Research Article

Development and *In-Vitro* Evaluation of Sustained Release Gastroretentive Microspheric Drug Delivery System of Ciprofloxacin Hydrochloride

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ABSTRACT

The objective of this present investigation was to develop gastroretentive microspheric drug delivery system of ciprofloxacin hydrochloride due to its have narrow absorption window in the gastrointestinal tract, stomach specific absorption, low bioavailability and short biological half-life. The design of this delivery system was based on the sustained release formulation coupling with floating features in order to achieve prolong the gastric retention time as well as sustain the drug release for longer period of time. All the formulations were prepared by ionic gelation technique using natural hydrophilic polymer (pectin), effervescent substance (sodium bicarbonate) and cross-linking agent (barium chloride). The effect of polymeric concentration on various physicochemical parameters, *in-vitro* buoyancy and *in-vitro* drug release were studied to optimize the concentration of pectin required for 12 h. sustain release. SEM, thermal analysis and stability study were performed to investigate the surface morphology, drug-polymer interactions and shelf life of the optimized formulation. It was found that by increasing the polymer concentration, mean particle size and encapsulation efficiency were increased. All the formulations exhibited excellent floating and swelling properties. *In-vitro* drug release study revealed that pectinate microspheres could able to sustain the drug release for only 8 h. SEM and thermal analysis study revealed that there was no interaction between drug and polymer. So, it is concluded from the present research that single polymeric micro-matrix was not able to achieve the desire sustain release of ciprofloxacin i.e. for 12 h. and a polymer blend is required for developing twice daily gastroretentive SR microspheres to delivery ciprofloxacin hydrochloride.

Keywords: ciprofloxacin hydrochloride, gastroretentive microspheres, sustain release, pectin, *in-vitro* buoyancy, shelf life.

INTRODUCTION

Oral sustained release (SR) dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, site specific drug delivery, reduce dosing frequency, more patient compliance and flexibility in formulation.[1] But the drugs which have a narrow absorption window in the upper part of the gastrointestinal tract (i.e. stomach and small intestine) or which are less soluble or unstable in the alkaline pH or which are absorbed from the upper gastrointestinal tract, this delivery system is not suitable.[2] This may be due to the short transit time of the dosage form in the anatomical segments and within 6 hour, this dosage form has left the upper GIT and the drug get released in the non-absorbing distal segments of the gastrointestinal tract. This directly alters the drug absorption and results in by lesser bioavailability.[3]

These problems can be overcome by developing gastroretentive drug delivery systems (GRDDSs) which helps to prolonged the gastric residence time by retaining themselves in the stomach as well as sustaining the drug release for prolong period of time in the upper part of gastrointestinal tract.[4] There are several approaches which helps to achieve extended gastric residence time for the oral sustain drug delivery systems[5] such as bioadhesive system, swelling and expanding systems, floating systems,[6] biodegradable hydrogels,[7] low density systems, high density systems and expandable systems. Among all the gastroretentive drug delivery systems, gas generating floating drug delivery system is the most preferred system that offers a simple and practical approach to achieve prolongs gastric retention. Gastroretentive floating drug delivery systems are formulated as floating tablets, capsules, pellets, microparticles etc. But sometime using of single unit formulations may be problematic if they cause dose dumping.[8] So among all the formulations, gastroretentive SR microparticulate system is more effective than the single unit dosage forms.[9]

Ciprofloxacin hydrochloride, a broad-spectrum fluoroquinolone antibiotic used for the treatment of gram-negative infections, diarrhoea, mycobacterial infections, urinary tract infections (UTI),[10] chronic bacterial prostatitis[11] and the drug of choice for the treatment of *H.pylori* infection which is considered as a risk factor of gastric cancer and duodenal ulcer.[12] Ciprofloxacin hydrochloride is absorbed from the stomach and the proximal part of the small intestine.[13] It has a short elimination half-life of about 4 hrs and the oral bioavailability is about 70%. The short biological half-life (about 4 h), low oral bioavailability (about 70%) and absorption site make ciprofloxacin hydrochloride an ideal candidate being designed in to gastroretentive sustained release drug delivery system.[14]

