



Original Article

Formulation and *In-vitro* Evaluation of Ciprofloxacin Hydrochloride Mucoadhesive Microspheres by Ionic Gelation Method

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ABSTRACT

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The aim of the present work is to study the prepared Ciprofloxacin HCL in mucoadhesive pharmaceutical form by two type of formulations methodology i.e. with solvent evaporation method and ionic gelation method. The main objective of the research work is to study the drug and polymer interaction. The formulations were characterized for their physico-chemical parameters like swelling ratio, water uptake, gel fraction, percentage yield, drug content, SEM analysis, drug entrapment efficiency and size analysis. FTIR studies reveal the drug excipients compatibility. In-vitro drug release studies revealed that the high % drug release for IF6 was 99.68% up to 14hrs. Entrapment efficiency, particle size for IF6 was found to be $92.6 \pm 1.52\%$, 1.28 ± 0.05 respectively. Swelling ratio and water uptake by IF6 formulation were 12.5 ± 0.1 and found to be good swelling ratio, high water absorbing ability and high % adherence. Results from stability studies indicate that the formulated mucoadhesive microspheres are stable for a period of 3 months under two different conditions at $25 \pm 2^\circ\text{C} / 65 \pm 5\% \text{RH}$ and $40 \pm 2^\circ\text{C} / 75 \pm 5\% \text{RH}$. Among all formulations, IF6 showed controlled drug release up to 14 hrs and considered as ideal formulation.

Key words: Ciprofloxacin HCl, Sodium alginate, Sodium carboxy Methyl Cellulose, Carbopol, ionic gelation method.

1. INTRODUCTION

Microspheres are defined as homogeneous, monolithic particles in the size range of about $1\mu\text{m}$ - $1000\mu\text{m}$ and are widely used as drug carriers for controlled release. These systems have significant importance in biomedical applications. Microspheres can be produced for protection of core material, reduction of gastric irritation decrease in volatility, conversion of liquid to pseudo-solid, cell

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microencapsulation and for designing pulsatile drug delivery systems. Administration of the drug in the form of microspheres usually improves the treatment by providing the localization of the active substances at the site of action and by prolonging release of drugs [1].

- ✓ Mucoadhesive microspheres include microparticles and microcapsules of 1 to 1000 μm in diameter consisting either entirely of mucoadhesive polymer or having an outer coating with adhesive property.
- ✓ Incorporating mucoadhesiveness to microspheres leads to efficient absorption and enhanced bioavailability of drug [2].

Mucoadhesion is a promising approach in the design of the drug delivery systems to prolong the residence time of the dosage form the site of application or absorption and to facilitate intimate contact of the dosage form with the underlying absorption surface to improve and enhance the bioavailability of drugs. Several studies reported mucoadhesive drug delivery systems in the form of tablet, films, patches and gels for oral, buccal, nasal, ocular, and topical routes [3].

Ciprofloxacin hydrochloride is a broad-spectrum antimicrobial carboxy fluoroquinolone. It is used for the treatment of urinary tract contaminations, intense uncomplicated cystitis, lower respiratory tract contaminations, intense sinusitis, skin and skin structure diseases, bone and joint contaminations, typhoid fever (enteric fever), uncomplicated cervical and urethral gonorrhea, and inhalational bacillus anthracis (post-exposure). It is soluble in water and belongs to class III (High solubility, low permeability) with a bioavailability approximately 70%, protein binding 20 to 40%. It undergoes hepatic metabolism including CYP1A2. Hence the objective of the present work was to formulate the mucoadhesive microsphere of Ciprofloxacin hydrochloride by solvent evaporation method to improve residence of dosage form in GIT, reduced dosing frequency and enhance bioavailability [4-8].

2. MATERIALS AND METHODS

Ciprofloxacin hydrochloride was obtained from Drugs India, HYD, Sodium alginate from Finar chemicals Ltd, Ahmedabad, Carbopol 934 P from Qualigens fine chemicals, Mumbai, Sodium Carboxy Methyl Cellulose from SD fine chemicals, Mumbai.

