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Original Article

Preparation and *ex vivo* evaluation of Microspheres for treatment of Urinary tract infections

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ABSTRACT: Urinary tract infections (UTI) are the most frequent bacterial infections affecting about 150 million people each year. The most common cause of infections is E. Coli. UTI's are treated with short course antibiotics. Ofloxacin is a synthetic fluorinated carboxy quinolone that has a broad spectrum of activity against both gram positive & gram-negative bacteria. Multiple doses of ofloxacin are required to attain steady state concentration. The main objective of this study was to prepare and characterize ofloxacin microspheres to prolong the release rate so as to decrease the necessity of multiple dosing especially in patients with UTI. Nine formulations of ofloxacin microspheres were prepared using sodium alginate, sodium CMC and HPMC K 15M in various concentrations. Microspheres were prepared by ionic cross-linking method using calcium chloride as cross-linking agent. The prepared microspheres were evaluated for percentage yield, drug loading, entrapment efficiency, particle size analysis, swelling index, SEM studies, in-vitro dissolution, kinetics of drug release and *ex-vivo* studies. All the formulations exhibited satisfactory results in evaluations. DSC studies revealed no evidence of interaction between ofloxacin and polymers. Formulation F6 was selected as best formulation as it has good drug loading, percentage yield, entrapment efficiency and sustained the drug release for 8h. Results of *ex-vivo* studies indicate significant antimicrobial activity of microspheres. All the result demonstrated that ofloxacin microspheres can be effectively used in the treatment of urinary tract infections.

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INTRODUCTION

Urinary tract infection (UTI) is a common disorder at all ages and in both sexes. A healthy and normal urinary tract is generally resistant to infection. However, for anatomical reasons, the female lower urinary tract is more susceptible to infection. In at least 50% of patients, a predisposing cause cannot be demonstrated in spite of adequate investigation. 95% of the UTI are due to gram negative bacilli. Escherichia coli (E. coli) is the commonest offender (80%) and next to it are *Proteus mirabilis*, *Klebsiella*, *aerobacter* and *Pseudomonas aeruginosa* (pyocyanea), *Enterococci*, *Streptococci* and *Staphylococci* account only for 5% of cases. Mixed infections are lightly to be present in chronic cases and are more difficult to treat [1].

Flouroquinolones such as ciprofloxacin, ofloxacin, moxifloxacin and gatifloxacin are considered ideal agents for treatment of nosocomial pyelonephritis and complicated UTI [1]. Ofloxacin is a synthetic fluorinated carboxy quinolones that has a broad spectrum of activity against both gram-negative and gram-positive bacteria. It is indicated for uncomplicated skin infections, complicated urinary tract infection, respiratory tract infections and some sexually transmitted diseases. Normal dosage regimen varies from 200-600 mg administered twice or thrice a day, depending on severity of infection. Biological half-life of drug is from 5-6 h [2]. As it requires multiple dosing to obtain the required therapeutic efficacy, this drug has been chosen to be the model of our study.

The formulation of sustained release dosage form through the design of Ofloxacin microspheres could also potentiate the drug's ability to reduce the development of drug resistant bacteria.

Microspheres are small spherical particles, with diameters 1µm to 1000µm. They are spherical free flowing particles consisting of proteins or synthetic polymers which are biodegradable in nature. Microspheres can be manufactured from various natural and synthetic materials. Microsphere plays an important role in providing constant, prolonged therapeutic effect, improving bioavailability of conventional drugs and minimizing side effects [3].

Ionic gelation is based on the ability of poly electrolytes to cross link in the presence of counter ions to form hydrogel beads. Ionic gelation technique; has been a growing interest by the use of natural polymers as drug carriers due to their biocompatibility and biodegradability. In spite of having a property of coating on the drug core these natural polymers also act as release rate retardants [4, 5].

The present research aims to prepare and evaluate ofloxacin microspheres by orifice ionic gelation method using sodium alginate as polymer & sodium carboxy methyl cellulose (Sodium CMC), hydroxypropyl methylcellulose (HPMC)-K15M as co-polymers.

Table 1: Formulation Table of Ofloxacin Microspheres

Formulation Code	Drug: Polymer Ratio	Ofloxacin (g)	Sodium Alginate (g)	Sodium CMC (g)	HPMC- K 15M (g)
F1	1:1	2	2	---	---
F2	1:1.5	2	3	---	---
F3	1:2	2	4	---	---
F4	1:1	2	1	1	---
F5	1:1.5	2	1.5	1.5	---
F6	1:2	2	2	2	---
F7	1:1	2	1	---	1
F8	1:1.5	2	1.5	---	1.5
F9	1:2	2	2	---	2

Sodium carboxy methyl cellulose (Sodium CMC), Hydroxypropyl methylcellulose (HPMC)

The resultant homogenous bubble free alginate dispersion was extruded using a 21G syringe needle into the calcium chloride (5% w/v) gelation medium, which was kept under stirring. The added droplets were retained in calcium chloride solution for 20min to complete the curing reaction, to produce spherical rigid microspheres and also to prevent the aggregation. The obtained microspheres were filtered using filter paper, washed thrice with distilled water and dried at 37°C for 24 h.

EVALUATION OF OFLOXACIN MICROSPHERES

Percentage Yield

The dried microspheres were weighed and percentage yield of the prepared microspheres was calculated by using the following formula [6].

MATERIALS & METHODS

MATERIALS

Ofloxacin was received as gift sample from Aurobindo Pharma, Hyderabad. Sodium CMC, sodium alginate and HPMC K15M were procured from Himedia, Mumbai. All other reagents used were of analytical grade.

PREPARATION OF OFLOXACIN MICROSPHERES BY ORIFICE IONIC GELATION METHOD

Sodium alginate microspheres of Ofloxacin were prepared by orifice ionic gelation method as presented in Table 1. Nine different formulations were prepared with various quantities of the polymer (sodium alginate) and co polymer (sodium CMC & HPMC K 15M) with drug in different drug-polymer ratios. Alginate solution was prepared by dissolving sodium alginate in distilled water and the solution was stirred thoroughly.

