RESEARCH PAPER

Development and evaluation of ciprofloxacin hcl microspheres through emulsion gelation with various combinations of polymers.

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ABSTRACT

This exploration is based on preparation of Ciprofloxacin HCl microspheres with emulsion gelation method. Ciprofloxacin HCl is a well-known first-generation fluoroquinolone antibiotic with versatile usage. Plasma elimination half-life of proposed drug is 4 hours approximately. Controlled release drug delivery system was highly recommendable and successfully achieved for these formulations. Microspheres were generated with polymers like sodium alginate, methyl cellulose, gelatin, magnesium stearate and cross-linked with calcium chloride. Overall, three different combinations of formulations were prepared and evaluated by percentage yield, swelling index, microscopic size analysis, *In Vitro* drug release study, drug release kinetics, drug entrapment efficiency and stability study. Reports generated from evaluation study represents F3 with highest value of regression coefficient for zero order and Higuchi release kinetics with respective data of 0.941 and 0.981. During *In Vitro* drug release study F1, F2 and F3 shows 85.024 %, 88.252 % and 89.479 % of drug release after 4 hours study. Ultimately it was found that F3 batch had shown progressive results even after 1 month stability study with less alterations. This particular study had been utilized emulsion gelation method for microsphere preparation and applied magnesium stearate in minimum concentration as release modifier to get controlled release drug delivery system.

Keywords: Ciprofloxacin HCl, Microsphere, Controlled release, Stability Study.

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INTRODUCTION

Ciprofloxacin Hydrochloride has comprehensive applications in the treatment of bacterial infections includes respiratory tract infection, skin infections, urinary tract infection, typhoid fever and anthrax exposure. Hydrochloride salt form of Ciprofloxacin is known as Ciprofloxacin Hydrochloride which belongs to fluoroquinolone class with antibacterial activity. Ciprofloxacin hydrochloride strives its antibacterial activity by creating interference with bacterial DNA gyrase and ultimately inhibits DNA synthesis by altering cell growth of bacteria [1]. Microspheres possess several benefits in pharmaceutical industries by acting as valuable carriers for drugs and promotes controlled or sustained release with reduced dosage frequency. They have ability to enhance therapeutic efficiency and minimize systemic side effects due to made up with biodegradable and biocompatible polymers [2]. They can protect sensitive drugs from degradation from enzymatic or chemical reasoning. Microsphere are Particle size of microspheres are generally lying in between 1 µm to 1000 µm. This particular dosage forms are also termed as microparticles [3]. Stability of carrier molecules depends upon the microstructures of particles. This particular dosage forms able to crucially increase bioavailability of drugs [4]. Sodium alginate acts as the vital polymer for generation of microsphere structure. Alginates are texture modifiers, increases stability and maintains efficacy at long-term basis for active compounds [5]. In this study emulsion gelation method was chosen for alginate beads preparation. This method is based on addition of the discontinuous phase within continuous oil phase oil [6]. Methylcellulose was applied for preparation which facilitate a distinctive characteristic to generate reversible physical gels [7]. Methylcellulose works as a binder or thickening agent [8]. Magnesium stearate was exploited during processing for stabilizing the droplets of emulsion with magnesium stearate [9]. Introducing gelatin in formulations had several advantages like generation of viscous formulation according to polymer concentration and thermal stability of formulation [10]. Addition of crosslinking agent calcium chloride ($CaCl_2$) improves mechanical strength and promotes barrier strategies of materials [11]. Another vital excipient gelatin interacts with calcium chloride where the **calcium ions** bind with carboxyl groups of gelatin chain and forms ionic bridges. Current is based on preparation of microspheres with different

concentration of Methyl Cellulose. Experimental works represents how this varying amount can alter drug release characteristics, kinetics, particle size, drug entrapment efficiency and swelling index. Controlled release delivery system of Ciprofloxacin HCl can reduce the antimicrobial resistance of drug [12]. At the end of stability study of one month it confirms the efficacy of dosage form. Novelty of this study is preparation of microspheres with decreased particle size and higher swelling index with optimum amount of magnesium stearate.

MATERIALS AND METHODS

Materials

Active pharmaceutical ingredient, Ciprofloxacin HCl was purchased from Yarrow Chem Products, Mumbai. Sodium Alginate, Gelatin, Methyl Cellulose and Calcium chlorides was procured from Loba Chemie Private Limited, Mumbai. Entire reagents and ingredients utilized were belongs to analytical reagent grade. Materials quantity used in all formulations were in accordance to Table 1.

