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SYNTHESIS, CHARACTERIZATION AND OPTIMIZATION OF COLON TARGETING CIPROFLOXACIN LOADED MICROSPHERES

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ABSTRACT

Our objective in this research is to develop an enteric-coated capsule device filled with microencapsulated drug formulation by the crosslinking of microbially degradable matrix loaded with Ciprofloxacin to investigate its release behaviour. Because the gelatin capsule was enteric coated with Eudragit L-100, it prevented the disintegration of the capsule in the gastric fluid of pH 1.2 (acidic) and thereby, released the drug in a controlled manner on reaching the small intestine at basic pH 7.4, the capsule lost its enteric coating, microspheres swelled slowly, and started to release Ciprofloxacin in the colonic region. The prepared microspheres were evaluated for Micromeritic properties, Particle size, Solubility studies, Entrapment efficiency, Drug polymer compatibility (IR and DSC study), Swelling Index, Scanning Electron Microscopy and In vitro *drug release. The microspheres produced exhibited good encapsulation efficiencies and micromeritic properties. Encapsulation efficiency of microsphere is around 89%. The mean diameters of microspheres were found in required micrometer range. The results of optimized formulations showed a narrow size distribution and smooth surface. The DSC and the FTIR analysis showed the absence of any potent incompatibility between the drug and the polymer.* In-vitro *release showed 86.3% drug release after 12 hours. Results of present study suggest that Ciprofloxacin loaded microspheres for colon targeting can be successfully prepared by Ionotropic gelation method.*

KEYWORDS: *Ciprofloxacin, Microencapsulation, Colon targeting, Entrapment efficiency, Particle size, In vitro release stability studies.*

1. INTRODUCTION

With gradual advancement detected in the field of biopharmaceutics, several useful corners have been evolved for discussion on designing and fabrication of drug delivery systems. Several useful information collected upto date directed modern research to have accuracy and rationality with sufficing every possible need of pharmaceutical technology. Dosage form development has rendered some new useful aspects of reliable drug carrier system with their conventionally popular counterpart. Of several developed drug administration methods, oral route has found its way to prove potential convenience to offer the greatest potential for more effective therapeutics, but they do not facilitate drug that easily cross mucosal surfaces and biological membranes; they are easily denatured or degraded, prone to rapid clearance in the liver and other body tissues and require precise dosing. At present, susceptible drugs are usually administered by injection but this route is less pleasant and also poses problems of oscillating blood drug concentrations. Despite the barriers for successful drug delivery that exist in the gastrointestinal tract (such as acid-induced hydrolysis in the stomach, enzymatic degradation throughout the gastrointestinal tract by several proteolytic enzymes, bacterial fermentation in the colons), the oral route is still the most intensively investigated as it offers advantages of convenience and economic in administration, and potential manufacturing cost savings. The design of oral control drug delivery systems (DDS) should be primarily aimed to achieve more predictable and increased bioavailability.[1] Historically, oral drug administration has been recognized as the predominant route for drug delivery. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. Control release implies the predictability and reproducibility to control the drug release, drug concentration in target tissues and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose.[2] However the oral route of drug administration presents its own unique set of problems and constraints. The time frame, or “window,” for absorption is limited to the total GI residence time. Taking into account gastric emptying and small and large intestine transit time, it would seem that a reasonable duration in the GI tract is approximately 24 hours. The absorption, distribution and elimination of drugs are normally simplified by considering them all to be simple first-order processes. Given the average 24-hour residence time and high individual variability in the GI tract, only drugs with relatively short elimination half-lives should be considered for membrane-controlled reservoir systems.[3] All these mechanisms employ physical transformation of constituents involved in