So, the aim of the present research work was to develop gastroretentive floating pectinate microspheres of ciprofloxacin hydrochloride and investigate the effect of pectin on *in-vitro* drug release. It was also studied that whether this pectin polymer was able restrict the drug release in stomach region and able to sustain the drug release for 12 h. or not. All the gastroretentive formulations were prepared by ionic gelation technique (using barium chloride ($BaCl_2$) as a cross-linking agent and $NaHCO_3$ as gas generating agent) due to its simple processing, cost effectiveness and non utility of organic solvents.

These advantages make this system more acceptable in microencapsulation field as compared to other processes of encapsulation.

MATERIALS AND METHODS

Materials

Ciprofloxacin hydrochloride was a gift sample from DR. Reddys Laboratories Ltd., Hyderabad, India. Low methoxy (LM) pectin (degree of esterification 36%) was obtained as a gift sample from CP Kelco, Lille Skensved, Denmark. Sodium bicarbonate was purchased from S.D. Fine Chemical Pvt. Ltd., Mumbai, India. Calcium chloride was purchased from Loba Chem., India. Other chemicals and solvents used were of analytical grade.

Method

Fabrication of Pectinate Floating Polymeric Microspheres

Table 1: Composition of ciprofloxacin HCl loaded pectinate floating microspheres.

Formulation Code	Drug : Polymer	Sodium bicarbonate (mg)	Rigidiging agent/level (5% w/v)	Stirring Speed (rpm)
FP1	1 : 1	100	$BaCl_2$	1000
FP2	1 : 2	100	$BaCl_2$	1000
FP3	1 : 3	100	$BaCl_2$	1000
FP4	1 : 4	100	$BaCl_2$	1000
FP5	1 : 5	100	$BaCl_2$	1000
FP6	1 : 6	100	$BaCl_2$	1000

FP: pectinate floating microspheres.

Ciprofloxacin hydrochloride loaded pectinate floating microspheres were prepared by ionic gelation method (Table 1). The polymeric excipient i.e. pectin (low methoxylated) solution was prepared by dissolving pectin in sufficient amount of water under gentle agitation. Then the drug was added slowly to the polymer solution and the mixture was stirred at 4000 rpm to obtain a homogenized drug-polymer mixture. In the prepared drug-polymer mixture, sodium bi-carbonate ($NaHCO_3$) was added and mixed at 8000 rpm for 2 min. Then the drug containing polymeric solution was extruded drop wise employing a 24 G needle to a 5 % (w/v) barium chloride solution with continuous stirring at 1000 rpm. The stirring process was continued for 30 minutes for complete reaction. After 30 minutes, the microspheres were collected, washed with distilled water and dried overnight at room temperature. Then the prepared microspheres were kept in desiccator for future use.

Characterization of Microspheres

Physicochemical Characterization of Pectinate Floating Microspheres

% Yield

Percentage yield for each batch of prepared microspheres was calculated using the weight of final product (microspheres) after drying with respect to the initial total weight of the drug and polymer used for preparation of microspheres (Table 2). The percentage yield of each batch was calculated using the following formula:

$$\% \text{ Yeild} = {}^{W_f}/_{W_i}$$

W_f is the final weight of the dried microspheres; W_i is the initial total weight of drug and polymer.