Drug polymer compatibility studies:

1. Fourier Transform Infrared Spectroscopy (FTIR):

Ten milligrams of drug alone, mixture of drug and polymer were weighed and mixed properly with KBr uniformly. A small quantity of the powder was compressed into a thin semitransparent pellet by applying pressure. The IR-spectrum of the pellet from 450- 4500 cm^{-1} [9].

2. Differential Scanning Calorimetric (DSC):

Differential scanning calorimeter (DSC) was performed using Perkin Elmer instruments,

(Perkin Elmer DSC-7, Norway, USA.) to study the thermal behaviour of Ciprofloxacin hydrochloride and mixture of drug and polymers. (Table no. 7 Figure no 9, 10) [10].

Formulation of Ciprofloxacin hydrochloride mucoadhesive microspheres by ionotropic gelation method :

The Mucoadhesive microspheres were arranged by the strategy of physical crosslinking (ionotropic gelation method) (Table no. 1). A precisely weighed amount of sodium alginate, Na CMC, carbopol 934 P and Ciprofloxacin hydrochloride as per table: 3 were weighed and added in required amount of refined water (50ml) and this polymeric solution is being homogenized at 500 rpm for 30 min to form a viscous dispersion. The resulting viscous dispersion was added drop wise into 10 % w/v CaCl_2 (crosslinking agent)solution using a syringe fitted with a 18 Gauge needle and the shaped mucoadhesive microspheres were cured for 2hrs . These mucoadhesive microspheres were washed with refined water and dried at 45°C temperature for 12 hrs [11].

Table 1: Compositions of Ciprofloxacin hydrochloride mucoadhesive microspheres by ionic gelation method

Formulation	Drug (mg)	Polymers			
		Na. alginate (mg)	Na. CMC (mg)	Carbopol 934P (mg)	CaCl_2 (ml)
IF0	500	500	-	-	-
IF1	500	500	250 (1:05)	-	250
IF2	500	500	500 (1:1)	-	250
IF3	500	500	750 (1:1.5)	-	250
IF4	500	500	-	250 (1:05)	250
IF5	500	500	-	500 (1:1)	250
IF6	500	500	-	750 (1:1.5)	250

Physicochemical evaluation:

1.Swelling ratio

Swelling of mucoadhesive microspheres was carried out in triplicate by gravimetric method. Known weight of mucoadhesive microspheres were taken and immersed in pH 7.4 phosphate buffer solution at 37°C. The difference in weight has given the amount of pH 7.4 phosphate buffer solution uptake by mucoadhesive microspheres after definite time intervals (60 min). (Table no. 2 Figure no.1) [10].

$$\text{Swelling ratio} = \frac{W_t - W_o}{W_o}$$

Where, W_t = weight of mucoadhesive microspheres at time.

W_o = initial weight of mucoadhesive microspheres .

2. Water uptake

Known weight of mucoadhesive microspheres for were taken and immersed in excess of distilled water at 37°C. The difference in weight has given the amount of water uptake by mucoadhesive microspheres for definite period of time. (Table no.3 Figure no 2) [11].

$$\text{Water uptake} = \frac{W_s}{W_D}$$

Where, W_s = weight of swollen mucoadhesive microspheres

W_D = weight of dried mucoadhesive microspheres .

3. Gel fraction:

To extract the insoluble parts of mucoadhesive microspheres (i.e., the gelled part), the prepared mucoadhesive microspheres were soaked in water for 48 h. Then they were taken out and washed with hot water to remove soluble part, dried and weighed. Gel fraction was determined from equation given below. (Table no.4 Figure no.2 and 3) [11].

$$\text{Gel fraction} = W_g / W_o \times 100$$

Where, w_o = weight of dried mucoadhesive microspheres after crosslinking.

w_e = weight of Sample after extraction of soluble parts

4. Size analysis by optical microscopy

After drying at 37°C for 48 hours, the mean diameter of the dried beads was measured by using an optical micrometer fitted with a calibrated eye piece [12].

