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# Formulation and Characterization of Floating Gastroretentive Drug Delivery System of Ciprofloxacin Hydrochloride

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**ABSTRACT: Objectives:** The main objective of this study was to develop and evaluate the ethyl cellulose and HPMC coated ciprofloxacin hydrochloride floating microspheres.

**Methods:** The floating microspheres were prepared by the solvent evaporation method incorporating ciprofloxacin hydrochloride. The prepared floating microspheres were characterized for particle size, % yield, % drug loading and % entrapment efficiency, compatibility study, % buoyancy, surface morphology, and in vitro drug release and kinetic release.

**Results:** The result ciprofloxacin hydrochloride loaded floating microspheres was successfully prepared and the particle size range from109.32 to 289.77µm and the entrapment efficiency range from 81.33 to 84.82%, the capacity range from drug loading 15.29 to 17.12%, and the buoyancy range 68.71 to 89.64%. The FTIR inveterate no interaction between drug and excipients and surface morphology confirmed rough surface. The floating microsphere shows a maximum of 96% drug release in pH 0.1N HCl and follows the Korsmeyer Peppas model of the super case-2 transport mechanism.

**Conclusion:** The conclusion suggests that ciprofloxacin-loaded floating microspheres could be retained in the stomach for elongated time and give site-specific drug release in a controlled manner.

**Keywords:** Floating capability, Ethyl Cellulose, and Ciprofloxacin

## I. INTRODUCTION

The oral transmit is full as a highest gifted technique of drug provision. The oral drug deliverance retains been identified for decades as the greatest commonly used route of administration among all the ways that have been explored for the complete delivery. Floating microspheres are gastro-retentive drug manner systems based on non – effervescent approaches [1]. However, this way has various physiological issues, i.e. gastric emptying time, in which GIT time was (8-12hrs), and with the presence of intestinal absorption window of different drugs [2]. All these difficulties provoked the investigators to upgrade a DDS which acts upon its pharmacological action into the GIT for a considerable quantity of time. Numerous complications are handled in designing controlled released systems for improved absorption and enhanced bioavailability. The control of gastrointestinal transit of orally administered dose forms by being able to enhance the bioavailability of drugs, preserve exhibit site-specific absorption. Extended gastric retention can be achieved by using floating, swelling, bio-adhesive, or high-density systems [3]. Microspheres are well-defined as homogenous, huge particles in the magnitude sort of about 1µm-1000 µm and are generally used as carriers for controlled release. These systems give big imperative in biomedical application [4].

Ciprofloxacin hydrochloride is a broad-spectrum antimicrobial carboxylic fluoroquinolone. It is used for the treatment of urinary region contamination, intensely uncomplicated cystitis, lower respiratory area infection, skin and skin structure diseases, bone and combined contamination. It is water-soluble in water and belongs to class III. Ciprofloxacin hydrochloride is more absorbed from the stomach and the proximal part of the intestine and the bioavailability 70%, which can be improved when the drug is incorporated in the floating microspheres.

## II. MATERIALS AND METHODS

Ciprofloxacin hydrochloride was a gift sample from Intas Pharmaceutical Ltd., Dehradun. India. HPMC was procured from the LOBA Chem. Pvt. Ltd., Mumbai, and the ethylcellulose was procured from the Central Drug House Pvt. Ltd., New Delhi. All the chemicals and solvents used in the study were of analytical grade.

### Preparation of floating microspheres

Floating microspheres were prepared by emulsion solvent evaporation method using a

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varying concentration of HPMC, ethyl cellulose. Polymer mixture was formulated by mixing polymers (HPMC, Ethylcellulose) in a different ratio to a mixture of solvents (ethanol, dichloromethane) with vigorous shaking, and an aqueous solution containing tween80 was taken in another beaker. The polymer solution was then added, manually drop-wise into the aqueous solution through a syringe (needle size 22 gauges) under continuous stirring at 100 rpm. The extra droplets were kept dispersed in the aqueous solution for 30 minutes and to a circular profile. After preparing the blank microspheres, drug-loaded microspheres were prepared by solvent evaporation method according to the above-described method with varying concentrations of polymers (HPMC, Ethylcellulose) and drug. The composition of the floating microspheres is given in table no.1 and the method given in the figure. 1[5].

**Table 1: Composition of the floating microspheres of each batch**

| TrialNo. | Formulation Code | Ethyl Cellulose (mg) | HPMC(mg) | DCM+ Ethanol(ml) (1:1) | Drug (mg) | Aqueous phase containing 1% Tween 80(ml) |
|---|---|---|---|---|---|---|
| 01. | F-1 | 100 | 50 | 6 | 0 | 10 |
| 02. | F-2 | 200 | 50 | 6 | 0 | 10 |
| 03. | F-3 | 300 | 50 | 6 | 0 | 10 |
| 04. | F-4 | 400 | 50 | 6 | 0 | 10 |
| 05. | F-5 | 400 | 50 | 6 | 100 | 10 |
| 06. | F-6 | 400 | 50 | 6 | 150 | 10 |
| 07. | F-7 | 400 | 50 | 6 | 200 | 10 |