Table 1: Composition of Ciprofloxacin HCl microsphere

Ingredients	Formulation		
	F1	F2	F3
Ciprofloxacin HCl	250 mg	250 mg	250 mg
Methyl cellulose	150 mg	200 mg	250 mg
Gelatine	300 mg	300 mg	300 mg
Sodium Alginate	400 mg	400 mg	400 mg
Sunflower oil	2 ml	2 ml	2 ml
Magnesium stearate	150 mg	125 mg	100 mg
Calcium Chloride	4 gm/100 ml	4 gm/100 ml	4 gm/ 100 ml

Method of Preparation by Emulsion Gelation Technique

Process was initiated by dissolving gelatin in warm distilled water to obtain a viscous solution. Magnesium stearate and methylcellulose were mixed with the previous solution. Sodium alginate was added to the aqueous phase to facilitate crosslinking. Ciprofloxacin HCl was dispersed into sunflower oil to obtain the oil phase. Aqueous phase blend of the polymers was emulsified into the oil phase with systemic stirring. This process generates water-in-oil (W/O) emulsion wherein aqueous drug-loaded droplets were suspended in oil and forms well-defined drug-loaded domains. Emulsion was dropwise extruded into a calcium chloride solution through a syringe and allowed for congealing the microspheres at least for 1 hour [13]. Microspheres were strained through appropriate mesh and washed thrice with distilled water to remove residues. Finally, microspheres were air dried for one day.

Evaluation method of Ciprofloxacin Microspheres

Percentage yield

Weight of freshly strained microspheres were measured and after drying again the weight of microspheres were taken. At the end percentage yield of all three batches were calculated from the formula written below [14].

$$Percentage\ yield = \frac{The\ amount\ of\ microspheres\ obtained}{The\ theoretical\ amount} \times 100$$

Particle Size

Microsphere diameters were observed through Conventional microscopy. Number of ten microspheres were randomly chosen from each batch (F1, F2 and F3). Diameters were measured and average size of particles were measured ultimately [15].

Swelling Index

Fully dried microspheres (100 mg) were taken from each three formulations and initial weight was measured (W_0). It was allowed for swelling within 10 ml of distilled water in three different test tubes for 4 hours. After 4 hours, the weight of swelled microspheres was measured (W_s) and swelling index was determined by utilising the formula stated below [16].

$$Swelling\ index = \frac{W_S - W_O}{W_O} \times 100$$

Entrapment Efficiency of Drug

Microspheres containing 10 mg of Ciprofloxacin were derived from all formulations and pulverized through application of pestle and mortar. Powdered sample was merged within Phosphate-buffered solution (pH 6.8) of 100 ml and reserved for one hour [17]. Samples were diluted as per requirements and observed in UV-Visible Spectrophotometer at the λ_{max} of 275 nm to measure the absorbance.

$$\%\ Drug\ entrapment\ efficiency = \frac{Drug\ content(Actual)}{Drug\ content(Theoretical)} \times 100$$

Drug Release Study (*In Vitro*) [18]

In Vitro release study of Ciprofloxacin HCl microparticles was executed by Phosphate-buffered solution (pH 6.8) in a magnetic stirrer. Microspheres with 250 mg of embodied drug was taken along with 300 ml of dissolution medium and kept under magnetic stirrer. It was revolved at 50 rpm with upheld temperature 37 ± 0.5 °C. Measured parts of 5 ml was withdrawn and replenished with equivalent amount of Phosphate-buffered solution (pH 6.8) at every 15 minutes intervals for 4 hours. Withdrawn sample was diluted and measured at 275 nm in UV- Visible Spectrophotometer.

Kinetics of Drug Release

Kinetics of drug release of microspheres was estimated by plotting reaction models [19]. $F = K_o t$, this equation is utilized for estimation of zero order (kinetics); whereas t, F and K_o are release in time, drug fraction, and constant for zero order release simultaneously. In case of First order kinetics equation, $\ln (1-F) = - K_1 t$ is used; whereas t, F and

K_1 belongs to the released in time, drug fraction, and rate constant for first order release [20]. Model of Higuchi model is represented by the equation, $F = K_H t^{1/2}$; whereas t, F and K_H are release in time, drug fraction and constant for Higuchi model simultaneously.