5. Surface morphological studies by SEM analysis

The surface morphological studies and shape of the dried mucoadhesive microspheres were examined by using scanning electron microscopy. (Figure no 5) [13].

6. Percentage yield

Percentage yield was calculated using equation given below

$$\% \text{yield} = \text{Practical yield} / \text{Theoretical yield} \times 100 \text{ [13]}$$

7. Drug content

100 mg equivalent weight of Ciprofloxacin HCl mucoadhesive microspheres were triturated using mortar and pestle. Then the triturated mucoadhesive microspheres were placed in volumetric flask and the volume was made upto 100 ml with pH 7.4 phosphate buffer solution and kept aside for 24h. The absorbance was measured at 275 nm spectrophotometrically. The drug content was calculated by using the formula [14].

$$\text{Theoretical drug content} = (\text{Weight of drug} / \text{total weight of microspheres}) \times 100$$

$$\text{Practical drug content} = \text{Concentration} \times \text{dilution factor} \times \text{Conversion factor}$$

8. Drug entrapment efficiency

The 100 mg equivalent mucoadhesive microspheres s were soaked and digested in 100 ml of pH 7.4 phosphate buffer solution for 24 h and then the solution was filtered. The absorbance was analysed spectrophotometrically at 275 nm after a necessary dilutions [15].

$$\text{Drug Entrapment efficiency} = (\text{Actual drug content} / \text{Theoretical drug content}) \times 100$$

9. In vitro drug release studies:

In each formulation 100 mg Ciprofloxacin HCl equivalent mucoadhesive microspheres were taken and immersed in 900 ml of pH 1.2 HCl buffer for first two hours. Then acidic buffer is replaced with fresh buffer of 900 ml of pH 7.4 phosphate buffer which mimic stomach and intestinal pH conditions.

The aliquots of 5 ml were withdrawn at one hour time interval and replaced with equal volume of dissolution medium in order to maintain the sink condition throughout the study. Then the samples were filtered and analyzed spectrophotometrically at 275 nm after a suitable dilution. The cumulative amount of drug release was calculated. (Table no.5 Figure .no6) [16].

10. In-vitro mucoadhesion test:

In-vitro muco adhesion test was performed by using *in vitro* Wash- Off test. 100 particles of mucoadhesive microspheres were counted and placed on strip of goat intestine which was adhered to glass slide by using cyano acrylate glue. Then this slide consisting of particles was placed in disintegration apparatus for eight hours of time. After eight hours number of particles being adhered was counted and % of Adherence was calculated by using the formula. (Table no.6 Figure no 7 and 8) [17].

$$Na = (N/No) \times 100$$

Where,

Na = is the adhesion number

No = is the total number of applied particles

N = number of particles attached to the substrate.

11. Stability studies :

Stability studies were performed at a temperature of 30±2°C/65±5%RH & 40±2°C/75±5%RH, over a period of three months (90 days) on the mucohesive microspheres of ciprofloxacin hydrochloride (Table no. 8) [18].

3. RESULTS AND DISCUSSION

Swelling studies was done in triplicate using phosphate buffer. The swelling ratio of optimised formulation of IF6 was found to be 12.5 ±0.1 in 360 mins.

Table 2: Swelling ratio data for Ionic Gelation formulations

Formulation Code	Time in mins					
	60	120	180	240	300	360
IF0	1.3±0.05	2.7± 0.1	4.6±0.1	5.2± 0.15	7.5± 0.05	7.7± 0.05
IF1	1.4± 0.1	3.2± 0.15	4.8± 0.05	5.5± 0.05	7.6± 0.11	7.4± 0.11
IF2	1.8 ±0.1	4.7± 0.1	6.6± 0.15	7.4± 0.05	9.3± 0.05	9.3± 0.05
IF3	1.2±0.1	2.7± 0.1	5.4±0.11	9.6±0.05	9.4 ±0.05	9.2±0.05
IF4	1.6 ±0.1	3.3± 0.15	7.4± 0.05	8.2± 0.05	10.6± 0.05	10.6± 0.05
IF5	2.5 ±0.1	4.7± 0.05	7.5±0.05	9.5± 0.05	12.6± 0.05	12.6± 0.05
IF6	2.7 ±0.1	4.9± 0.05	7.8±0.05	9.7± 0.05	12.8± 0.05	12.5 ±0.1