Ofloxacin was dissolved uniformly in alginate solution under continuous stirring. The stirring was continued after complete addition until a uniform dispersion was obtained. Co-polymers were dispersed in water and added to drug-alginate dispersion.

$$\text{Percentage Yield} = \frac{\text{Weight Of Microspheres}}{\text{Weight Of Polymer} + \text{Drug}} \times 100$$

Drug Loading

About 100 mg microspheres were accurately weighed and transferred in to 100 ml phosphate buffer pH 7.4 at 37°C. The solution was shaken thoroughly until all the microspheres were dissolved. The solution was filtered and suitably diluted to determine amount of drug loading in microspheres by U.V-Visible spectrophotometer at 275nm. The studies were carried out in triplicate [7].

$$\% \text{ Drug Loading} = \frac{\text{Actual drug content in Microspheres}}{\text{Weight of microspheres}} \times 100$$

Entrapment Efficiency

The entrapment efficiency of the prepared microspheres was calculated by the formula [8].

$$\% \text{ Entrapment Efficiency} = \frac{\text{Practical Drug loading}}{\text{Theoretical Drug loading}} \times 100$$

Particle Size Analysis

The size distribution and average size particle of microspheres were studied by using optical microscope (Olympus CX21, ME0001947) fitted with eye piece micrometer which was then calibrated with stage micrometer. The prepared microspheres were dispersed in liquid paraffin; a drop of dispersion was spread on glass slide and observed under microscope. The average size was calculated by retrieving the size of about 500 microspheres from each batch. The average diameter was calculated by using following equation [9].

$$\text{Average diameter} = \frac{\epsilon n d}{\epsilon n} \times C.F$$

Table 2: Results of Ofloxacin Microspheres evaluations

Formulation	% Yield* ± S.D	Drug loading (%)* ± S.D	Entrapment efficiency (%)*± S.D	Mean particle size (µm) * ± S.D
F1	88.0 ± 1.32	39.09 ± 0.79	78.52 ± 1.3	643.18 ± 0.74
F2	84.5 ± 1.09	28.85 ± 0.4	72.33 ± 0.52	694.38 ± 0.17
F3	86.5 ± 0.54	24.86 ± 1.05	73.6 ± 1.26	720.64 ± 1.21
F4	89.6 ± 1.11	38.61 ± 0.99	76.66 ± 0.35	642.38 ± 1.64
F5	91.2 ± 0.86	33.1 ± 1.2	84.57 ± 0.4	660.85 ± 0.16
F6	92.0 ± 1.25	28.02 ± 1.4	85.57 ± 1.1	690.48 ± 0.88
F7	83.5 ± 0.75	36.25 ± 0.56	73.46 ± 0.31	738.28 ± 0.3
F8	91.9 ± 0.92	32.47 ± 0.28	80.1 ± 0.2	760.58 ± 1.55
F9	90.3 ± 0.58	25.68 ± 0.3	76.87 ± 0.11	794.56 ± 0.17

*Values shown in the table indicates mean ± standard deviation for n=3

Compatibility studies

Differential scanning calorimetry (DSC) studies

The DSC thermo grams were recorded on a universal V 2.5 H differential scanning calorimeter. Accurately transfer 3 mg of drug alone, a mixture of drug and excipients into the pierced DSC aluminum pan. The DSC studies on the samples were performed by heating samples at a heat rate of 20°/min over a temperature range of 50-300°C in a closed aluminum pans under a nitrogen flow of 40ml/min [11].

Fourier-transform infrared spectroscopy (FTIR) studies

FTIR spectra matching approach was used for detection of any possible chemical interaction between the drug and polymer. FT-IR (Shimadzu IR spectrophotometer, model 840, Japan) was used for the analysis in the frequency range between 4000 cm and 500/cm. Infra-red spectra of 2 mg pure drug and drug-loaded microspheres were analyzed separately [12].

Scanning electron microscopy (SEM) Studies

SEM has been used to determine surface topography, texture and to examine the morphology of fractured or sectioned surface. SEM

Where, n = number of microspheres, d = diameter of microspheres, C.F = calibration factor

Swelling Index

The extent of swelling was measured in terms of % weight gain by the microspheres. The microspheres (100mg) were placed in a petridish with phosphate buffer pH-7.4 and swelling was allowed at room temperature and changes in Weight variation between the initial weight of microspheres and weight due to swelling was measured by taking weight periodically. Swelling ratio was found by using the formula [10].

$$\text{Swelling Index} = \frac{(M_t - M_0)}{M_0} \times 100$$

Where, M_0 = Initial weight of the dry microspheres at time $t=0$,

M_t = Weight of the swollen microspheres at time "t".

studies were carried out by using JEOL JSMT-330A scanning microscope (Japan). A small amount of microspheres was spread on aluminum stub. After words the stub containing the sample was placed in the scanning electron microscope chamber. Scanning electron photomicrograph was taken at the acceleration voltage of 20 KV, chamber pressure of 0.6mm Hg, at different magnification. SEM of selected best formulation at different magnifications was studied.

In-vitro Drug release Studies

The drug release study was performed using USP XXIV type-I (basket) dissolution apparatus. 900ml of phosphate buffer pH-7.4 was used as dissolution medium. Temperature was maintained at $37 \pm 0.5^\circ\text{C}$ and fluid was agitated at 100 rpm. A quantity of microspheres equivalent to 100mg of Ofloxacin was used. 5 ml samples were withdrawn at various time intervals of 0.5, 1, 2, 3, 4, 5, 6, 7 & 8 h and filtered through Whatman filter paper.

Equal volume of fresh dissolution medium was replenished immediately to maintain sink condition. After suitable dilution, the samples withdrawn were analyzed spectrophotometrically at 275 nm using ultraviolet-visible spectrophotometer.