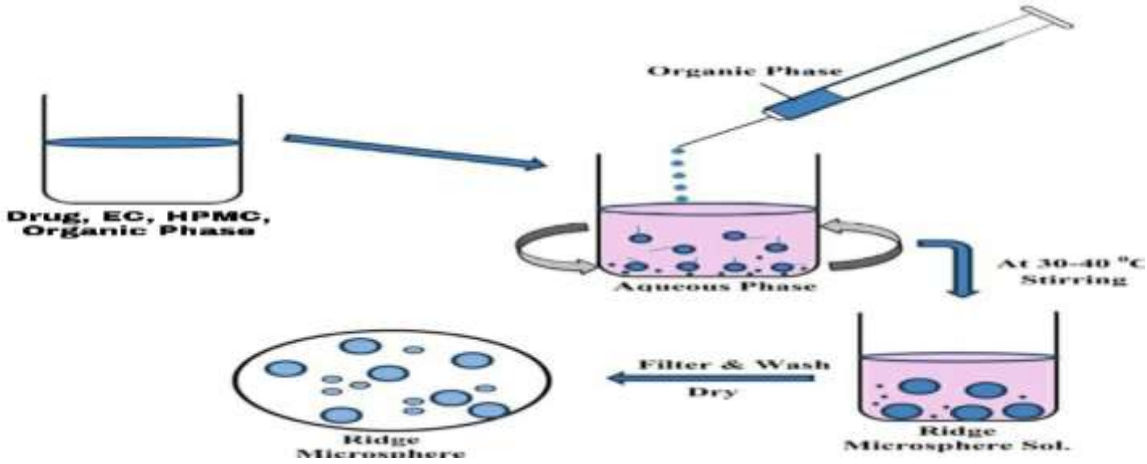


**Figure 1: Preparation of floating microspheres**

**PARTICLE SIZE**

The particle size of the blank and ciprofloxacin hydrochloride-loaded microsphere was determined by optical microscopy method using a compound microscope (Olympus) equipped with ocular and calibrated step micrometers. The particle size is determined after the calibration of the ocular micrometer by placing the ocular lens and focusing on the object to be measured and determine the size in ocular units, then placing the samples on the slide and measuring the size of microspheres [6].

One ocular unit $= \frac{\text{divisio n(mm )stage micrometer}}{\text{ocular micrometer division}} \times 100\mu m/mm$

**PERCENTAGE YIELD**

The % yield of the blank and ciprofloxacin hydrochloride microspheres was calculated by measured wt. of microspheres obtained separated

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by the total amount of all excipients and drug used [7].

$$\% \text{ Yield} = \frac{\text{Weig ht of the microsp heres obtained}}{\text{total weig ht of the drug and excipients}} \times 100$$

## PERCENTAGE BUOYANCY

The % buoyancy of the microspheres was calculated by placing the 500mg of the microspheres in a USP dissolution type II instrument filled with 900 ml of 0.1 N hydrochloric acid consisting 1% w/v of tween 80 with stirring for 12 hrs at 50 rpm. After twelve hrs the particles of floating particles and the precipitated particles were taken out dried and weighed. Percentage buoyancy was determined by the following formula [8].

$$\text{Percentage buoyancy} = \frac{wF}{wf + ws} \times 100$$

Where, wf= Weight of floating particles, ws=Weight of settled particles

## DETERMINATION OF DRUG CONTENT OF MICROSPHERES

The 50 mg ciprofloxacin-loaded microspheres were dissolved in a few ml of Ethanol and diluted with 50 milliliters of 0.1N hydrochloric acid in a 100 ml volumetric flask and the mixture was shaken until the formulation was distracted. The solution was passed through Whatman Filter Paper (No. 41) [9].

$$\text{Loading drug content} = \frac{\text{wt.of MHin the microsp heres}}{\text{wt.of the microsp heres}} \times 100$$

## DRUG ENTRAPMENT EFFICIENCY (E.E)

E.E. of microspheres was determined by extraction of drug from the microspheres. Accordingly, a weighed sample of dried microsphere was crushed in a mortar & pestle. The powdered microspheres were dissolved in a few ml of Ethanol and diluted with 50 mL of 0.1N HCL for 24 hours. After 24 hours, the solution was passed through a 0.45µm filter and the conc. of the ciprofloxacin hydrochloride present in the filtrate was evaluated spectrophotometrically at 275 nm using UV-Visible Spectrophotometer with respect to 0.1N HCL as blank [5].

$$\text{DEE} = \frac{\text{wt.of CH in microsp heres}}{\text{wt.of the fed CH}} \times 100$$

## MORPHOLOGICAL CHARACTERIZATION

The shape and size of ciprofloxacin hydrochloride-loaded microspheres were assessed by SEM. The samples were organized by mounting sample onto a metal stub with adhesive tape on both sides. Carbon coating was done in a high vacuum evaporator. Then the process of scanning and taking images was done [10].