the system when they are put into a biological environment. Although there are feasible chemically driven drug delivery systems, they involve chemical modifications with active agents and carrier vehicles for which regulatory approval and adequate toxicology and safety profiles are needed before reaching final application. For such reasons, simpler systems with approved active agents and excipients are often utilized in the preparation of the controlled drug delivery systems used for medical applications. Sustained (or continuous) release of a drug involves polymers that release the drug at a controlled rate due to diffusion, out of the polymer or by degradation of the polymer over time.[4] Pulsatile release is often the preferred method of drug delivery, as it closely mimics the way by which the body naturally produces hormones such as insulin. It is achieved by using drug-carrying polymers that respond to specific stimuli (e.g., exposure to light, changes in pH or temperature). Ciprofloxacin is a fluoroquinolone (flor-o-KWIN-o-lone) antibiotic used to treat a number of bacterial infections.[5] This includes bone and joint infections, intra abdominal infections, certain type of infectious diarrhea, respiratory tract infections, skin infections, typhoid fever, and urinary tract infections, among others.[6] For some infections it is used in addition to other antibiotics.[7] It can be taken by mouth, as eye drops, as ear drops, or intravenously. Ciprofloxacin is a bactericidal antibiotic of the fluoroquinolone drug class. It inhibits DNA replication by inhibiting bacterial DNA topoisomerase and DNA-gyrase. Of the fluoroquinolone class, ciprofloxacin is the most potent against gram-negative bacilli bacteria (notably, the *Enterobacteriaceae* such as *Escherichia coli*, *Salmonella* spp., *Shigella* spp., and *Neisseria*).[8] Ciprofloxacin also has effectiveness against some gram-positive bacteria. Ciprofloxacin is the most active against *Pseudomonas aeruginosa,* among the quinolones.[9] Progressively decreasing susceptibility among *P. aeruginosa* has been reported in Europe, North and South America, predominantly in the hospital or nursing home settings with identifiable risk factors. Ciprofloxacin is readily absorbed but typically does not achieve complete absorption. The bioavailability of oral ciprofloxacin is 70 to 80%.[10] Ciprofloxacin is one of the few oral antibiotics able to treat *P. aeruginosa* infections.[11]

2. MATERIALS AND METHODS

2.1 Materials

Ciprofloxacin was purchased by Thomas baker (Chemicals) Pvt. Ltd. (Chandigarh, India). Eudragit-L-100 was purchased from Central Drug House (P) Ltd – CDH, (New Delhi, India). HPMC was purchased by Lobe Chemie Laboratories, (Mumbai, India). Sodium alginate was purchased by Nice Laboratories Reagents, Kochi. Barium chloride was purchased by Nice

Laboratories Reagents, Kochi. Xanthan gum was purchased by Ranbaxy Laboratories Pvt. Ltd. Guar gum was purchased by Arora & company Pvt. Ltd. All the reagents were of analytical grade and used without further purification.

2.2 Preparation of Microspheres of Ciprofloxacin for colon targeted delivery

2.2.1 Method employed in preparation of multiparticulate system

1. Ionotropic gelation method was selected for preparation of microspheres.
2. Xanthan gum, Guar gum and HPMC were selected individually as polymer along with Sodium alginate.
3. Barium chloride was used as cross linking agent.
4. Microspheres were filled into hard gelatin capsules and then coated with Eudragit L 100 by solvent evaporation method.

2.2.2 Method of preparation of microspheres

1. Xanthan gum, Guar gum and HPMC individually were dissolved in distilled water and allow swelling for few hours (I).
2. Sodium alginate dissolved in distilled water and drug dispersed into this solution (II).
3. I and II solution were mixed kept on magnetic stirrer at room temperature with constant speed.
4. The bubble free dispersion was dropped into different cross linking agent solution with a needle of 21 gauze.
5. The microspheres allowed hardening in solution for 15 minutes.
6. Then microspheres were filtered and dried primarily at room temperature and after it, in hot air oven at 35°C for about 30 min.
7. Microspheres were then stored in glass bottles, capped tightly.

2.2.3 Coating process of microspheres by solvent evaporation method

1. Microspheres were weight equivalent to dose of drug and filled manually into hard gelatin capsule shells.
2. For coating, Eudragit L 100 dissolved in acetone.
3. The hard gelatin capsules filled with microspheres were dipped into polymer solution and solvent evaporated on magnetic stirrer.
4. At definite time intervals, capsules were removed from solution and dried with hot dry air.