Kinetic Modeling of Drug Release Profiles

The dissolution profile of best formulation was fitted to zero-order, first-order, Higuchi and Hixon-Crowell, Korsmeyer-Peppas kinetic models. The model with the highest correlation coefficient was considered to be the best fitting one [13].

Ex-vivo study of activity (Cup plate method)

The cup plate assay of drug potency is based on measurement of the diameter of zone of inhibition of microbial growth surrounding cups, containing various compounds. A sterile borer was used to prepare two cups of 6 mm diameter in the agar medium with the micro-organisms and 0.1 ml of inoculum by spread plate technique. Accurately measured (0.05 ml) solutions of test and reference standards were added to the cups with a micropipette. All the plates were kept in a refrigerator at 2 to 8°C for a period of 2 h for effective diffusion of test compounds and standards. Later, they were incubated at 37°C for 24 h. The presence of definite zone of inhibition of any size around the cup indicated antibacterial activity [14].

RESULTS & DISCUSSION

Percentage yield

Percentage yield of different formulations were calculated and the % yield was found in between 83.5% to 92.0%. The same was showed in Table no.2. The maximum percentage practical yield was found to be 92.0% for formulation F6.

Drug loading & Encapsulation efficiency

The actual drug loading and encapsulation efficiency of all nine formulations is given in Table no.2. Drug loading of all formulations are varied between 24.86 ± 1.05 to 39.09 ± 0.79 and drug entrapment efficiency varied from 72.33 ± 0.52 to 85.57 ± 1.1 .

This result will indicate that increase in sodium alginate concentration will increase the drug content as well as drug entrapment efficiency. The Formulation containing sodium alginate and sodium CMC polymer has shown the maximum drug content as well as drug entrapment efficiency. The standard deviations among the values were found to be less. This indicates that the drug was distributed almost uniformly throughout the batch of microspheres. This improved encapsulation efficiency simply by due to the greater proportion of polymer with respect to amount of drug.

Particle Size

The particle size of ofloxacin microspheres was analyzed by optical microscopy. The average particle size was found to be in the range of 642.38 ± 1.64 to 794.56 ± 0.17 . The average particle size of microspheres was found to be increased as the concentration of the polymer was increased. This may be due to increased coat thickness with increasing polymer proportion. This was agreeing with the finding that there was lower particle size obtained when sodium CMC is used as polymer and highest particle size was observed when HPMC K15M used as polymer. The results are shown in Table 2.

Swelling index (SI)

The degrees of swelling of formulations F1-F9 was in the range of 1.35% to 4.18%. Swelling index is increased as the polymer concentration increases. Swelling increases as the time passes because the polymers gradually absorb water due to hydrophilic nature of polymer. The outer most polymers hydrate and swell resulting in formation of gel barrier at the outer surface. As the gelatinous layer progressively dissolves and / or dispersed, the hydration swelling release process is continuous towards new exposed surface. Sodium alginate, sodium CMC polymers showed less swelling while the HPMC KI5M swelled rapidly at the beginning because of its high viscosity. The formulation F9 containing HPMC K15M showed good degree of swelling. Swelling properties of all formulations up to 6 h is represented in Figure 1.

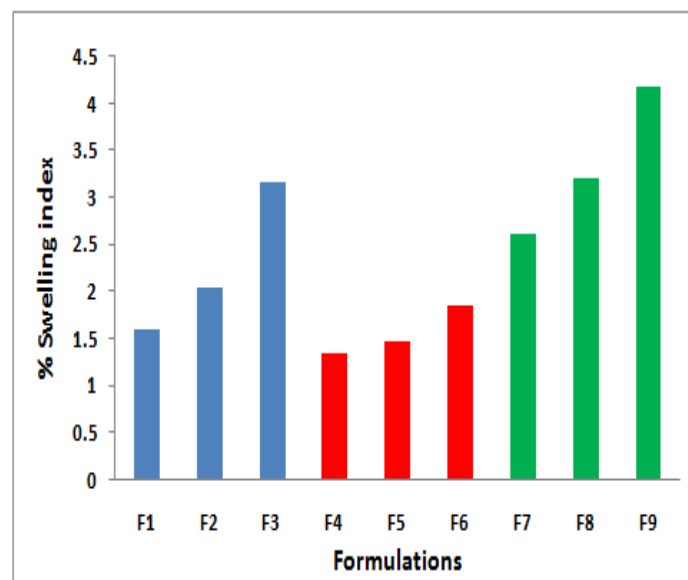


Figure 1: Swelling Index of Ofloxacin Microspheres

Compatibility Studies

DSC studies

The DSC thermograms of pure drug and drug loaded microspheres prepared with different cross-linking agents are shown in Figure 2 & 3. Ofloxacin exhibited a sharp endothermic peak at 273.8°C corresponding to its melting point. The peak of drug did not appear in the thermogram of any type of the prepared microspheres containing the drug. It may indicate that the drug was uniformly dispersed at the molecular level in the microspheres.

FTIR studies

FTIR studies were done to detect the possible interactions between the drug and the polymers in the microspheres. Figure 4 & 5 are the IR spectra of pure drug and best formulation F6 respectively. Comparing the IR spectral pattern of individual drug with those of microspheres revealed that the same fundamental peaks were also present in the drug-polymer combinations indicating there was no interaction between the drug and the polymer.