## MICROMERTIC PROPERTIES OF MICROSPHERES

Floating microspheres were characterized by their micromeritic properties like bulk density, tapped density, carr's index, Hausner's ratio, and angle of repose [11].

**BULK DENSITY (B.D.):** For calculation of bulk density floating microspheres were placed in a measuring cylinder and observed the volume occupied by the sample. The initial volume was calculated. B.D. was calculated using the formula [12].

$$\textbf{Bulk density} = \frac{M}{V^{\circ}}$$

Where, M = Weight of microsphere sample, $V^0$ = Apparent volume of the microsphere

**TAPPED DENSITY (T.D.):** T.D. was calculated by mechanical tapping of a graduated measuring cylinder which consists of the microspheres. It is the ratio of the initial microsphere volume with the tapped volume of microsphere (after tapping) [13].

**COMPRESSIBILITY INDEX (C.I.):** The compressibility index is a tendency of microspheres to be compressed. It's calculated by this formula.

$$\textbf{CI} = \frac{TD - BD}{TD} \times 100$$

Where, TD =Tapped Density, BD = Bulk Density

**ANGLE OF REPOSE:** This property was evaluated by the maximum angle possible b/w the surface of the pile of the microspheres & the horizontal flat surface, it found by the funnel in a fixed position [13].

$$\theta = \tan^{-1}(h/r)$$

Where, θ- angle of repose, h- the height of pile,r- the radius of pile

**HAUSNER'S RATIO (H.R.):** By calculating TD and BD Hausner's ratio for microspheres were estimated by use of the following equation:

$$HR = BD/TD$$

**FTIR STUDY:** The FTIR study of drug-loaded & empty preparation was achieved to find any possible drug polymers interaction using FT-IR (Perkin Elmer Spectrum., U.K.) in the series of frequency 4000 to 400 cm¹ [14].

## IN VITRO DRUG RELEASE STUDY

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In-vitro drug release was performed in USP dissolution apparatus type 1, which rotates at 100rpm in 900 ml of 0.1N HCL, pH 1.2 which serves as dissolution fluid, and the temperature was maintained at 37C. Samples were taken at a suitable interval of time and analyzed spectrometrically at 275 nm. To maintain sink condition the same quantity was refilled by fresh dissolution medium. Then cumulative drug release % was calculated.

**IN VITRO RELEASE KINETICS STUDY :**

To investigate the drug release mechanism from the microspheres, in-vitro drug release data was fitted to many kinetic models like zero order, first order, Higuchi equation, and Korsmeyer-Peppas equation. By comparing the r values obtained, the best fit model was selected [15,16].

- **Zero Order Kinetics**

Dissolution of the drug from the dosage forms that do not disaggregate and release the drug slowly can be represented by the following equation:

$Qt = Q0 + K0t$

Where, Qt, - the amount of drug dissolved in time t, $Q_0$- is the Initial amount of drug in the solution and $K_0$ is the zero-order release rate constant. To study the release kinetics, statistics found from the in vitro drug release studies were graph as % CDR vs. Time.

- **First Order Kinetics**

This kinetics model has been used to define the absorption or elimination of drugs. The release of the drug following first-order kinetics can be expressed by the following equation.

$$LogC=logC_0 - \frac{Kt}{2.303}$$

Where C is the amount of drug release in time t, $C_0$ is the amount of drug in the solution and K is the first-order release rate constant. To study the release kinetics, data obtained from the in-vitro drug release studies were plotted as log % drug unreleased vs. Time.

- **Higuchi Model**

This model defines the release of $H_2O$ soluble and low water-soluble drugs from the solids or semisolid matrix system. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. The arithmetical expression of the higuchi model is as follows:

$$Qt = KH.t^{1/2}$$

Where Qt is the amt. of drug release in time t and $K^H$ is the Higuchi dissolution constant. To study the release kinetics, data found from the in vitro drug release were plotted as % CDR vs. Square Root of Time [17].

- **Korsmeyer-Peppas Model**

Peppas model used to describe the release of drug from the polymeric system when the release mechanism is not recognized or more than one type of release phenomena could be involved. The equation of the Korsmeyer-Peppas model is as follows:

$$\frac{Mt}{M\infty}=Kt^n$$

Where $\frac{Mt}{M\infty}$ -is the fraction of drug release, K- is the constant release rate, [redacted] the release exponent

To study the release kinetics, figures obtained from the in vitro drug release were plotted log % CDR vs. log time. Peppas used this n-value to characterized dissimilar release mechanisms as given in Table. 2

**Table 2: Different release mechanism:**

| Diffusion release exponent (n) | Overall drug diffusion mechanism | Time-dependence of drug release rate ($dM_t/dt$) |
|---|---|---|
| Higher than 0.89 | Super case II transport | $t^{n-t}$ |
| 0.89 | Case II transport | Zero-order (time-independent)release |
| 0.45<n=0.89 | Non-Fickian Diffusion | |
| 0.5 | Fickian Diffusion | |

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## III. RESULTS AND DISCUSSION

The ciprofloxacin hydrochloride-loaded microspheres were prepared by emulsification (o/w) solvent evaporation method according to the above-described method by the variable concentration of polymers (HPMC, ethylcellulose) & ciprofloxacin.