Particle Size Analysis

Particle size analysis of the prepared microspheres was done by sieve analysis method[15] (Table 2). The prepared microspheres were separated into different size fractions (% weight fraction) by sieving for 5 min. using standard sieves having nominal mesh apertures of 1.4, 1.2, 1.0, 0.85 and 0.71 mm. The study was conducted in triplicate and mean particle size of microspheres was calculated using the following formula:

$$\text{Mean particle size} = \frac{\sum(\text{mean particle size of the fraction} \times \text{weight fraction})}{\sum \text{weight fraction}}$$

Entrapment Efficiency

The entrapment efficiency of the prepared pectinate floating microspheres was determined as per the reported method Chakraborty.[16] An accurately weighed quantity of microspheres (100 mg) were placed in 100 ml of 0.1 N HCl (pH 1.2) and vigorous stirred for 4 h. Dispersion of microspheres was sonicated at 125 W for 30 min (Imeco Sonifier, Imeco Ultrasonics, India) and the solution was filtered through Whatman filter paper (0.45 mm). Then, the polymeric debris was washed with fresh solvent (0.1 N HCl) to extract any adhere drug. The drug content of the filtrate was determined spectrophotometrically at 271 nm (UV-2450, Shimadzu, Japan). Each determination was made in triplicate and entrapment efficiency values (Table 2) were calculated using the following formula:

$$\text{Entrapment ef iciency (\%)} = \frac{\text{Total amount of drug in microspheres}}{\text{Total amount of drug added initially}} \text{ X } 100$$

In-vitro Floatability Studies

In-vitro floatability studies of the microspheres were carried out in 0.1 N HCl using USP apparatus II at 37 ± 0.5 °C with a rotation speed of 50 rpm. 0.02 % v/v tween 80 was used as a surfactant. The time taken by the microspheres to rise to the solvent surface (FLT i.e.

floating lag time) and the total time up to which the formulations remain float (TFT i.e. total floating time) were determined and shown in Table 2.

Micromeritic Properties of Microspheres

The micromeritic properties such as angle of repose, Carr's index and Hausner ratio of pure drug and prepared pectinate microspheres were determined and shown in Table 3. The angle of repose was measured by fixed funnel method to evaluate the flowability of pure drug and prepared microspheres. Carr's index and Hausner ratio were studied to analyze the flowability and compressibility of the pure drug as well as prepared microspheres. Each experiment was conducted in triplicate and the values are shown in Table 3.

Swelling Studies

An accurately weighed quantity (100 mg) of microsphere was placed in 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C and allowed to swell. The swollen microspheres were carefully withdrawn from the medium at predetermined time intervals and weighed on a single pan balance. % swelling (Figure 1) was calculated using the following formula:[17]

$$\text{Swelling (\%)} = \frac{(\text{weight of microspheres after swelling} - \text{initial weight of microspheres})}{\text{initial weight of microspheres}}$$

In-vitro Release Study

In-vitro release study of ciprofloxacin hydrochloride from the prepared pectinate floating microspheres was studied using USP dissolution rate test apparatus II (DISSO 2000, LABINDIA, India) at 37 ± 0.5 °C with a rotation speed of 50 rpm. An accurately weighed quantity of microspheres (equivalent to 100 mg of pure ciprofloxacin hydrochloride) was placed in dissolution flask containing 900 ml of 0.1 N HCl (pH 1.2).

At predetermined time intervals, 5 ml samples were withdrawn and replaced by an equal volume of fresh pre-warmed 0.1 N HCl.

After suitable dilutions, the samples were filtered and analyzed spectrophotometrically (UV-2450 Shimadzu, Japan) at 271 nm. The drug release studies were conducted in triplicate shown in Figure 2.

Analysis of Release Profiles

The rate and mechanism of release of ciprofloxacin hydrochloride from the prepared microspheres were analyzed by fitting the dissolution data into different rate equations such as,

Zero-order equation,

$$Q = k_0 t$$

Where, Q is the amount of drug released at time t and k_0 is the zero order release rate constant.

First order equation,

$$\ln(100 - Q) = \ln 100 - k_1 t$$

where k_1 is the first order release rate constant. The dissolution data was fitted to Higuchi's equation,[18]

$$Q = k_H t^{1/2}$$

Where, Q is the percentage of drug released at time t, k_H is the Higuchi release rate constant.