All values are expressed in SD (n=3)

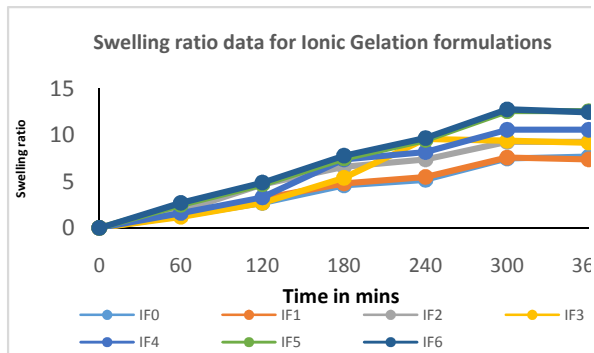


Fig 1: Swelling ratio for ionic gelation

The ability of mucoadhesive microspheres to absorb water and swell without losing its structure is done by water uptake studies. The water uptake of IF6 was found to be 10.5 ± 0.05 in 360 mins.

Table 3: Water uptake data for Ionic Gelation formulations

Formulation code	Time in mins					
	60	120	180	240	300	360
IF0	2.2±0.05	3.7± 0.1	5.6± 0.1	6.6 ± 0.05	8.3± 0.05	8.5± 0.05
IF1	3.3±0.05	4.5 ±0.05	5.4± 0.05	7.2± 0.05	8.6± 0.05	9± 0.05
IF2	3.7 ±0.11	5.3± 0.05	7.3± 0.11	8.3± 0.1	11.8± 0.57	11.8± 0.57
IF3	1.6± 0.15	3.6± 0.15	4.4± 0.05	5.3± 0.05	7.6± 0.05	7.6± 0.05
IF4	2.3± 0.1	4.5± 0.15	5.8± 0.05	6.4± 0.05	8.3± 0.11	8.3± 0.11
IF5	2.7± 0.1	5.6± 0.1	7.6± 0.15	8.5± 0.05	10.6± 0.05	10.6± 0.05
IF6	2.1± 0	3.7± 0.1	6.4± 0.11	10.5± 0.05	10.5± 0.05	10.5± 0.05

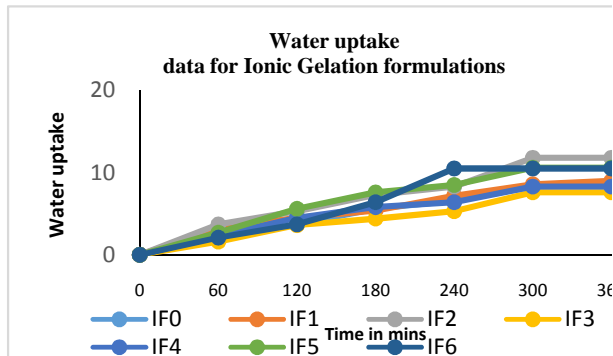


Fig 2: Water uptake data for Ionic Gelation formulations

Gel fraction is the amount of insoluble parts of polymer obtained after formulation. The obtained results were in the range of 98 ± 0.1 to 99.3 ± 0.1 . The obtained results were in the range of 1.20 ± 0.11 to 1.65 ± 0.1 for dried beads and 2.30 ± 0.01 to 2.66 ± 0.32 for wet beads. Percentage yield obtained was in the range of 92.3 ± 1.15 to 95.6 ± 2.08 .

Drug content mainly gives the amount of drug present in the formulation. The drug content was in the range of 82 ± 0.03 to 91.3 ± 0.05 .

Drug entrapment efficiency gives the amount of drug being entrapped in the polymer during formulation of mucoadhesive microspheres. The entrapment efficiency was in the range of 85.6 ± 0.57 to 92.7 ± 1.15 .