### CHARACTERIZATION AND OPTIMIZATION OF THE FORMULATIONS

### % YIELD & PARTICLE SIZE

The particle size of the optimized formulation was determined by optical microscopy. The particle size of the formulations were found to be in the range 109.32 to 289.77µm. The % yield of the formulations from F1 to F4 were calculated. % yield of the formulation F4 was found to be higher i.e. 71.45%. Then the other three may be due to reason of higher proportion of EC. So, new formulations F5, F6, and F7 were prepared by loading the formulation F4 with varying amounts of the drug.

On loading with 100mg of drug F5 was found to be 80.73% and further increasing amount of drug to 150mg in formulation F6, the % yield was improved to 87.59%. On additionally increasing amount of drug to 200mg in formulation F7, the % yield was increased.

The higher % yield was found to be for formulation F7 as results shown in table- 3

**Table 3: %YIELD & PARTICLE SIZE**

| Formulation | % Yield | Particle size (µm) |
|---|---|---|
| **F1** | 51.11 ± 0.02 | 109.32 ± 1.00 |
| **F2** | 49.74 ± 0.07 | 209.18 ± 1.20 |
| **F3** | 57.70 ± 0.01 | 242.20 ± 0.90 |
| **F4** | 71.45 ± 0.06 | 199.78 ± 0.32 |
| **F5** | 80.73 ± 0.04 | 281.28 ± 0.92 |
| **F6** | 87.59 ± 1.10 | 230.21 ± 1.14 |
| **F7** | 89.83 ± 0.14 | 289.77 ± 1.11 |

Data are presented as mean±SD (n=3)

### % BUOYANCY OF THE FORMULATION

The %buoyancy of the formulation was found to be between 68.71% to 89.64%, respectively. So, a large number of microspheres stay floated after 12 hours. The % buoyancy of formulation F1-F3 was found to be between 68.71% to 70.95%. Lower values of % buoyancy were because of less proportion of EC.

However, % buoyancy of formulation F4-F6 were found to be between 78.37-89.64%, respectively. The % of buoyancy was observed to increase from the formulations F4 to F6. The reason behind this is the increase in the amount of EC and drug amount. But the % buoyancy of formulation F7 was found to be 84.23%. Which is low because of a higher amount of drug which may report the air bubble inside the microspheres. The table-4.

**Table 4:** % Buoyancy

| Formulation | % Buoyancy |
|---|---|
| **F1** | 68.71 ± 0.14 |
| **F2** | 69.43 ± 0.13 |
| **F3** | 70.95 ± 0.10 |
| **F4** | 78.37 ± 0.09 |
| **F5** | 82.52 ± 0.04 |
| **F6** | 89.64 ± 1.16 |
| **F7** | 84.23 ± 0.15 |

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**DRUG LOADING & DRUG ENTRAPMENT**

The % Drug loading & % Entrapment efficiency of the formulation were found to be between 15.29% to 17.12% and 81.33 to 84.12%, respectively. Out of the three drug-loaded formulations (F5-F7), the formulation F7 was found to have maximum % drug loading and maximum % entrapment efficiency due to the higher amount of drug content.

The drug loading and entrapment efficacy of formulations were determined by the direct extraction method and the results are shown in Table- 5.

**Table 5: Drug loading and entrapment efficiency**

| Formulation | % Drug Loading | % Drug Entrapment |
|---|---|---|
| **F5** | 15.29 ± 0.40 | 81.33 ± 0.09 |
| **F6** | 17.02 ± 0.38 | 83.88 ± 0.11 |
| **F7** | 17.12 ± 0.09 | 84.12 ± 0.08 |

**MICROMERITIC PROPERTIES :**

The floating microspheres of Ciprofloxacin hydrochloride were formulated via the emulsion solvent evaporation method. The bulk density of formulations were found in the range from 0.126 to 0.178. The tapped density of formulations were found in the range from 0.175 to 0.325. The angle of repose of formulations were found in the range from 26.30 to 33.42. The angle of repose of formulation F 5 and F6 was found to be less than 25°. So, the flow was excellent for the two formulations. The Hausner's ratio of the formulation was found in the range of 1.10 to 2.57. Only the formulation F5 and F6 shown Hausner's ratio of less than 1.25, which confirms the excellent flowability of formulation F5 and F6. The Carr's Index of the formulation F1 to F7 was found in the range between 9.83 to 61.23% and the formulation F5 and F6 were found to have excellent flow-ability as the values are between 5 and 1.5. and F7 to have fair flowability due to carr's index of 18.01. So, all micromeritic properties were observed to be in a suitable range for all formulations F5 and F6. The results are shown in Table 6.