2.2.4 Optimization of polymers ratio

Based on the literature survey six formulations of Ciprofloxacin loaded Microspheres were prepared as shown in **Table 1**.

Table 1: Optimization of Sodium alginate - Polymers ratio and its effect on Particle Size and Entrapment efficiency.

Batch Code	Ratio	SA: Guar gum wt(mg)	SA: Xanthan gum wt(mg)	SA: HPMC wt(mg)	Particle Size (nm)	Entrapment Efficiency (%w/w)
F1	**4:1**	**2:0.5**	**2:0.5**	**2:0.5**	**210.37 ±1.27**	**55.31 ± 1.45**
F2	4:2	2:1.0	2:1.0	2:1.0	367.58 ±0.72	80.02 ± 0.68
F3	4:3	2:1.5	2:1.5	2:1.5	290.35 ±1.48	74.23 ± 0.02
F4	4:4	2:2.0	2:2.0	2:2.0	459.12 ±1.67	78.89 ± 1.26
F5	4:5	2:2.5	2:2.5	2:2.5	382.96 ±0.65	72.95 ± 0.76
F6	**4:6**	**2:3.0**	**2:3.0**	**2:3.0**	**588.18±0.31**	**86.42 ± 0.25**

***Each value is ± SD of three independent determinations**

2.3 Design of the experiment

A 2^3 full factorial design was used in this study. In this design 3 factors were evaluated, each at 2 levels, and experimental trials were performed at all 8 possible combinations. The Three independent variables were selected which were the SA: Guar gum ratio (X_1) and SA: Xanthan gum (X_2) SA: HPMC (X_3) as given in **Table 2**.

Table 2: Test factors for optimization of process parameters.

Factor	Name	Units	Low Level (-)	High Level (+)
A (X_1)	SA: Guar gum	----	4:1	4:6
B (X_2)	SA: Xanthan gum	----	4:1	4:6
C (X_3)	SA: HPMC	----	4:1	4:6

2.4 Optimization of various parameters by 2^3 Full factorial design

The results obtained after implementing 2^3 Full Factorial Design are summarized in **Table 3**.

Table 3: Effect of various parameters on characteristics of microspheres.

Batch code	SA: Guar gum (X_1)	SA: Xanthan gum (X_2)	SA: HPMC (X_3)	Y1:Cumulative Drug Release After 24 hrs (%)	Y2: Entrapment Efficiency (%w/w)
F1	-(4:1)	-(4:1)	-(4:1)	71.20 ±1.32	72.34 ± 0.84
F2	+(4:6)	-(4:1)	-(4:1)	76.91 ± 1.74	75.16 ± 0.45
F3	**-(4:1)**	**+(4:6)**	**-(4:1)**	**86.32 ± 1.05**	**89.15 ± 1.12**
F4	+(4:6)	+(4:6)	-(4:1)	65.75 ± 0.43	61.57 ± 1.90

F5	-(4:1)	-(4:1)	+(4:6)	73.52 ± 0.74	78.72 ± 1.73
F6	+(4:6)	-(4:1)	+(4:6)	82.69 ± 1.89	82.52 ± 0.69
F7	-(4:1)	+(4:6)	+(4:6)	68.74 ± 0.52	63.17 ± 1.14
F8	+(4:6)	+(4:6)	+(4:6)	69.85 ± 1.77	72.72 ± 0.78

3. Evaluation of prepared microspheres

3.1 Evaluation parameters of microspheres

Various parameters have been studied for prepared microspheres. The flow properties of Microspheres were examined in terms of Bulk density, Tapped density, Angle of repose Carr's index and Hauser's ratio.

3.2 Particle size analysis

The particle sizes of the prepared Microspheres were measured by Beckman Coulter Delsa^{TM} Nano C Particle Analyzer. The dried powder samples were suspended in deionised water and sonicated for 1 min with an ultra-sound probe before measurement.

3.3 Surface and Shape analysis by scanning electron microscopy

The shape and surface characteristics of Microspheres were analyzed by field emission scanning electron microscopy operating at 10 kV. The samples were mounted on an aluminium stub with adhesive tape and excess samples were removed and coated with gold for 20 seconds. Then the metal stub was placed in E-1010 Ion sputter for 20 minutes under vacuum. After 20 minutes samples were analyzed under field emission scanning electron microscope.