Peppas equation,[19]

$$\frac{M_t}{M_\infty} = kt^n$$

Where, n is the release exponent; indicative of the mechanism of release, M_t/M_∞ is the fraction of the drug at time t, K is the release rate constant.

Coefficient of determination (r^2) of all the models and release exponent (n) values (Table 4) were calculated to determine the most appropriate kinetics model and mechanism of drug release.

Statistical Analysis

Statistical analysis of the dissolution data was performed by using the PRISM software (Graph pad, San Diego, CA) at a confidence limit of $P < 0.05$. Drug release data of all the formulations were subjected to one way analysis of variance (one way ANOVA) to find out whether any significant difference was present among the formulations or not. $t_{50\%}$ values of all the formulations were subjected to Holm-Sidak multiple comparison analysis to find out the significant difference among the formulations.

Surface Topographical Analysis

The surface topography of the optimized microsphere formulation was studied by scanning electron microscope imaging instrument (SEM). The samples of the microspheres was spread on stub and coated for 120 s with a layer of gold using a sputter coater. Then the particles were placed in the scanning electron microscope (S 3700 VP FE-SEM, Hitachi High-Technologies, Europe) chamber at the acceleration voltage of 20 kV and chamber pressure of 0.6 mm Hg. SEM photographs were taken at different magnifications and shown in Figure 3.

Differential Scanning Calorimetric Analysis

Thermal analysis of pure ciprofloxacin hydrochloride (PD) and drug-loaded optimized microsphere formulation (OF) was performed using a differential scanning calorimeter (DSC) (Diamond DSC, PYRIS, Perkin Elmer, USA). Both the samples were heated at constant rate of 10 °C/min between 30 and 250 °C. The system was purged with nitrogen gas to maintain the inert atmosphere. The DSC thermograms were shown in Figure 4.

Stability Studies

From all the microspheres, optimized pectinate floating microsphere formulation was tested for six months stability studies following ICH guidelines. Tested formulation (microspheres) were divided into 6 sample sets, sealed in tubes and stored at room temperature (25 ± 2 °C and 60 ± 5 % RH) and accelerated condition (40 ± 2

°C and 75 ± 5 % RH). After each 30 days interval, one tube was used to evaluate % drug content, shelf life and physical appearance of the samples (Table 5a and Table 5b).

RESULTS AND DISCUSSION

Physicochemical Characterization of Pectinate Floating Microspheres

The % yield of the prepared pectinate floating microsphere formulations was found within the range of 76.42 ± 3.97 % to 91.13 ± 4.32 % (Table 2). The percentage entrapment efficiency and particle size of all the formulations were found with in the range of 36.73 ± 1.53 % to 73.02 ± 2.30 % and 542.40 ± 10.32 µm to 814.16 ± 8.72 µm respectively (Table 2). It was observed that percentage entrapment efficiency and particle size were increase with increase in polymer concentration which may be due to higher concentration of polymer may produces a viscous dispersion which may formed larger microspheres and entrapped greater amount of drug.[20] It may also due to the fact that increase in polymer concentration increases the viscosity of the inner phase as well as rigidity of the coacervate which may increase the particle size.[21]

In-vitro Floatability Studies

In vitro floatability studied revealed that floating lag time of all the formulations was found with in the range of 66 ± 4 second to 136 ± 8 second and total floating time was more than 8 hours (except formulation FP6) (Table 2). It was observed that floating lag time was increased by increasing the polymer concentration. This may be due to the fact that higher concentration of polymer increases the sphere size as well as overall density of the system. As a result the solvent take much more time to enter in the microsphere system and react with $NaHCO_3$ to evolve CO_2.