Model equation of Hixson-Crowell is $Q^{1/3} = kt + Q_0^{1/3}$; in which drug release in time, the starting value and rate constant are t, Q and Q_0 respectively. Equation, $F = K_p t^n$ is utilized model of Korsmeyer-Peppas, wherein t, F, n and K_p are shown as release in time, drug fraction, exponent for release serially and constant for Korsmeyer-Peppas model [21].

Stability Study

Selected batches after evaluation were undertaken for stability study. Samples from those batches were kept in storage at 30 ± 2˚C for one month. Microspheres were checked for *In Vitro* release study of drug after completion of one month [22, 23].

Results and Discussion

Percentage yield

Results obtained from three respective batches indicating highest value for F3. This particular batch was contained highest amount of methyl cellulose which had stabilized emulsion thus it had been provided proper recovery after microsphere with less product loss [24]. Values regarding percentage yield are provided in Table 2.

Table 2: Results of Percentage yield

Formulation	Percentage yield (%)
F1	84.9
F2	91.7
F3	92.2

Microsphere Size Analysis

According to microscopic size analysis particle sizes were ranges from 70 to 96.2 µm. All of the respective batches had promising results from size analysis smaller size ranges can increase drug release characteristics [25]. In comparison to three batches F3 had lowest size so this confirmed that optimum polymer levels had been reached.

Swelling Index

Results had shown 52 %, 73 % and 100 % of swelling index for F1, F2 and F3 simultaneously. Improved swelling Index of F3 was able to facilitate drug release pattern and drug diffusion [26]. Magnesium stearate in higher concentrations generates barrier for hydration, so minimum polymer expansion taking place with lower swelling index.

Drug Entrapment Efficiency

Observations from Drug Entrapment efficiency were stating that F3 had achieved higher value rather than other formulations. Methyl cellulose provided increased viscosity of formulation which reduces molecular diffusion of drug from internal level to external level while crosslinking process takes place, thus drug remains entrapped in between polymer matrix. Thus, drug entrapment efficiency increased with high rise in polymer concentration [27]. Results are presented in detail in Table 3.

Table 3: Results of Drug Entrapment Efficiency

Formulation	Entrapment efficiency (%)
F1	79
F2	88
F3	92

Drug Release study (*In Vitro*)

After evaluation it was derived that F1, F2 and F3 had 85.024 %, 88.252% and 89.479 % of drug release simultaneously after 4 hours study. Specifically, F3 formulation had shown maximum release according to Table 4 and Figure 1. This particular batch contains greater amount of methyl cellulose which conclusively shows that it promotes drug release from microspheres. There were no obstacles or fluctuations observed in graphical representation during study.

Table 4: Results obtained from Drug Release Study (*In vitro*)

Time (minutes)	% Drug Release		
	F1	F2	F3
15	23.443	29.460	27.714
30	30.802	39.431	36.019
45	38.075	42.694	39.226
60	43.609	50.904	48.640
75	53.122	54.554	56.145
90	66.267	63.056	59.468
105	72.033	64.910	66.192
120	73.575	68.096	68.904
135	76.148	73.061	72.018
150	78.958	76.893	74.606
165	81.165	80.117	79.273
180	82.987	83.920	83.252
195	85.024	86.133	87.091
210	83.796	88.252	89.479
225	82.731	87.445	86.461
240	81.015	86.385	84.511

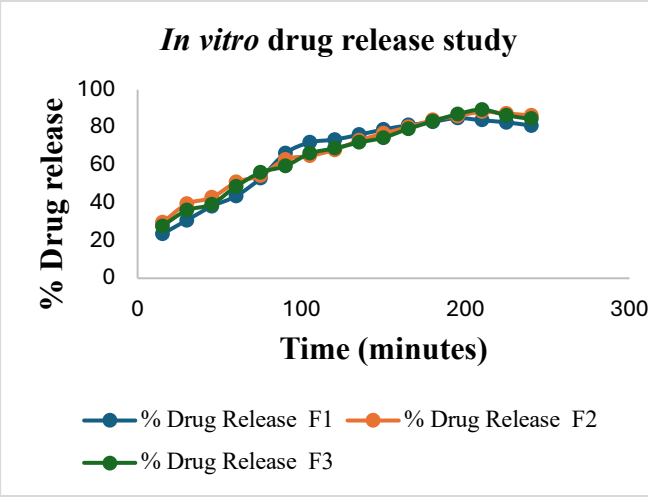

Figure 1: Drug Release Study of F1, F2 and F3

Kinetics of Drug Release

According to release kinetics study it was examined that all of the formulations mostly followed Zero Order, Higuchi reaction and Korsmeyer-Peppas Reaction in comparison to other models. In contrast to all three batches F2 and F3 had revealed noticeable values for Zero order model (0.941 and 0.929 simultaneously) which indicates controlled release from microspheres. In addition, F2 and F3 had pointed out favourable results in Higuchi model which represents enhanced drug diffusion from polymer matrix. Most significantly F3 had subsequently followed Korsmeyer Peppas model which conforms controlled release pattern with superior drug diffusion. Greatest swelling index was exhibited by F3 which finally facilitates overall drug diffusion. Entire specifications are mentioned in Table 5 and Figure 2 to 6.