3.4 Solubility studies

The most widely used approach to study inclusion complexation is the phase solubility method described by Higuchi and Connors, which examines the effect of a Microsphere, on the solubility of a drug. Phase solubility diagrams indicate the degree of complexation.

3.5 Entrapment efficiency

The entrapment efficiency of the Microspheres was determined spectrophotometrically. A sample of Ciprofloxacin Microspheres (10 mg) was dissolved in 10 ml of methanol and kept it for overnight. 1 ml of the supernatant was taken and diluted to 10 ml with a solution containing phosphate buffer of pH 7.4 and was analyzed at 223 nm using UV-Visible spectrophotometer. From the absorbance, the % entrapment efficiency of the Microspheres was calculated by the following Equation.

$$\% \text{ Entrapment Efficiency} = \frac{\text{actual drug content}}{\text{practical drug content}} \times 100$$

3.6 *In-vitro* drug release study

In-vitro drug release study was done on the release pattern of the drug from the Microspheres formulations prepared by Ionotropic Gelation method. After separating the un-entrapped drug, the Microspheres containing capsules after coating with Eudragit L-100 was put into the dialysis bag which was previously soaked and washed several times with distilled water. This was placed in 100 ml of phosphate buffer solution (pH 1.2, pH6.8, pH7.4) and kept with constant agitation on a magnetic stirrer maintaining a temperature of 37ºC at each periodical time the whole sample were withdrawn and same volume was replaced with buffer. Then the samples were assayed spectrophotometrically at 200 nm-400 nm using medium as blank.

3.7 Stability study

Freeze-dried optimized Microspheres formulation F_3 was subjected to stability studies as per ICH guidelines. The samples were placed in vials and kept at 25±2°C/60 ±5% RH and 4±2°C C/75 ± 5% RH atmospheric conditions using stability chamber over period of three months. The samples were analyzed physical appearance at specified time intervals (0, 15, 30, 60, 90 days of storage). Cumulative drug release study was also carried out at the end of stability study for both storage conditions.

4. RESULT AND DISCUSSION

4.1 Morphological study

All the prototype batches of Xanthan gum, Guar gum and HPMC microspheres were evaluated on basis of morphological characteristics like shape, colour, stickiness odour and mentioned in **Table 4**.

Table 4: Morphological characters of ciprofloxacin microspheres with Xanthan gum, Guar gum, HPMC.

S. No.	Formulation code	Shape	Colour	Stickiness	Odour
1	F1	Spherical	Pale yellow	Absent	Odourless
2	F2	Slightly Spherical	Pale yellow	Absent	Odourless
3	F3	Slightly Spherical	Pale yellow	Absent	Odourless
4	F4	Spherical	Brown	Absent	Odourless
5	F5	Slightly Spherical	Brown	Absent	Odourless
6	F6	Slightly Spherical	Brown	Absent	Odourless
7	F7	Spherical	Pale yellow	Absent	Odourless

8	F8	Slightly Spherical	Pale yellow	Absent	Odourless

4.2 Swelling studies

The extent of swelling was determined by swelling behaviour of dried microspheres during GI passage; by measuring of water uptake in 1.2 pH for 2 hr. and in phosphate buffer of pH 7.4 for 3hr and pH 6.8 until weight equilibrium has attained, maintained at physiological temperature of 37°C, means in terms of percentage weight gained by microspheres. It was found that swelling of microspheres was occurred in stomach and it was gradually increasing when microspheres were transferred to intestine. As microspheres are prevented from acidic pH 1.2, the swelling studies are also performed by escaping this medium. This study was mentioned in table form and it is given below. As microspheres are prevented from 0.1N HCl medium in final dosage form, swelling studies are also performed by escaping this medium as shown in **Table 5** given below. Chosen formulation F3 for swelling studies because the release rate is better as compare to other formulations.

Table 5: % Swelling index of microspheres at different physiological pH.