**Table no. 6: Micromeritic Properties**

| Formulation | Bulk density (g/ml) | Tapped density (g/ml) | Angle of repose (ɵ) | Hausner's ratio | Carr's index |
|---|---|---|---|---|---|
| **F1** | 0.126 ± 0.02 | 0.325 ± 0.04 | 26.30 ± 0.03 | 2.57 ± 0.03 | 61.23 ± 0.02 |
| **F2** | 0.134 ± 0.03 | 0.310 ± 0.03 | 27.29 ± 0.01 | 2.31 ± 0.06 | 56.77 ± 0.05 |
| **F3** | 0.138 ± 0.05 | 0.281 ± 0.04 | 28.31 ± 0.4 | 2.03 ± 0.08 | 50.88 ± 0.08 |
| **F4** | 0.163 ± 0.06 | 0.241 ± 0.09 | 29.35 ± 0.8 | 1.47 ± 0.12 | 32.36 ± 0.12 |
| **F5** | 0.165 ± 0.04 | 0.183 ± 0.15 | 19.37 ± 0.03 | 1.10 ± 0.15 | 9.83 ± 0.15 |
| **F6** | 0.170 ± 0.09 | 0.175 ± 0.20 | 24.30 ± 0.09 | 1.18 ± 0.20 | 12.21 ± 0.10 |
| **F7** | 0.178 ± 0.12 | 0.230 ± 1.10 | 33.42 ± 0.06 | 1.25 ± 0.22 | 18.01 ± 0.09 |

**OPTIMIZATION OF FORMULATION**

Formulation F6 was found to be optimized based on % yield, % buoyancy, % drug loading, % entrapment efficiency, and various micromeritic properties. Further studies i.e. FTIR study, scanning electron microscopy, and % drug released were performed on the optimized formulation (F6).

**DRUG POLYMER COMPATIBILITY STUDY**
**FTIR STUDY**

FTIR spectra were recorded to assess the compatibility of the pure drug and formulated compound. The FTIR spectrum of optimized formulation F6 of microspheres was recorded separately and compared with the spectrum of blank microspheres to verify the possible interaction between the constituent and the characteristic peaks are shown in Figure-2, & 3. The results showed that there is no chemical interaction took place during the formulation of microspheres and the drug was found to be compatible with the polymer.