Micromeritic Properties of Microspheres

The micromeritic properties of pure drug (PD) and the prepared microspheres were found to be within the desired theoretical level (Table 3). The angle of repose and Carr's index of the pure drug was found to be 42.9 ± 1.41 degrees and 37.4 ± 3.11 % respectively, indicates the poor flow nature of ciprofloxacin hydrochloride. In case of pectinate microsphere formulations, the angle of repose and Carr's index were found to be within 15.3 ± 2.10 to 26.7 ± 2.80 degrees and 12.6 ± 1.37 % to 22.4 ± 1.76 % respectively. The micromeritic study revealed that these microsphere formulations help to improve the flow properties and compressibility of the pure drug. The improvement of flow property was further confirmed by Hausner ratio. The Hausner ratio of pure drug was found to be 1.68 ± 0.39 whereas for the prepared microspheres the value was found within the range of 1.17 ± 0.06 to 1.27 ± 0.17.

This micromeritic study suggests that all pectinate microspheres exhibited good flow property and excellent compressibility as compare to pure ciprofloxacin hydrochloride.

Table 2: Evaluation of Ciprofloxacin Hydrochloride Loaded Pectinate Floating Microspheres.

Formulation Code	Yield (%)	Entrapment efficiency (%)	Particle size (µm)	FLT (sec.)	TFT (h.)
FP1	78.87 ± 3.22	36.73 ± 1.53	542.40 ± 10.32	66 ± 4	> 8 h.
FP2	76.42 ± 3.97	45.47 ± 1.45	654.08 ±15.26	74 ± 7	> 8 h.
FP3	83.29 ± 3.22	58.95 ± 2.52	660.20 ± 9.07	87 ± 5	> 8 h.
FP4	89.91 ± 2.10	63.33 ± 2.50	775.25 ± 8.18	83 ± 7	> 8 h.
FP5	91.13 ± 4.32	73.02 ± 2.30	785.40 ± 12.52	94 ± 12	> 8 h.
FP6	84.12 ± 3.06	71.04 ± 2.96	814.16 ± 8.72	136 ± 8	< 8 h.

Mean ± SD, n = 3; FLT: Floating lag time; TFT: Total floating time.

Table 3: Micromeritic Properties of Pure Drug and Pectinate Microspheres.

Formulation	Angle of Repose (^{0})	Carr's index (%)	Hausner's ratio
PD	42.9 ± 1.41	37.4 ± 3.11	1.68 ± 0.39
FP1	26.7 ± 2.80	22.4 ± 1.76	1.27 ± 0.17
FP2	20.9 ± 1.18	18.7 ± 2.99	1.24 ± 0.11
FP3	19.2 ± 1.97	19.4 ± 1.80	1.21 ± 0.09
FP4	16.1 ± 2.26	14.6 ± 2.55	1.22 ± 0.12
FP5	15.3 ± 2.10	12.6 ± 1.37	1.17 ± 0.06
FP6	17.4 ± 1.16	13.1 ± 2.01	1.19 ± 0.13

Mean ± SD, n = 3; PD: Pure drug; FP: pectinate microspheres.

Swelling Studies

Swelling studies of the prepared pectinate microspheres were performed in 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C and % swelling at different time intervals was shown in Figure 1. It was observed from the experiment that all the formulations exhibited excellent swelling property in 0.1 N HCl (pH 1.2). This may be due to the fact that when the microspheres came in contact with dissolution medium, they absorbed the media and swelled up due to presence of swellable pectin polymer. It was also observed that swelling capacity of the formulations was increased with increasing in polymer concentration. The swelling capacity of all the formulations were found in the order of FP6 > FP5 > FP4 > FP3 > FP2 > FP1. Formulation FP6 shows maximum swelling in comparison to other formulations. This may be due to the fact that as polymer concentration was maximum in formulation FP6, maximum viscous gel was produced around it which helps in absorbing maximum fluid and showed maximum swelling.