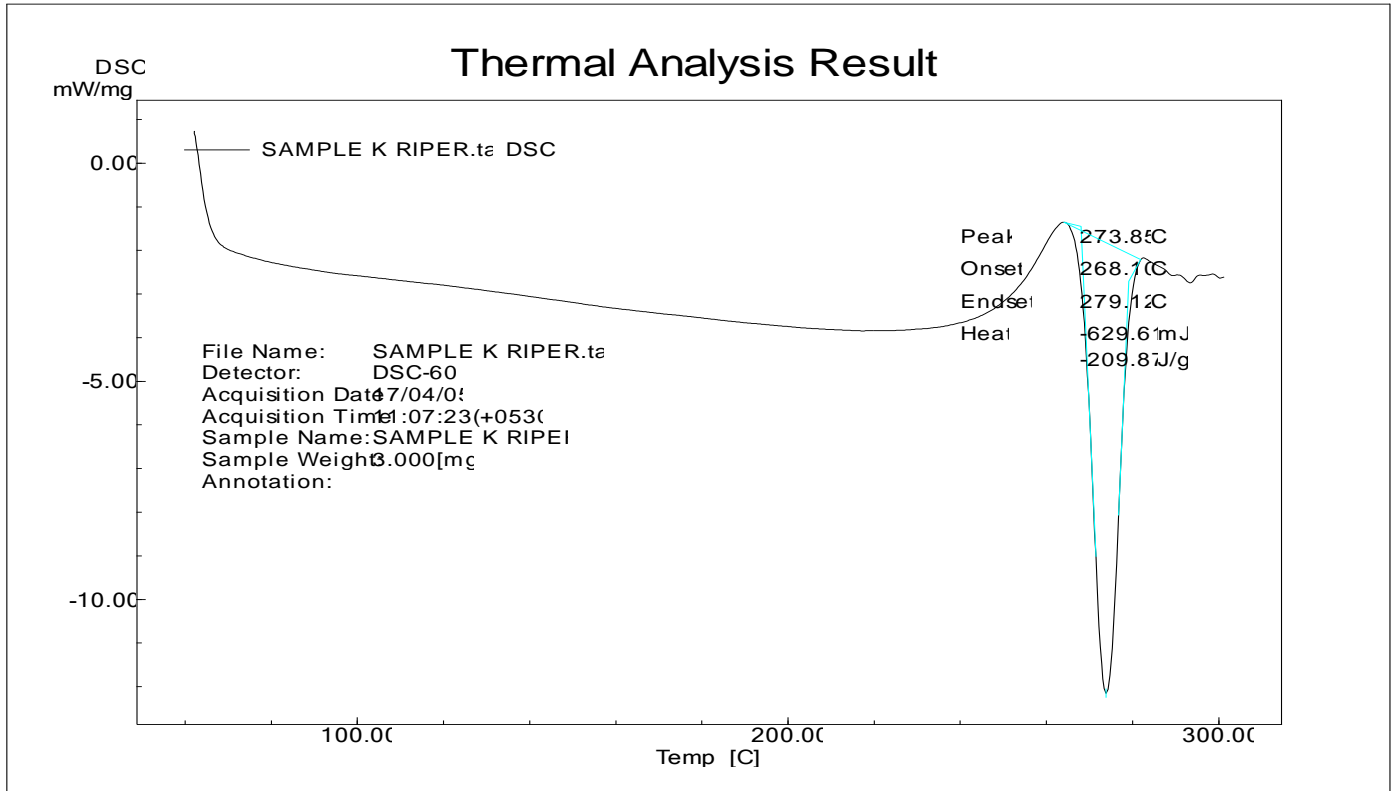


Figure 2: DSC thermogram of pure ofloxacin

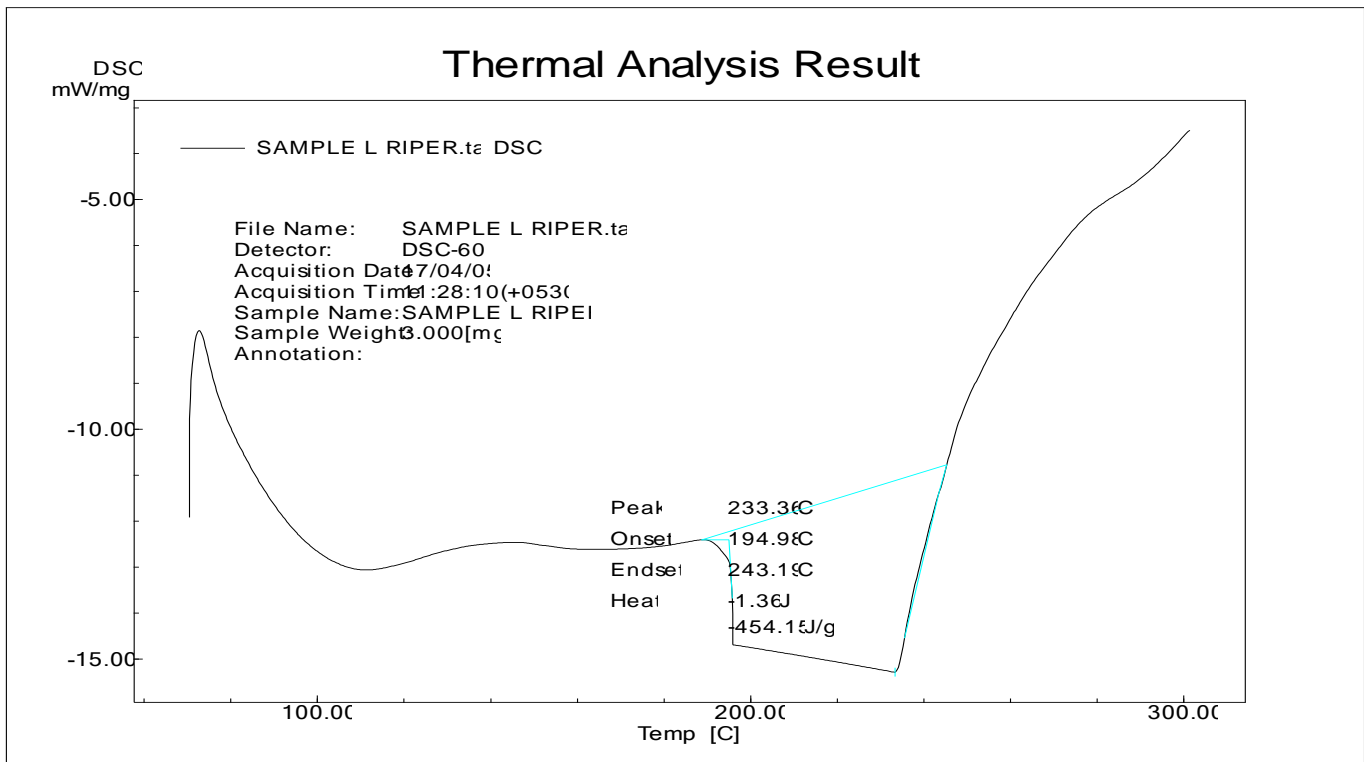


Figure 3: DSC thermogram of best formulation

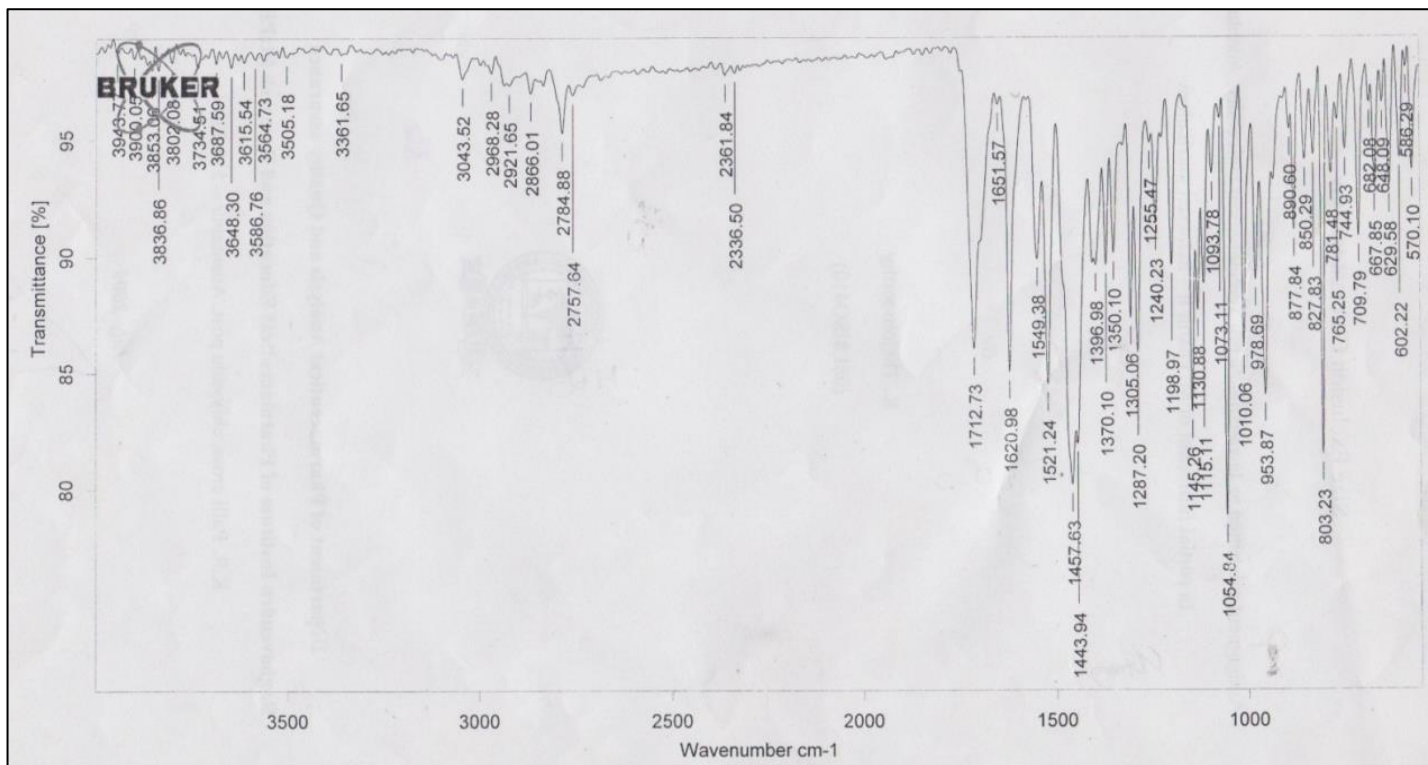


Figure 4: FTIR spectrum of pure ofloxacin

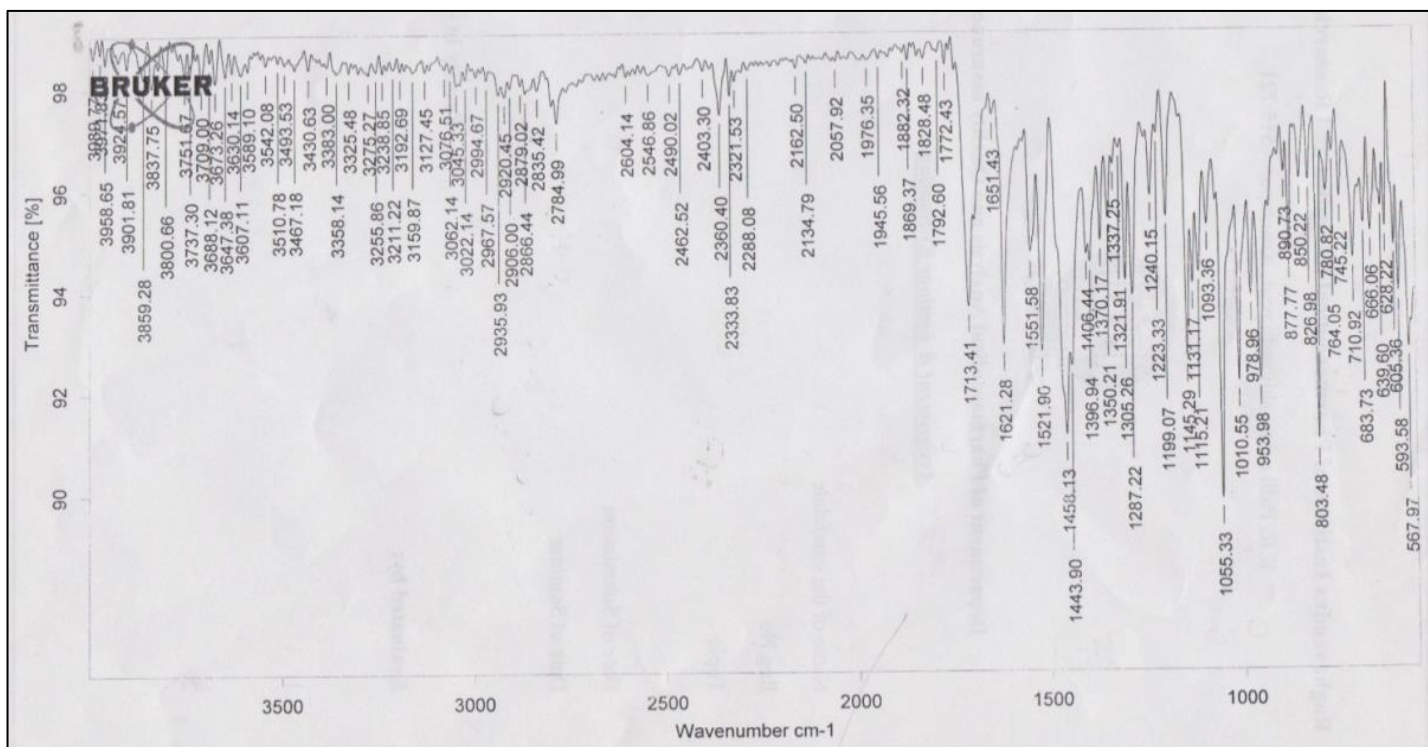


Figure 5: FTIR spectrum of best formulation

SEM Studies

The scanning electron micrographs of F6 are shown in the Figure. no. 6 at different magnifications. The SEM results revealed that all the ofloxacin loaded microspheres were discrete and spherical in shape with the smooth to rough outer surface. The surface of