Table 4: Physicochemical evaluations of Ciprofloxacin HCl Ionic Gelation formulations

Formulation	% Yield	Drug content	Drug Entrapment	Gel Fraction	Size analysis
IF0	94.6±1.52	82± 0.03	85.6± 0.57	98.4±0.1	1.20±0.32
IF1	94.3±1.53	86± 0.01	87± 1	99.3±0.1	1.38±0.12
IF2	93.3±1.15	91.2±0.03	92.7± 1.15	99.56±0.05	1.48±0.32
IF3	95.6±2.08	90.1± 0.03	91.6± 1.52	98±0.1	1.20±0.17
IF4	95.6±1.52	85± 0.01	85.6± 1.15	98.43±0.15	1.50±0.14
IF5	94.6±0.5	90.4± 0.04	91± 1	98.6±0.1	1.65±0.12
IF6	92.3±1.15	91.3±0.05	92.6± 1.52	99.1±0.1	1.28±0.09

Code	(mg)	efficiency (%)	n	Dried Beads	Wet Beads
IF0	94.6±1.52	82± 0.03	85.6± 0.57	98.4±0.1	2.30±0.01
IF1	94.3±1.53	86± 0.01	87± 1	99.3±0.1	2.43±0.12
IF2	93.3±1.15	91.2±0.03	92.7± 1.15	99.56±0.05	2.66±0.32
IF3	95.6±2.08	90.1± 0.03	91.6± 1.52	98±0.1	2.32±0.17
IF4	95.6±1.52	85± 0.01	85.6± 1.15	98.43±0.15	2.40±0.51
IF5	94.6±0.5	90.4± 0.04	91± 1	98.6±0.1	2.51±0.21
IF6	92.3±1.15	91.3±0.05	92.6± 1.52	99.1±0.1	2.41±0.09

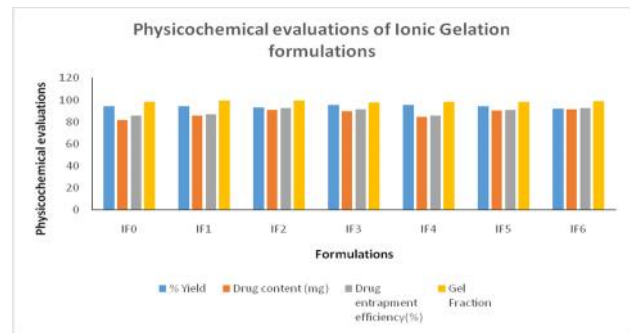


Fig 3: Physicochemical evaluations of Ionic Gelation formulations

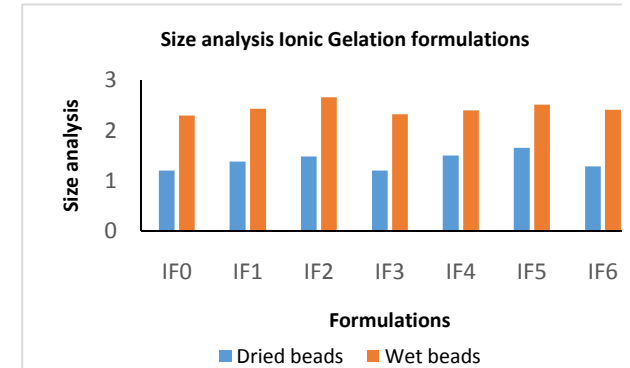


Fig 4: Size analysis Ionic Gelation formulations

The SEM reports obtained showed good spherical shape and also surface morphological characters.

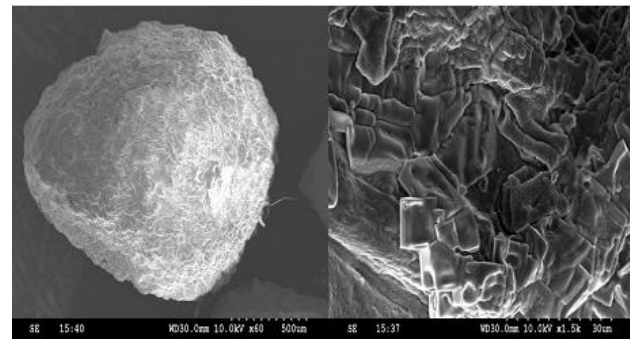


Fig 5: SEM photograph of IF6 Formulation

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 IF6 showed 99.68% of cumulative % drug release within 10 hrs