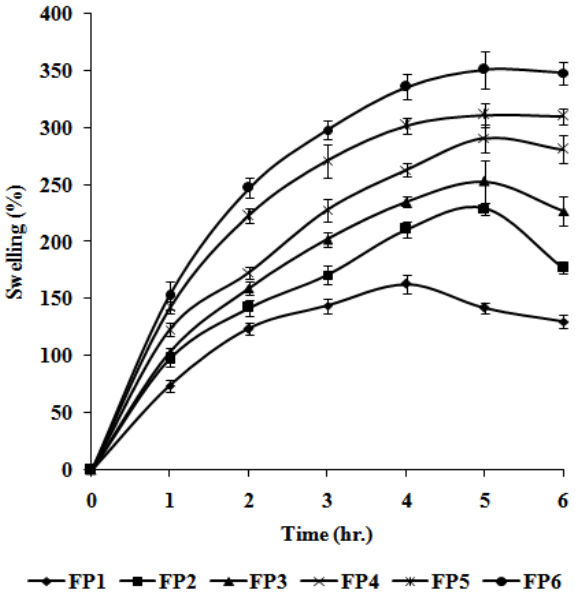

Figure 1: Swelling study of ciprofloxacin hydrochloride loaded pectinate floating microsphere.

In-vitro Drug Release Behavior

The release profiles of ciprofloxcin hydrochloride from the prepared formulations FP1 to FP6 are shown in Figure 2. Formulation FP1, FP2, FP3 and FP4 (containing pectin 1%, 2%, 3% and 4% respectively) were able to sustain the drug released for 4, 5, 6 and 7 hours respectively. On increasing the polymer concentration in formulation FP5 (containing pectin 5%), drug release was sustained up to 8 hours. Further increasing the concentration of pectin in formulation FP6, no significant difference was observed with respect to drug release as compare to formulation FP5.

It was observed that as the polymer concentration increased, the drug release from the pectinate microspheres decreased. This may be due to the fact that at higher polymeric concentration the gel layer thickness around the microsphere was increased which acted as a barrier for the penetration of the medium, thereby suppressing the diffusion of ciprofloxacin hydrochloride from the microspheres. It may also due to the fact that higher polymeric concentration increases the densities of the polymer matrix which results larger microspheres as well as increases the diffusion path length, which the drug molecules have to traverse.

Prepared barium-pectinate floating microspheres showed rapid drug release and sustained the drug release for only 8 hours. It may be due to the fact that barium being divalent forms two-dimensional bonding structure with pectin inside the microspheres. This two-dimensional bonding results in loose cross-linking and produces soft barium-pectinate microspheres with high swelling properties. This high swelling property of the microspheres increase the spheres disintegration and faster the drug dissolution.[22]

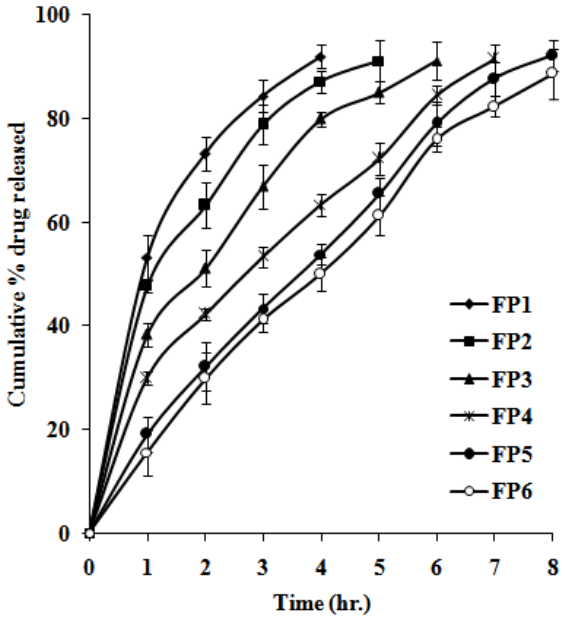

Figure 2: *In-vitro* drug release study of ciprofloxacin hydrochloride floating microspheres.