the microspheres was rough due to the density of the polymer matrix which in turn justifies its sustained release. The dense network of drug-polymer increases the tortuosity, thus delaying the release of the drug and retarding the penetration of water (penetration of medium) required to make the sphere well for disintegration.

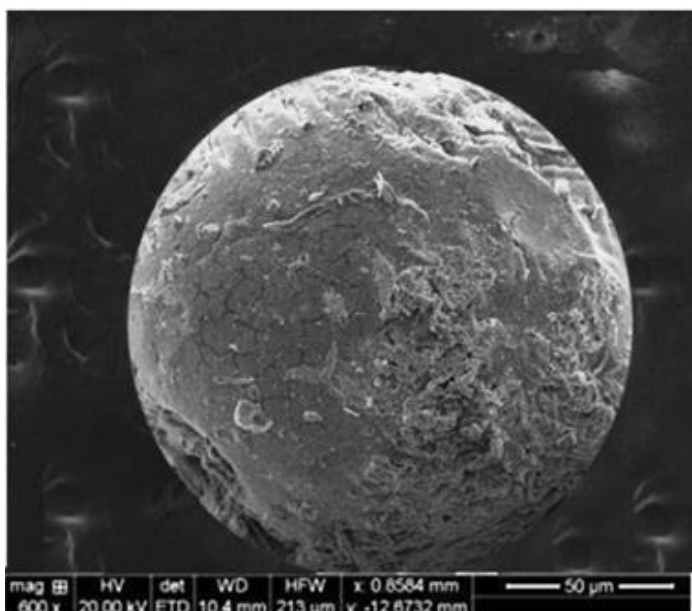
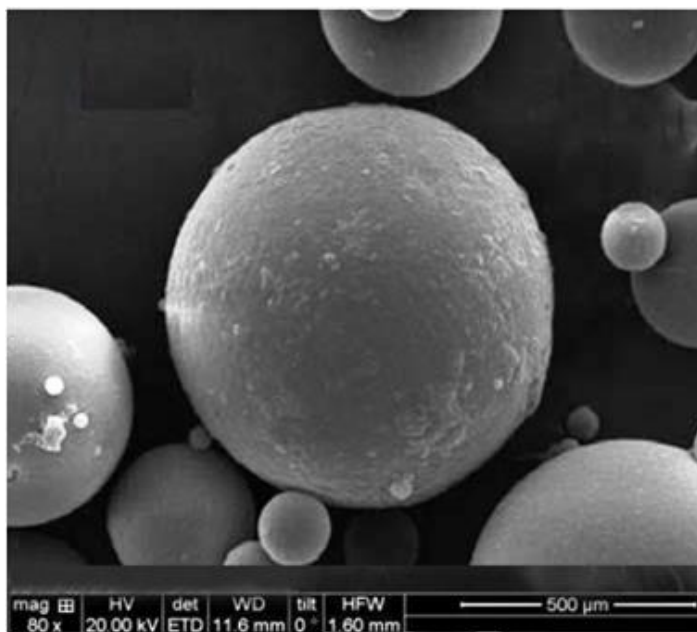


Figure 6: SEM of ofloxacin microspheres

In-vitro drug release studies

The *in-vitro* drug release study of microspheres was performed using USP XXIV type-I (basket) dissolution apparatus. The percentage drug release from formulations, F1-F9 was observed for 8 h in phosphate buffer pH-7.4 as represented in Figure. no 7. The formulations F1-F3 containing sodium alginate as polymer showed drug release of 96.38% to 97.07%, up to 7 h. The formulations F4-F6 containing sodium alginate and sodium CMC as polymer showed drug release of 92.32% to 98.77% up to 8 h, and formulations F7-F9 containing sodium alginate and HPMC K15M as polymer showed drug release of 78.87% to 91.08% up to 8 h. Drug release from the microsphere was slow, extended and dependent on the type of polymer and concentration of polymer used. From the *in-vitro* drug release profiles, it was observed that the drug release from microspheres was decreased with an increase in polymer concentration.