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**Spectrum**

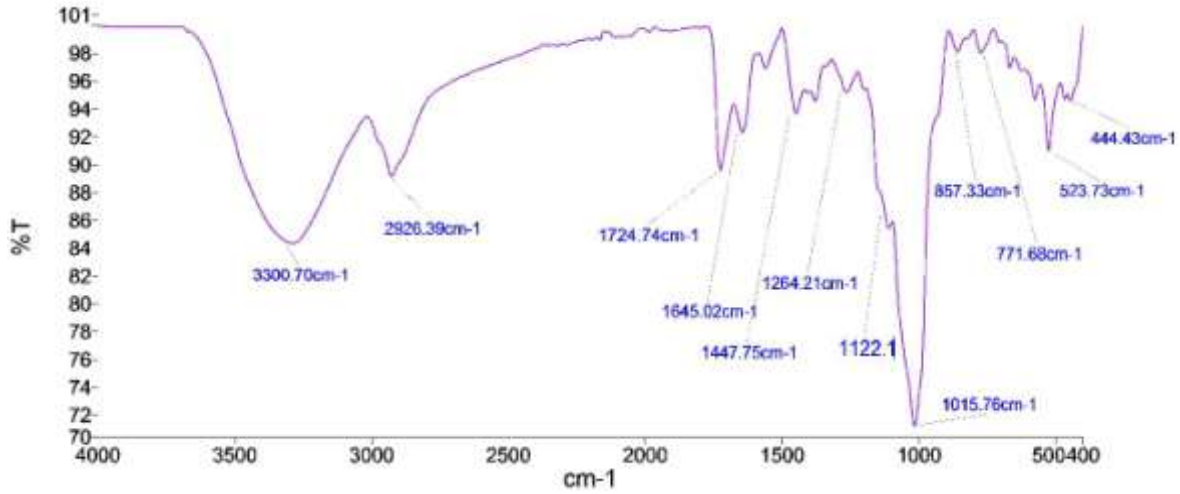


**Fig.2:** FTIR spectrum of the blank floating microspheres

**Spectrum**

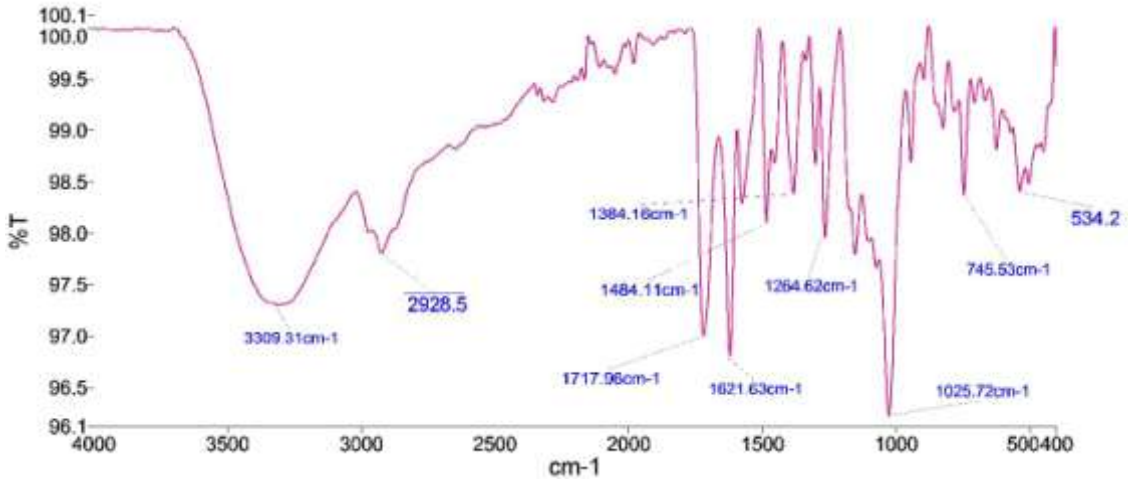


**Fig.3:** FTIR Spectrum of the optimized ciprofloxacin loaded microspheres

**SEM (Scanning Electron Microscopy)**

The morphological examination of the surface was carried out using scanning electron microscopy and characterization of optimized formulation (F6) was conducted by SEM analysis. The microspheres were found to be having a rough surface. The SEM photograph of microspheres is shown in Figure-4.

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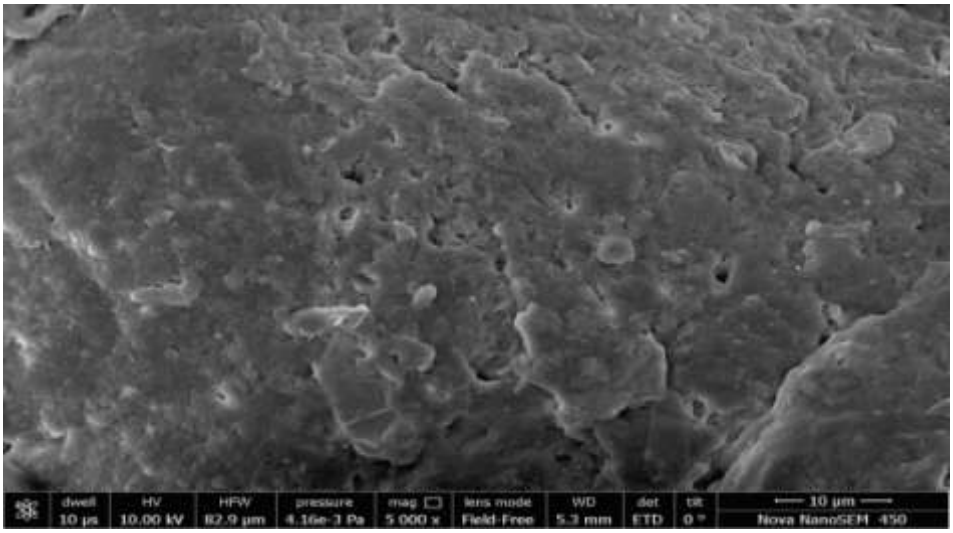


**Fig.4:** SEM of optimized drug-loaded microspheres

**IN-VITRO DRUG RELEASE STUDY**

The in-vitro study of optimized formulations (F6) was performed by using USP Dissolution Test Apparatus Type 1 (Basket Type) in 0.1N HCL. The percentage release of ciprofloxacin hydrochloride from optimized formulation was investigated for 24 hours and the sample was analyzed in triplicate. The statistics obtained from in vitro release studies were fitted to different kinetic equations to find out the mechanism of drug release from the optimized drug-loaded formulation (F6). The kinetic models used were a zero-order equation, first-order equation, Higuchi model, and Korsmeyer-Peppas model. Drug release kinetics was best fitted for Korsmeyer-Peppas model kinetics as the $R^2$ value for the model was 0.9851 which was nearer to 1, than the $R^2$ value for the other models. The drug release mechanism was of super case-2 transport as the release exponent, n was found to be 0.2317, which was greater than 1. The graphical representation of different kinetic models of in-vitro drug release profiles is shown in Figures 5 to 8 and Tables-7.

**Table. No.7. Regression Coefficient ($R^2$) value obtained from various formulations**

| Formulation Code | Zero-order | First-order | Higuchi model | Korsmeyer-Peppas |
|---|---|---|---|---|
| | ($R^2$) value | ($R^2$) value | ($R^2$) value | ($R^2$) value |
| **F-6** | 0.7641 | 0.7937 | 0.9322 | 0.9851 |