Formulation Code	% Swelling index		
	at 1.2 Ph	at 7.4 pH	at 6.8 Ph
F1(Guar gum)	12.1	16.4	19.1
	-	12.3	16.9
F3 (HPMC)	10.4	14.6	18.2
	-	11.4	13.3
F5(Xanthan gum)	9.2	15.2	17.2
	-	10.7	14.1

4.3. Surface analysis and Shape by field emission scanning electron microscopy

Surface morphology of the Microsphere's was examined by FESEM as shown in **Figure.1**

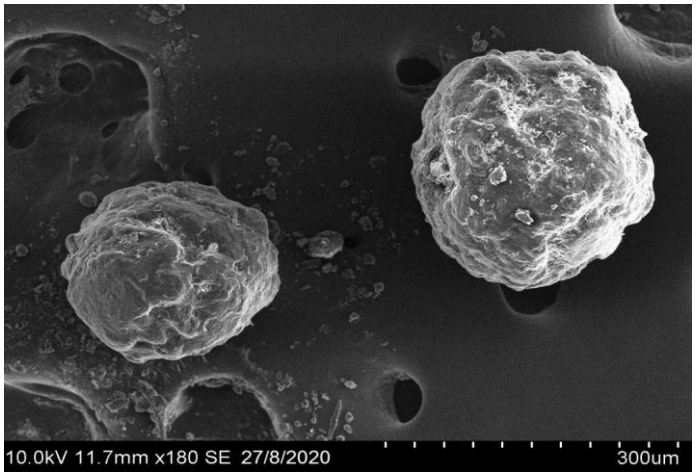

Figure 1: FESEM photograph of Ciprofloxacin loaded Microsphere's.

4.4 Determination of particle size

Determination of particle size is determined by optical microscopy.

The mean particle size of microspheres (µm) of all the batches are depicted in **Table 6.**

Table 6: Mean particle size Ciprofloxacin microspheres with Xanthan gum, Guar gum and HPMC.

Formulation code	Mean particle size (µm)
F1	563.9
F2	576.7
F3	**589.3**
F4	567.2
F5	559.7
F6	598.1
F7	623.4
F8	646.8

The graph plotted in **Figure 2** shows the comparison of microspheres size prepared with Different polymers.

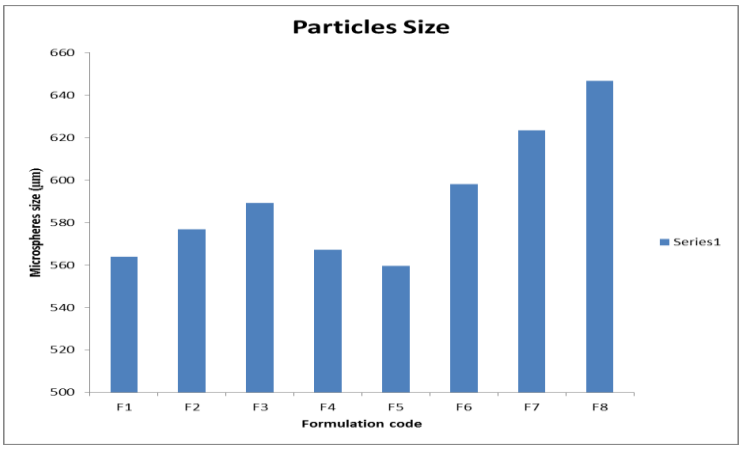

Figure 2: Particle size of microspheres prepared with different polymer.

4.5 Evaluation of flow properties of all formulation batches

The microspheres of all the formulation batches with Xanthan gum, Guar gum and HPMC were evaluated for the flow properties. In **Table 7**, all the flow properties determinant parameters of microspheres are given with value.

Table 7: Evaluation of flow properties of all formulation batches with Xanthan gum, Guar gum and HPMC.