As viscosity of polymer increase in the formulation, the release of drug from formulation is decrease which may be due to increase in strength of gel matrix of the polymer. Similar type or results were observed with alginate microbeads of Norfloxacin developed by Anuranjita et al., [15]. Sodium alginate is a cross linked polymer with high molecular weight and viscosity. So, it would swell and hold water inside its micro gel network. Among all formulation F6 was found to be best formulation with 98.77% drug release for 8 h.

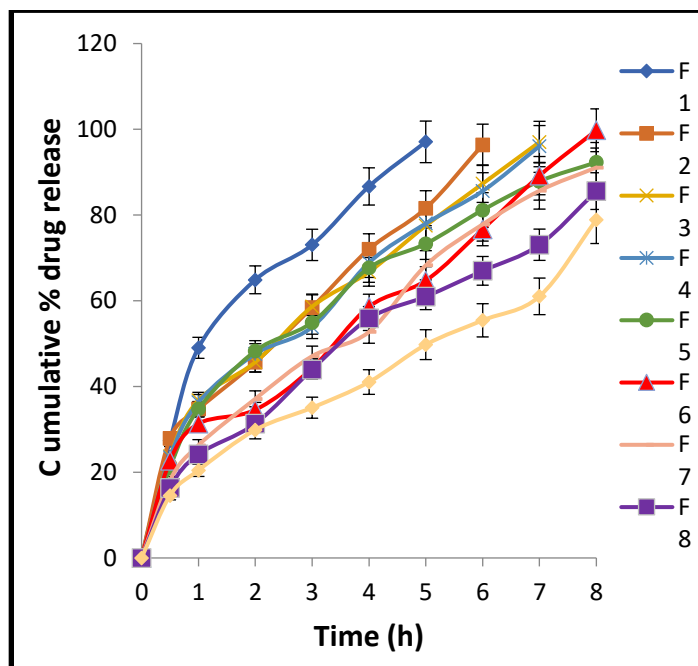
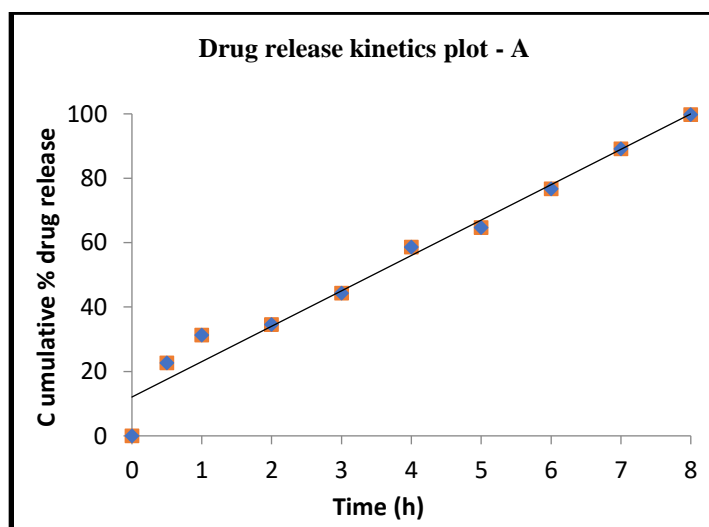


Figure 7: *In-vitro* drug release study of ofloxacin microspheres

Kinetic Modeling of Drug Release Profiles

The release data of the formulation, F6 showed better drug loading and release characteristics, and was fitted into the equations of various kinetic models as illustrated in Figure. no.8. The linear regression values for zero order (0.971) was higher than first order release (0.911) which means that ofloxacin release from the microspheres obey controlled fashion of zero-order release and drug release was dependent on the concentration gradient.