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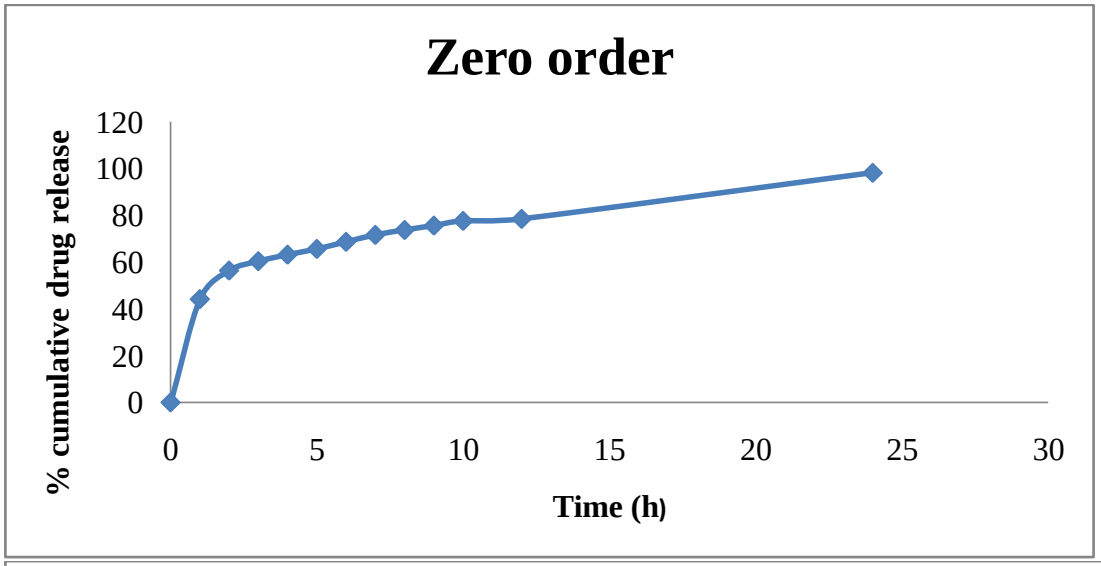