Table 5: Results derived from Drug Release Kinetics Study

Equation name	F1		F
	K	R^2	K
Zero order	0.175	0.829	0
First order	0.000	0.718	0
Higuchi	5.690	0.918	5
Hixson Crowell	-0.000	0.721	-
Korsmeyer-Peppas	-0.003	0.888	-

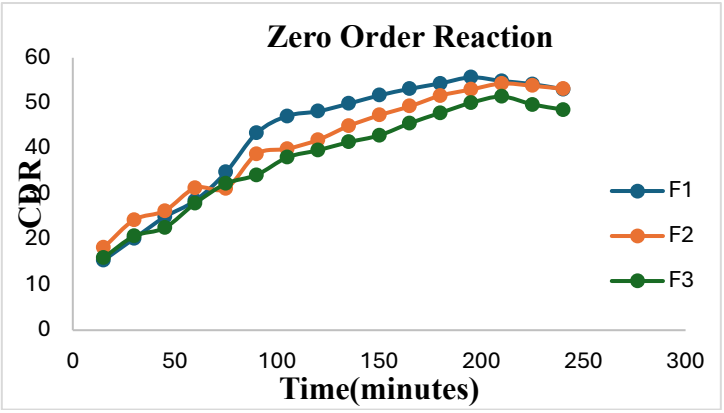

Figure 2: Zero Order kinetics study results of F1, F2 and F3

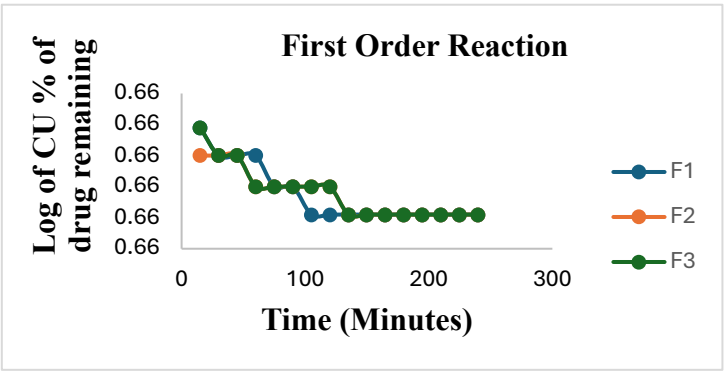

Figure 3: First Order kinetics study results of F1, F2 and F3

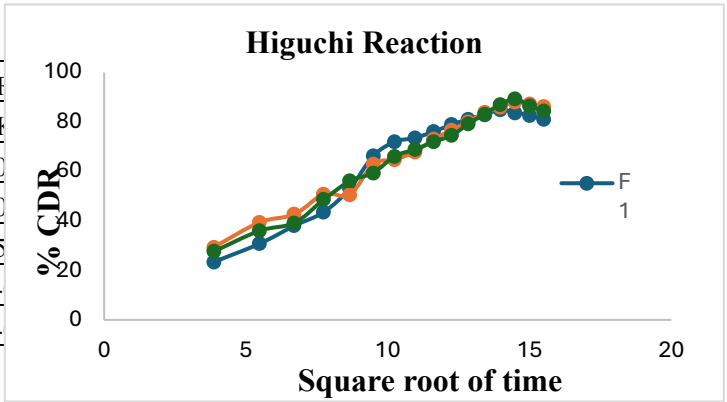

Figure 4: Higuchi kinetics study results of F1, F2 and F3

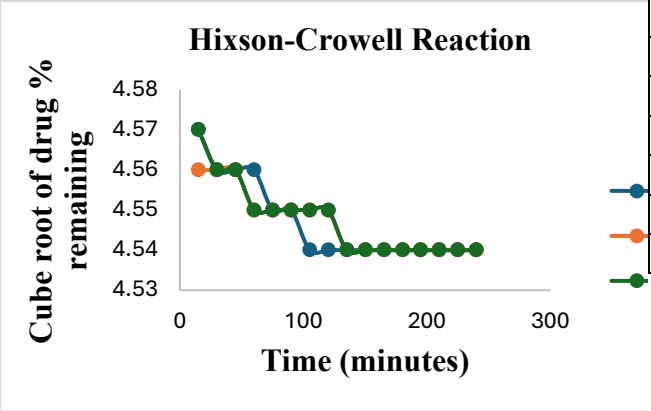

Figure 5: Hixson-Crowell kinetics study results of F1, F2 and F3

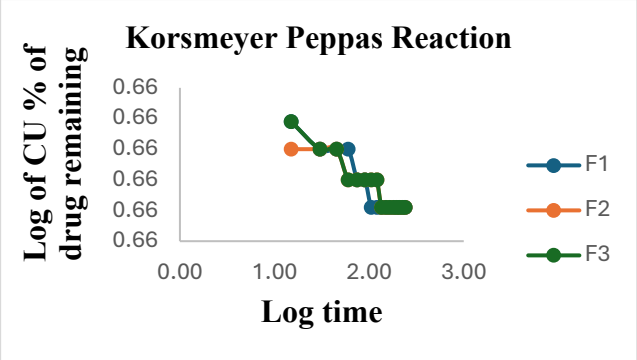

Figure 6: Korsmeyer Peppas kinetics study results of F1, F2 and F3

Stability Study

Regarding release study (*In Vitro*), release kinetics and other evaluation reports F2 and F3 were preferred for stability studies due to promising release pattern. *In Vitro* release study (4 hours) report after one month storage had been indicated very less difference with previously generated reports. Specially F3 had achieved noticeable results with 85.112 % of maximum release. Complete reports generated from release studies are mention in Table 6 and Figure 7.

Table 6: Result of *In Vitro* drug release study for Stability

Time (minutes)	% Release	
	F2	F3
15	22.456	26.748
30	28.250	34.325
45	37.072	38.379
60	41.506	48.057
75	50.244	55.834
90	64.702	62.261
105	71.703	67.001
120	72.584	70.902
135	73.997	71.453
150	76.489	73.386
165	79.111	77.426
180	81.092	80.567
195	83.371	83.292
210	82.310	85.112
225	81.073	83.397
240	80.991	81.980

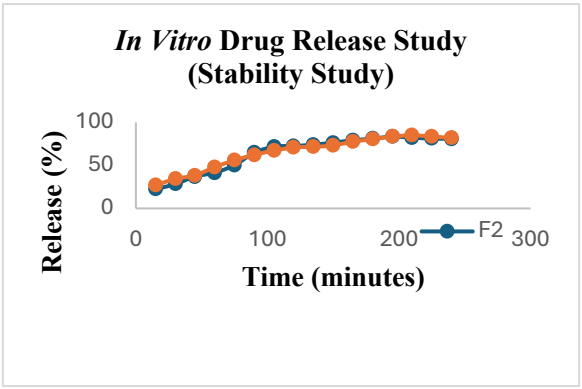