Table 5: Cumulative % *in-vitro* drug release studies formulations IF1–IF6

Time (Hrs)	IF ₀	IF ₁	IF ₂	IF ₃	IF ₄	IF ₅	IF ₆
1	7.82±0.02	9.56±0.07	8.56±0.04	11.33±0.06	12.04±0.03	7.34±0.05	11.26±0.05
2	17.55±0.02	18.35±0.07	14.72±0.04	19.44±0.06	19.25±0.03	17.12±0.05	18.32±0.05
3	23.28±0.02	27.23±0.07	23.33±0.04	30.33±0.06	30.96±0.03	23.34±0.05	29.45±0.05
4	37.74±0.02	34.37±0.07	33.29±0.04	39.22±0.06	45.86±0.03	37.56±0.05	36.86±0.05
5	45.28±0.02	42.82±0.07	44.45±0.04	48.87±0.06	59.84±0.03	45.67±0.05	45.58±0.05
6	58.16±0.02	58.45±0.07	54.56±0.04	61.34±0.06	71.45±0.03	58.92±0.05	57.32±0.05
7	66.27±0.02	64.27±0.07	66.39±0.04	68.92±0.06	79.58±0.03	66.85±0.05	69.65±0.05
8	77.96±0.02	77.46±0.07	72.47±0.04	79.34±0.06	80.94±0.03	77.25±0.05	76.45±0.05
9	79.43±0.02	80.22±0.07	84.43±0.04	85.87±0.06	82.25±0.03	87.26±0.05	89.30±0.05
10	82.65±0.02	83.12±0.07	85.23±0.04	88.38±0.06	89.67±0.03	90.35±0.05	99.68±0.05
11	84.61±0.02	85.12±0.07	87.25±0.04	89.80±0.06	90.12±0.03	92.35±0.05	99.68±0.05
12	88.61±0.02	87.48±0.07	89.44±0.04	90.14±0.06	91.67±0.03	95.37±0.05	99.68±0.05
13	90.61±0.02	89.48±0.07	90.44±0.04	93.14±0.06	91.67±0.03	95.37±0.05	99.68±0.05
14	94.61±0.02	90.48±0.07	92.44±0.04	93.14±0.06	91.67±0.03	95.37±0.05	99.68±0.05

All values are expressed in SD (n=3)

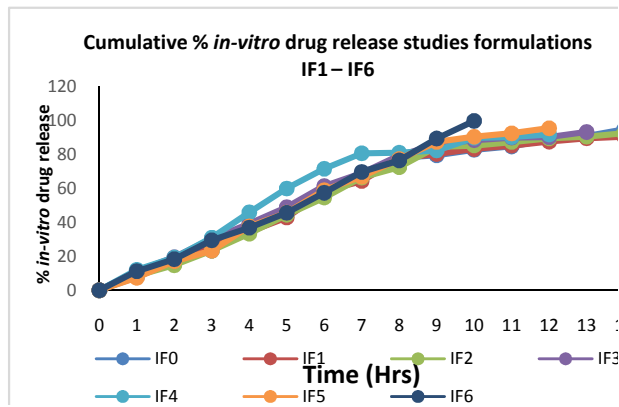


Fig 6: Cumulative % *in-vitro* drug release studies formulations IF1–IF6

In-vitro mucoadhesion test was performed by using *in vitro* Wash- Off test. The % Adherence was in the range of 77 % to 89%.