Batch No.	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	Hausner's Ratio	Angle of Repose
F1	0.68	0.76	10.52	1.11	13.35
F2	0.89	0.92	3.26	1.03	14.12
F3	**0.59**	**0.64**	**7.81**	**1.08**	**14.89**
F4	0.72	0.77	6.49	1.06	11.93
F5	0.64	0.72	11.11	1.12	12.32
F6	0.65	0.79	17.72	1.21	9.97
F7	0.62	0.71	12.67	1.14	10.21
F8	0.79	0.86	8.13	1.08	12.56

Bulk density values of microspheres were found to be in the range of 0.59-0.89 g/cm^3 while the corresponding tapped density values were in the range of 0.64-0.92 g/cm^3. The values of Carr's index for all the batches were found out to be less than 18, values of Hausner's ratio was also found to be less than 1.25 and values of angle of repose is less than 20 indicating that formulations of all the batches were excellent flow properties. Hence, it can be concluded that microspheres are easily filled in hard gelation capsules.

4.6 Determination of entrapment efficiency

Entrapment Efficiency of nine batches (F1-F8) is summarized in **Table 8**

Table 8: Entrapment efficiency of microspheres.

Formulation code	Entrapment efficiency (%) (Mean ± S.D)
F1	72.34 ± 0.84
F2	75.16 ± 0.45
F3	89.15 ± 1.12
F4	61.57 ± 1.90
F5	78.72 ± 1.73
F6	82.52 ± 0.69
F7	63.17 ± 1.14
F8	72.72 ± 0.78

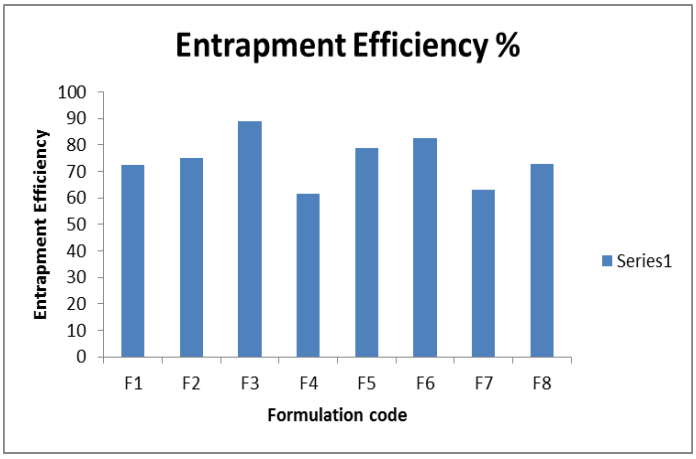

Figure 3: Entrapment efficiency of ciprofloxacin microspheres.

4.7 *In-vitro* drug release studies

In vitro drug release studies were performed to predict the release profile during transit of dosage form from stomach through small intestine and finally reaching to colon environment. The drug release studies were performed using Dialysis begs. Uses of small volume of buffer solution in this study help in better detection of drug concentration. Microsphere was encapsulated in hard gelatin capsule coated by double layer of Eudragit L100 which helps in preventing leaching out of microspheres. The stirring speed was set 50 rpm and temperature was maintained 37±0.5°C throughout drug release study. The pH of medium was kept as 1.2 pH for initial 2nd hr, 7.4 for next 3rd hr and pH 6.8 upto 12th hr. Samples were withdrawn every hr and analyzed for absorbance at UV spectrophotometer.

The cumulative drug release of different prototype batches are calculated by observing absorbance of different batches at different time intervals (upto 12 hrs.) and depicted in **Table 9.**

Table 9: *In Vitro* % cumulative drug release from microspheres.

Time (hrs.)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
0.5	0.554	0.723	0.32	0.31	0.68	0.82	0.32	0.44
1	1.72	1.923	2.68	0.62	1.72	2.11	0.76	0.92
2	2.932	3.40	3.83	1.56	2.16	3.23	1.77	1.92
3	5.36	5.92	7.65	3.86	4.86	6.10	4.12	4.23
4	6.85	7.62	10.32	5.98	7.34	9.13	6.23	6.78
5	9.31	12.40	15.92	7.85	11.76	13.62	9.11	9.26
6	11.98	18.24	23.65	9.67	17.91	20.42	11.34	11.78
7	14.2	26.96	34.16	12.62	23.12	32.14	13.76	14.17
8	23.16	38.22	46.69	20.41	37.64	45.79	22.15	23.01

9	34.95	48.14	53.94	33.84	40.78	49.70	36.69	37.84
10	45.96	57.65	61.96	41.37	53.67	58.63	42.64	44.79
11	62.4	66.78	72.60	56.98	64.23	69.25	58.79	60.28
12	71.2	76.91	86.32	65.75	73.52	82.69	68.74	69.85

The graphical representation of *In-vitro* drug release profile of different batches prepared are shown in **Figure 4**.

