheOfloxacinreleaseupto8h.Itreleasedcomplete drugat theendof4 h**(Table 4)**.

TABLE4: *INVITRO*RELEASECHARACTERISTICSOFFORMULATIONF

SerialNumber	Time(h)	SQRT	Logtime	Cum.%drugrelease	Log% drugremaining	Log%drugrelease
1	0	0	-	0	2	-
2	0.5	0.7071	-0.3010	65.92±1.71	1.5325	1.8190
3	1	1	0	74.47±2.20	1.4071	1.8721
4	1.5	1.2247	0.1760	82.01±0.77	1.2550	1.9139
5	2	1.4142	0.3010	86.26±1.04	1.1481	1.9358
6	3	1.732	0.4771	93.56±0.99	0.8089	1.9711
7	4	2	0.6020	99.14±0.86	-0.0655	1.9962

TABLE5:*INVITRO*RELEASECHARACTERISTICS OFFORMULATIONS

Time(h)	Cumulative%drugrelease								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	47.46±1.59	36.98±2.00	44.59±3.05	45.89±0.94	30.74±	47.71±1.28	40.16±0.96	32.6±1.91	32.6±1.91
1	51.68±1.52	45.55±2.73	52.33±2.29	57.21±2.17	43.50±2.96	58.12±1.04	44.84±0.91	38.78±0.99	40.09±0.15
1.5	58.01±1.56	52.62±1.23	57.47±0.57	59.51±3.02	46.37±2.60	61.28±1.52	49.91±2.28	44.76±0.76	45.13±0.79
2	60.36±2.25	57.15±3.35	59.89±1.46	63.16±1.98	48.34±1.05	63.94±3.49	52.77±2.56	47.47±0.37	47.47±0.37
3	68.36±1.88	61.1±3.42	61.59±1.04	66.49±2.06	51.01±3.13	66.39±0.98	55.92±0.62	51.15±1.03	51.15±1.03
4	71.6±1.84	65.65±3.51	63.81±2.59	68.27±3.01	53.14±2.69	68.37±1.84	58.67±0.68	55.13±0.59	55.13±0.59
5	77.65±0.27	69.07±1.47	66.83±2.58	71.97±1.81	54.86±0.60	71.71±1.29	60.89±1.07	57.92±0.62	57.92±0.62
6	78.48±0.84	70.28±0.91	69.71±0.32	75.58±1.14	56.66±2.42	73.50±0.98	63.78±0.96	60.44±1.51	58.87±0.51
7	83.05±3.47	73.09±1.082	72.52±1.08	78.78±0.37	58.96±1.19	75±0.24	66.59±0.27	63.47±3.21	60.66±0.57
8	87.51±1.14	74.33±0.04	74.76±1.90	80.74±4.11	59.85±2.15	76.41±2.89	68.52±0.96	66.00±1.16	62.40±1.87

FormulationscontainingGG;F1,F2andF3released87.51%,74.33and74.76%ofdrug,formulations containing XG;F4andF5 released80.74%and59.85%ofthedrug,formulationscontaining KG; F6, F7 and F8 released 76.41%,68.52%and66.00%ofthedrugandtheformulationscontainingGG,XGandKG;F9released62.40%ofthedrugatth eendof8hrespectively.Henceonthebasisof*invitro*dissolution studies formulation F1 was chosen asthe best formulation giving 87.51% of drug releasetill8 h**(Table 5).**

CONCLUSION: In order to increase the local action in the gastrointestinal area against Helicobacter pylori, the current research set out to establish a delivery mechanism that might enable the retention of ofloxacin. In light of this, the current study aims to solve the problem of increasing the drug's bioavailability after oral administration by creating zinc pectinate beads entrapped in rice bran oil that contain ofloxacin.

Ofloxacin floating beads in a variety of formulations were created by combining LMP with rate-controlling polymers including GG, KG, and XG, or by employing LMP alone. The beads were made using the emulsion gelation technique. The beads made using a combination of LMP and GG (F1) exhibited the maximum drug release compared to other formulations. Rice bran oil was used to add buoyancy to the beads because of its low density. During the two-month stability investigation, the chosen formulation exhibited no further changes in drug content, floatability, or in vitro drug release profile while stored at 75 ± 5% RH at 40 ± 2 °C. So, the goal of this study was successfully accomplished: to create a dosage form of Ofloxacin utilizing a low density oil and various combinations of polymers that regulate the release rate.

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