Figure 7: Drug release study (*In Vitro*) of Ciprofloxacin HCl microspheres after 1 month storage

Conclusion

Three diverse formulations of Ciprofloxacin HCl microspheres were developed by emulsion Gelation Technique. Polymer combinations of methylcellulose and sodium alginate specially in F3 yielded the highest efficiency in swelling capacity (100 %) and enhanced drug release with the lowest particle size (70 µm). Drug entrapment efficiency and percentage yield results showed substantial improvement in F3. *In vitro* drug release study had been indicated that F3 has superior drug release (89.479 %) in contrast to other combinations. After one month stability study (*In Vitro* drug release) F2 and F3 exhibited negligible variation. Drug release kinetics revealed that all three formulations specially followed Zero order and Higuchi model thus controlled release profile with improved drug diffusion was achieved. Significantly, F3 likewise followed Korsmeyer Peppas model which represents efficient drug diffusion and controlled release from polymer matrix. Regression coefficients of F2 and F3 was respectively 0.941 and 0.929 for Zero order release kinetics. Major emphasis of current study was to identify effect of applying magnesium stearate for release modification, swelling properties and particle size reduction. Magnesium stearate was able to reduce particle size and able to enhance swelling index with minimum concentration as followed by F3. Ultimately this study reveals that better swelling Index can simultaneously improve drug diffusion through microspheres with improved drug release.

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Conflict of interest: None

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