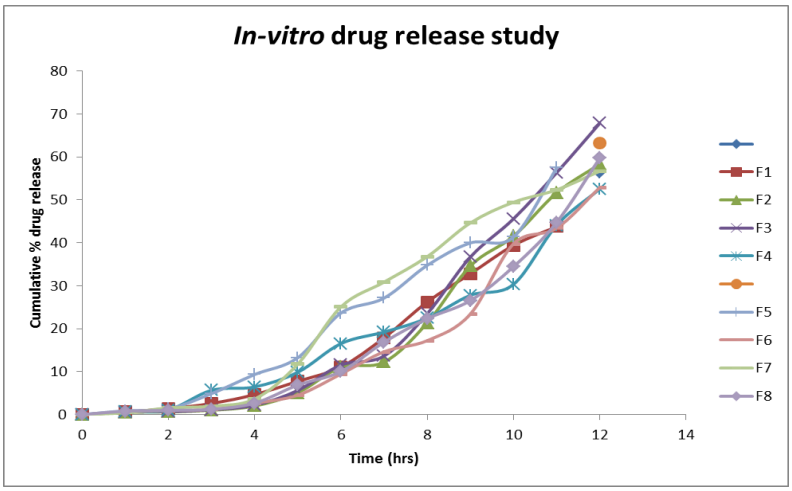

Figure 4: In-vitro drug release study.

4.8 % CDR Comparision of marketed formulation with Optimized batch (F3)

PENTASAL capsule (500mg) was selected as the marketed formulation which shows %CDR within 8 hours shown in **Table 10 and Figure 5.**

Table 10: Comparison of % CDR of formulation F3 with marketed formulation.

Time (hrs)	% CDR of F3	% CDR of marketed formulation
0	0	0
0.5	0.92	2.45
1	2.68	6.12
2	3.83	17.6
3	7.65	25.7
4	10.32	43.6
5	15.92	57.25
6	23.62	64.13
7	34.1	81.6
8	46.6	92.12
9	53.9	-
10	61.8	-
11	72.6	-
12	86.3	-

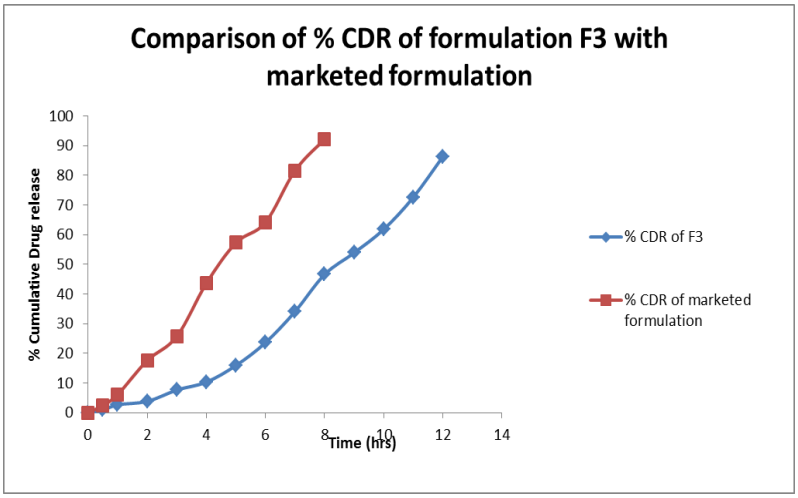

Figure 5: Comparison of % CDR of formulation F3 with marketed formulation.

4.9 Effect of aging on cumulative percent drug release

The stability studies indicate that the cumulative percent drug release of the optimized batch at the end of 3 months was found to be 62.89% at 4 ± 1˚C and 53.23% at room temperature as shown in **Table 11 and Figure 6.**

Table 11: Effect of aging on cumulative percent drug release before storage, storage at 4 ± 1˚C and room temperature.