Kinetic Modeling

In-vitro dissolution data were analyzed by different kinetic models in order to evaluate the coefficient of determination values and release exponent (n) values of all formulations, which describe the kinetics and mechanism of drug release.

The kinetic data of all the formulations shows best fit in korsmeyer model followed by non-Fickian diffusion mechanism (n = 0.61 to 0.79). All the kinetics datas are summarized in (Table 4).

Statistical Analysis

Statistical analysis suggested a significant difference in drug release values among all the microsphere formulations (except formulation FP5 and FP6). Holm-Sidak multiple comparison analysis also suggested a

significant difference among all the formulations with respect to $t_{50\%}$ values and *in-vitro* drug release.

Though formulation FP5 and FP6 shows similar type and rate of drug release (more than 90 % drug was released in 8 hours) and statistical analysis suggested no significant difference among these two formulations, so formulation FP5 have select as an optimized formulation for further studies.

Topographical Analysis

The topographical analysis of the optimized formulation (FP5) studied with SEM (Figure 3) suggested that prepared microspheres were rigid, rough and almost spherical in shape.

This study also revealed that the drug particles were homogenously distributed throughout the matrix.

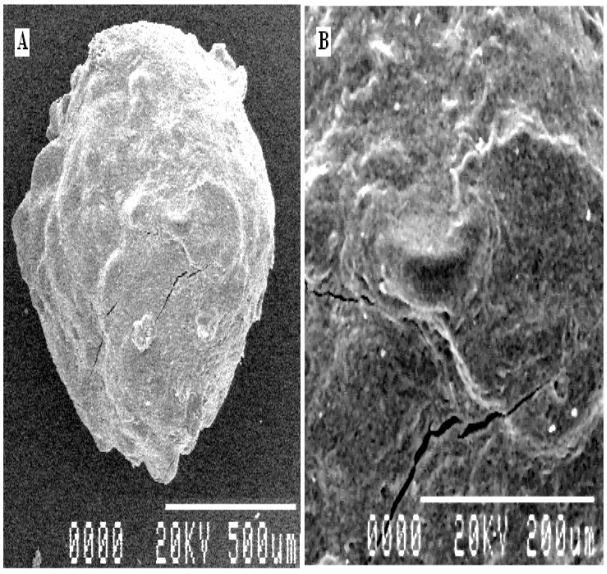

Figure 3: Scanning electron micrographs of the optimized pectinate microsphere formulation (FP5) (A=60 X, B=200 X).

Thermal Property Studies

Stability Studies

Optimized microsphere formulation (FP5) was tested for % drug content, shelf life ($t_{90\%}$) and physical appearance with six months stability studies following ICH guidelines.

It was observed that the shelf life of the optimized microspheres formulation (FP5) at room temperature (25 °C / 60 % RH) was 3.13 years (Table 5a) where as in accelerated condition (40 °C / 75 % RH) the shelf life was found to be 1.57 years (Table 5b).

It was also observed that no significant changes occurred in the physical appearance and % drug content of the microsphere formulation at room temperature but in case of accelerated condition, after 150 days, the microspheres were adhere to each other. The drug content in accelerated condition was reduced to 97.73 ± 3.78 % within 180 days whereas in case of room temperature good stability was observed (98.58 ± 3.12 % within 180 days).

The physicochemical state of drug in the formulation was assessed by DSC analysis. Thermograms of pure ciprofloxacin hydrochloride (PD) and drug loaded pectinate microspheres (OF) are shown in Figure 4. In the case of pure ciprofloxacin hydrochloride, a sharp endotherm was observed at 155.97 °C, corresponding to its melting point. In the optimized formulation (OF), the endotherm peak was observed at 157.12 °C which indicates there was no interaction between drug and polymer.