Fig 7: Glass side with mucoadhesive microspheres before test and after test

Table 6: *In-vitro* muco adhesion test for ionic gelation method

Formulation code	% Adherence
IF ₀	77%
IF ₁	81%
IF ₂	83%
IF ₃	82%
IF ₄	76%
IF ₅	75%
IF ₆	89%

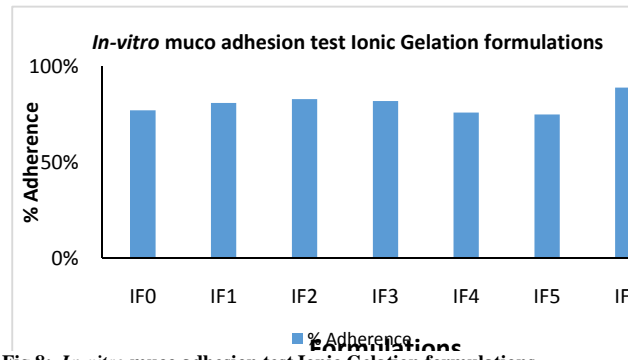


Fig 8: *In-vitro* muco adhesion test Ionic Gelation formulations

DSC method for drug-excipient interaction analysis:

Dsc studies reveal that there is no interaction between the drug and the excipients



Fig 9: DSC of drug

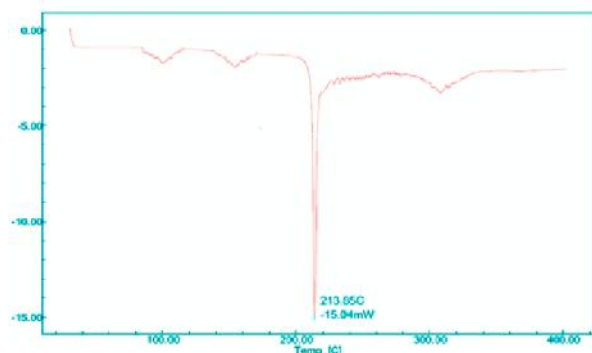


Fig 10: DSC of optimized formulation of ionic gelation method (IF6)

Table 7: DSC studies

Concentration µg/ml	Peak area		
	Ciprofloxacin HCl	SF6	IF6
20	1373684	2168213	2403243
25	1555545	2486654	2819254
30	1708280	2766713	3197738
35	1863167	3101485	3558368
40	2024329	3383824	3889324

Stability studies: There is no change in drug content and % drug release for the period of 3 months, so it is continued for the next three months as per ICH guidelines for stability studies.

Table 8 :Stability studies

Formulations	Time	% drug content	Cumulative % drug release	
			25±2°C 65±5%RH	40±2°C 75±5%RH
			IF6	First day
	30 days	92.01±1.10	99.84±1.50	99.83±1.56
	90 day	92.01±0.9	99.82±1.40.	99.81±1.10

All values are expressed in SD (n=3)

4. CONCLUSION

In our research work we have prepared ionic gelation method. In both optimized formulations IF6 is more suitable than other prepared formulations because of slow release than other formulations. The slow release of this formulation is because of high swelling and water uptake.

The formulation IF6- showed 99.68% drug release in 10 hrs. Particle size analysis was done by scanning electron microscopy (SEM). The Particle size of IF6 is 37.8 respectively. The swelling ratio of optimised formulation of IF6 was found to be 12.5 ±0.1 in 360 mins. The water uptake of IF6 was found to be 10.5± 0.05 in 360 mins. Gel fraction is the amount of insoluble parts of polymer obtained after formulation. The obtained results were in the range of 98±0.1 to 99.3±0.1The obtained results were in the range of 1.20±0.11 to 1.65±.0.1 for dried beads and 2.30±0.01 to 2.66±0 .32 for wet beads. Percentage yield obtained was in the range of 92.3±1.15 to 95.6±2.08. Drug content mainly gives the amount of drug present in the formulation. The drug content was in the range of 82± 0.03 to 91.3 ±0.05. The entrapment efficiency was in the range of 85.6± 0.57 to 92.7± 1.15. *In-vitro* mucoadhesion test was performed by

using *in vitro* Wash- Off test. The % Adherence was in the range of 77 % to 89%. DSC studies reveal that there is no interaction between the drug and the excipients. Stability studies reveal that there is no change in drug content and % drug release for the period of 3 months, so it is continued for the next three months as per ICH guidelines for stability studies.

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