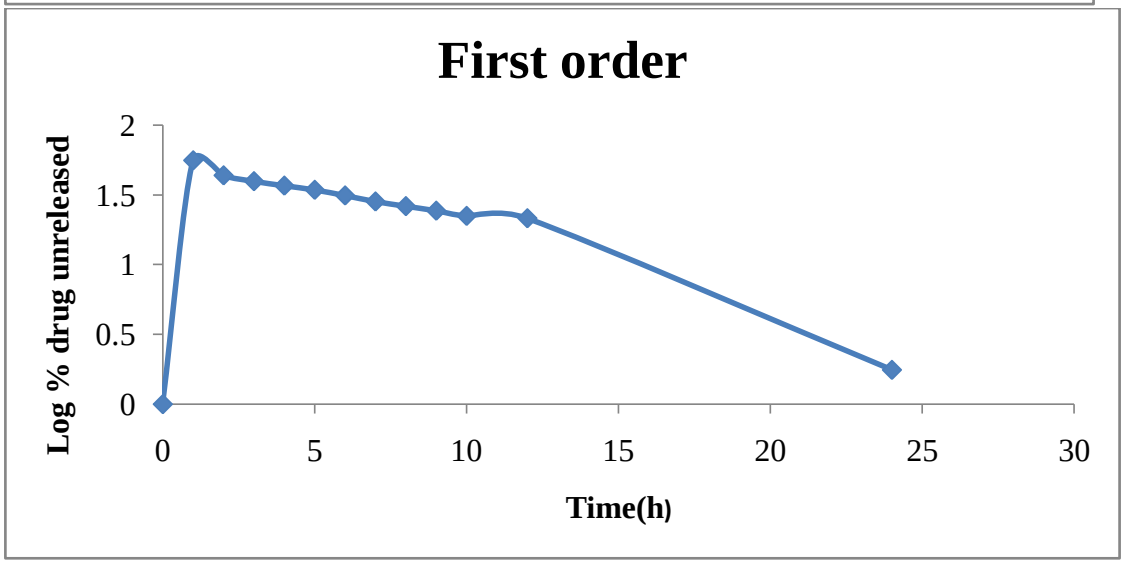


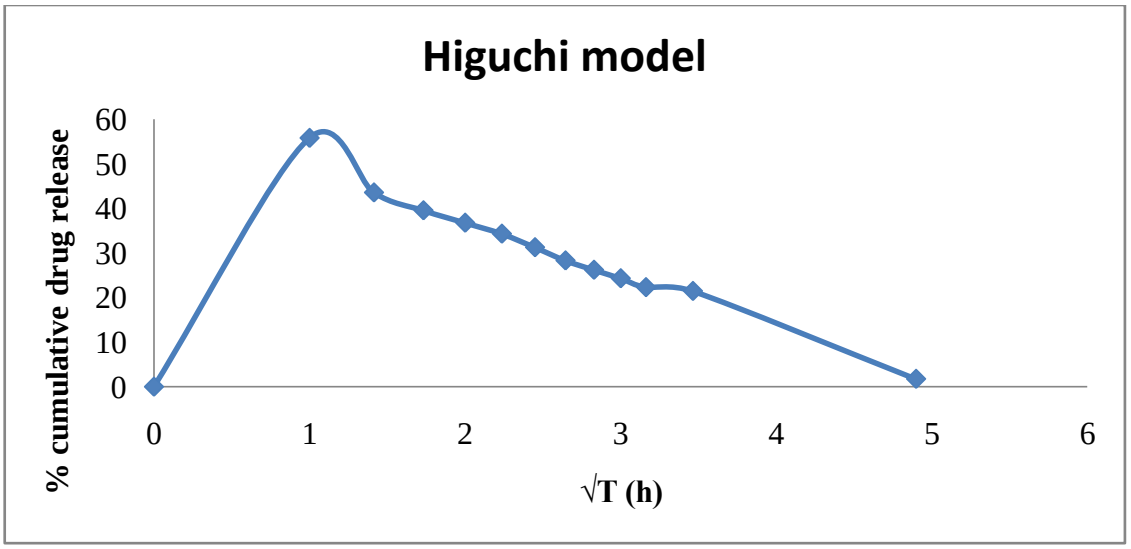

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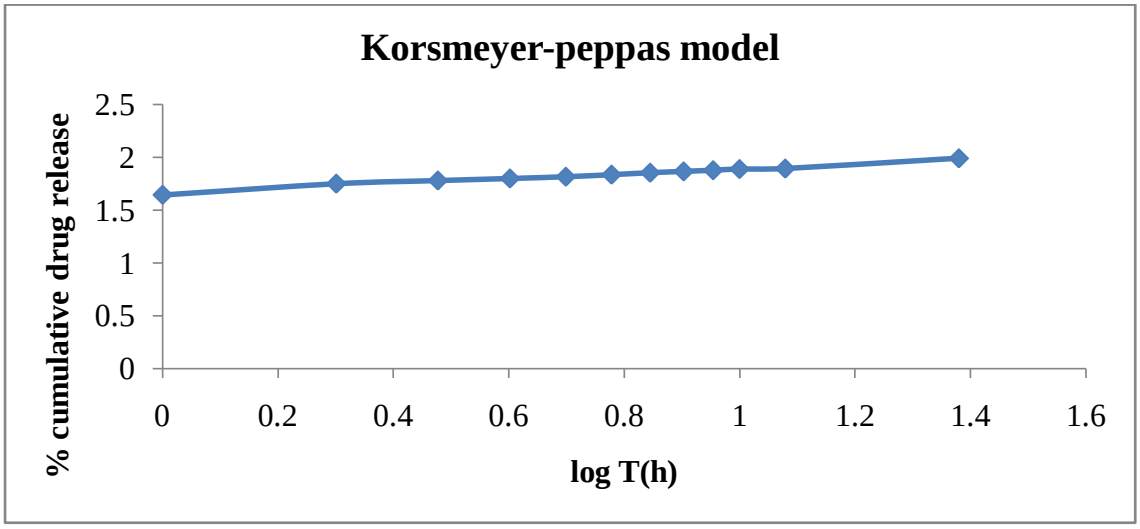


## IV. CONCLUSION

The goal of the current work, the HPMC and ethyl cellulose blend microspheres loaded with ciprofloxacin hydrochloride were formulated successfully by using of solvent evaporation technique. In current studies, seven formulations were formulated by using HPMC, EC, DCM, and ethanol in many proportions.

In pre-formulation studies, estimation of ciprofloxacin hydrochloride was carried out by Shimadzu UV Spectrophotometer at λmax 275nm using 0.1N HCl. The % yield was found to decrease with increasing the drug amount. The maximum % yield was found to be F7-89.83% and the particle size F7-289.77%. The higher % buoyancy of this formulation F6 was found to be 89.64%. The % buoyancy was observed to be affected by varying the proportion of polymer and drug. The maximum % drug loading formulation F7 was found to be 17.12% and the higher % entrapment efficiency was found to be formulation F7-87.12%.

Formulation F6 was found to be optimized based on % yield, % buoyancy, % drug loading, %entrapment efficiency, and micromeritic properties. The FTIR spectrum of optimized formulation (F6), were showed that near is no element interaction took place through the formulation of microspheres and the drug was found to be compatible with a polymer.

The SEM photomicrograph showed optimized floating microspheres (F6) with a rough surface. The in-vitro release studies presented that the microspheres were able to release drugs up to 24 hours, in a simulated gastric fluid. Drug release kinetics of F6 formulation was best fitted for the Korsmeyer-Peppas model and the $R^2$ value was found to be 0.9851, which was closer to 1, than the $R^2$ value of other models. The mechanism of drug released was observed to be super case-II transport and the release exponent, n was found to be 0.2317, which was greater than 1.

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**AUTHORS CONTRIBUTIONS**

Dr. Alok Mukerjee was a principal of my college United Institute of Pharmacy Prayagraj Naini, and also my project guide. Mukerjee Sir gives me a strong platform to perform this project. With the help of Mukerjee Sir, my college provided funding for the study, statistical support in analyzing data, and instrumental analysis.

Mr. Amit Kumar Singh worked as my co-guide. Singh Sir designed and conducted the study, data collection, and data analysis and too helped me with manuscript scheming.

I am Puja Prajapati carried out all works related to this assignment with the help of my guide, co-guide, and my colleague. And prepare all data that present in this manuscript and also design and sequence alignment and drafted all things in this manuscript.

All authors approved the final manuscript.

**CONFLICT OF INTERESTS**

The authors declare that they take part in no conflict of interest.

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