Time	Cumulative % drug release before storage	Cumulative % drug release (at 4 ± 1˚C)	Cumulative % drug release (at room temp.)
0	0	0	0
1	0.58	0.49	0.41
2	0.71	0.69	0.61
3	1.12	1.10	1.02
4	2.21	2.19	2.04
5	5.64	4.59	3.21
6	11.56	10.43	9.04
7	13.66	12.56	11.21
8	23.49	22.41	19.89
9	36.68	35.62	32.54
10	45.59	44.45	39.76
11	56.34	55.23	42.23
12	67.84	62.89	53.23

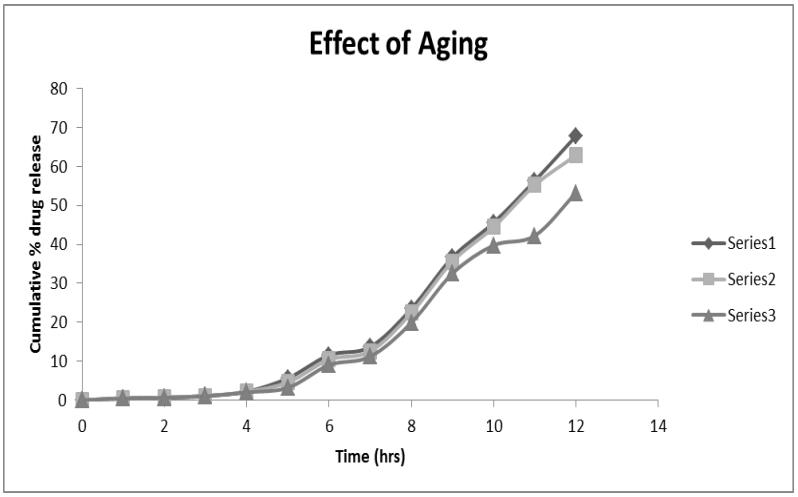

Figure 6: Effect of aging on cumulative % drug release before storage, storage at 4 ± 1˚C and at room temperature.

The percent residual drug content and log percent residual drug content was plotted against time (t), which reflected an almost linear relationship. Degradation rate constant (k) was calculated from which the time required for 10% drug leaching was calculated.

Microspheres were stored at 4 ± 1˚C showed the k value as 2.32×10^{-4} and $t_{10\%}$ value of nearly 378 days, while those stored at room temperature showed the k value as 5.21×10^{-4} and $t_{10\%}$ value of nearly 202 days.

The $t_{10\%}$ obtained in case of formulation stored at room temperature were found lower in comparison with the formulations stored at 4 ± 1˚C which indicated that the formulations tend to degrade faster at higher temperatures.

The results of stability studies indicate that for adequate shelf life of Microspheres formulation the ideal storage temperature is a cold place i.e. 4 ± 1 ˚ C.

5. CONCLUSION

In this study, Ciprofloxacin loaded Microspheres have been developed and characterized which exhibited many features such as low dosing frequency, and controlled release of drug. Ciprofloxacin loaded Microspheres have been prepared using Ionotropic Gelation method by the use of different Polymers for enhancing the controlled release of drug.

Morphological investigations showed that Microspheres were spherical in shape, having mean diameter of 589.3µm. Selection of the appropriate experimental conditions resulted in

the production of Ciprofloxacin loaded Microspheres and **F3** batch was found to be the optimized formulation having high entrapment efficiency of 89.15% (w/w) and high percent cumulative drug release of 86.32 % (w/w) at 12th hr which showed that Ciprofloxacin Microspheres have the potential for prolonged drug release.

Over three months of investigation on stability at 4 ± 1°C and room temperature, formulation shows faster degradation at higher temperature. The results indicate that the ideal storage temperature for the Microspheres is a cold place.

Hence, it can be concluded that it is possible to design Ciprofloxacin loaded Microspheres for the treatment of Bacterial infections where efficacy and patient compliance are of prime importance.

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