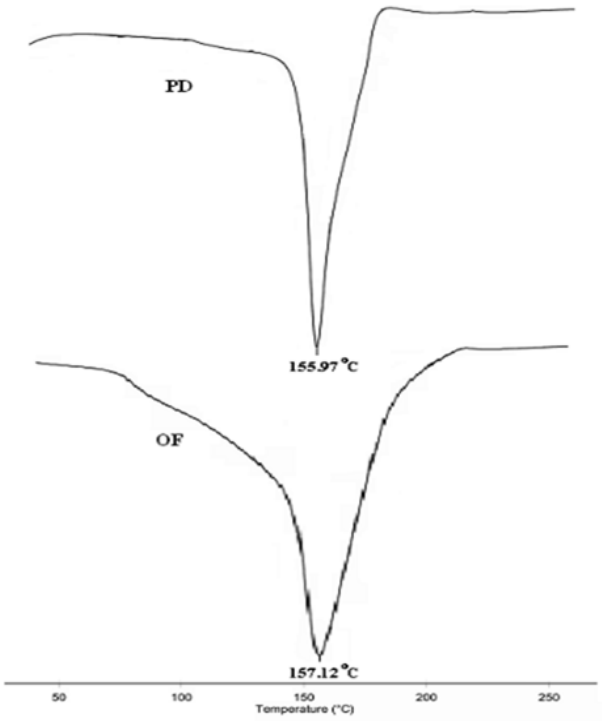

Figure 4: DSC thermogram of Pure Drug (PD) and optimized microsphere formulation (OF).

CONCLUSION

The results of the present research revealed that pectinate floating microsphere formulations exhibit promising properties as a sustain release dosage form of ciprofloxacin hydrochloride up to 8 hours.

It was observed that this microparticulate dosage form was able to float on the stomach environment for prolong period and release the drug at a sustained manner. Theoretical models of the drug release indicated that drug release from the microspheres was best fit in korsmeyer model followed by non-Fickian diffusion mechanism.

So, it is concluded that alone pectin polymeric micro-matrix was not suitable to develop twice daily SR dosage form for ciprofloxacin hydrochloride and combination of polymeric bland will further required to study to develop twice daily SR dosage form for ciprofloxacin hydrochloride.

Table 4: *In-vitro* Drug Release Kinetics Model Fitting*.

Formulations	Coefficients of determination 'r²'				Release exponent (n)
	Zero Order	First Order	Higuchi Model	Korsmeyer Model	
FP1	0.998	0.871	0.986	0.988	0.61
FP2	0.985	0.848	0.983	0.989	0.67
FP3	0.996	0.981	0.975	0.982	0.66
FP4	0.992	0.877	0.980	0.988	0.72
FP5	0.998	0.901	0.983	0.986	0.73
FP6	0.995	0.894	0.987	0.989	0.71

***** Analyzed by the regression coefficient method.

Table 5a: Stability Study of Optimized Formulation (FP5) at Room Temperature.

Parameters	25 °C / 60 % RH					
Sampling Interval (days)	30	60	90	120	150	180
Drug Content (%)	100 ± 1.98	100 ± 2.18	99.87 ± 2.89	99.41 ± 2.99	98.91 ± 3.44	98.58 ± 3.12
Physical appearance	+	+	+	+	+	+
Slope	-3.523×10^{-5}					
K ($days^{-1}$)	0.808×10^{-4}					
$t_{90\%}$ (years)	3.13					

+ No changes in physical appearance; **++** Changes in physical appearance.

Table 5b: Stability Study of Optimized Formulation (FP5) in Accelerated Condition.

2	40 °C / 75 % RH					
Sampling Interval (days)	30	60	90	120	150	180
Drug Content (%)	100 ± 1.29	99.46 ± 3.29	98.98 ± 3.02	98.27 ± 2.11	97.93 ± 3.93	97.73 ± 3.78
Physical appearance	+	+	+	+	+	++
Slope	-6.393×10^{-5}					
K ($days^{-1}$)	1.474×10^{-4}					
$t_{90\%}$ (years)	1.57					

+ No changes in physical appearance; ++ Changes in physical appearance.

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