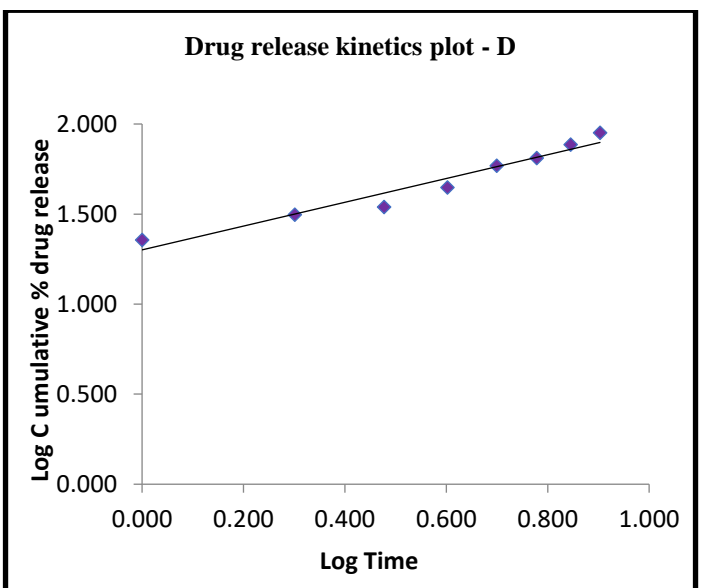
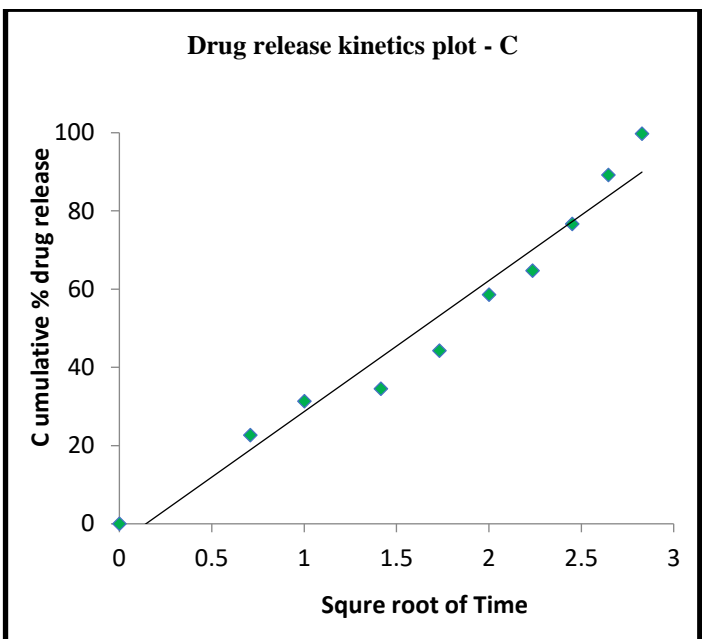
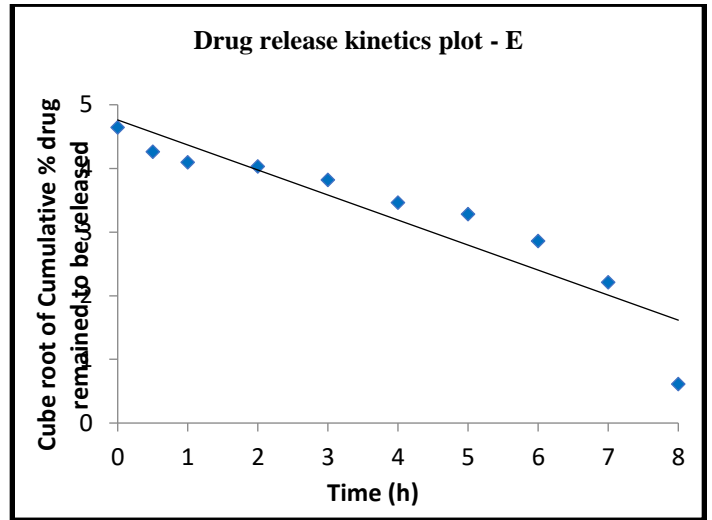
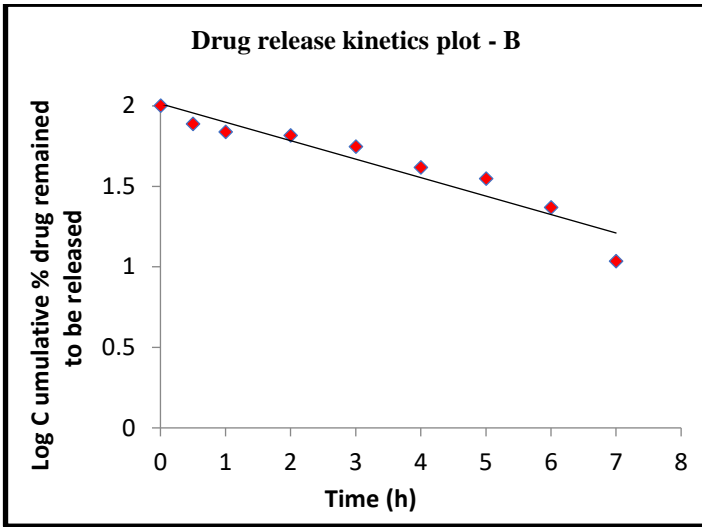


Figure 8: Drug release kinetics plots of ofloxacin microspheres- Zero-order (A), First-order (B), Higuchi (C), Korsmeyer–Peppas (D) and Hixon-Crowell (E).

Higuchi plot was linear with regression coefficient value 0.959, which explains the diffusion-controlled drug release mechanism from the microsphere. The release exponent ‘n’ was found to be 0.660; this indicates a non-fickian diffusion mechanism of drug release. According to Hixson-Crowell equation, the plot was not linear; the linear regression coefficient value was 0.858 that indicates a considerable erosion of the microsphere have taken place during the dissolution process.

Ex-vivo study of activity

The antibiotic activity of prepared microspheres was tested by cup plate method as depicted in Figure. no. 9. After the period of incubation, standard drug sample has zone of inhibition of 2cm and formulation F6 has zone of inhibition of 2.5cm. The zone of inhibition of prepared microspheres indicates the successful entrapment of drug in microspheres, its diffusion in to the medium and its effective antibacterial activity in comparison to standard.

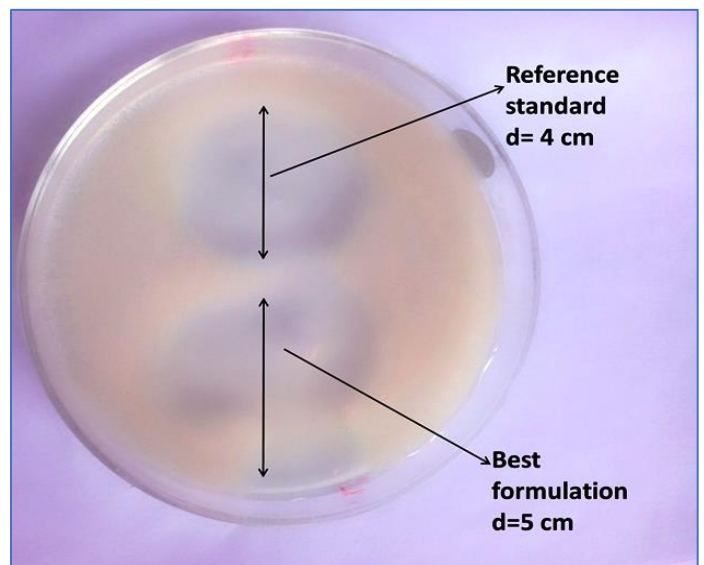


Figure 9: Ex-vivo studies of ofloxacin microspheres

CONCLUSION

From the present study, the following conclusions can be drawn: ofloxacin microspheres were successfully prepared by orifice ionic gelation method using sodium alginate, HPMC K15M and sodium CMC as polymers in different ratios, calcium chloride was used as cross-linking agent. Microspheres of selected best formulation F6 sustained the drug release over a period of 8h. Increasing the concentration of polymers in formulation decreased the rate of drug release dramatically. Hence prepared ofloxacin microspheres may be an effective and safe method for treatment of urinary tract infection. In future the research can be extended to *in-vivo* studies and development of *in-vivo* and *in-vitro* co-relation for release rate of ofloxacin microspheres.

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