ejpmr, 2025, 12(6), 675-681

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

COMPARATIVE EVALUATION OF CIPROFLOXACIN HYDROCHLORIDE LOADED NANOPARTICLES USING NATURAL, SYNTHETIC AND SEMI-SYNTHETIC POLYMERS

Ganesh N. S.*, J. Adlin Jino Nesalin, Risha Jahana, Reinhard David and Vineeth Chandy

Department of Pharmaceutics, T. John College of Pharmacy, Bengaluru – 560083, Karnataka, India.

***Corresponding Author: Ganesh N. S.**

Department of Pharmaceutics, T. John College of Pharmacy, Bengaluru - 560083, Karnataka, India.

Article Received on 25/04/2025 **Article Revised on 15/05/2025** **Article Published on 04/06/2025**

ABSTRACT

The present study was undertaken with an aim to formulate and comparatively evaluate Ciprofloxacin hydrochloride loaded nanoparticles using natural, synthetic and semi-synthetic polymers. Nanoparticles were prepared by Nanoprecipitation technique using natural (chitosan), synthetic (PVA) and semi-synthetic (HPMC) polymers and its combinations. The influence of the polymer and combination of polymers was demonstrated. From the FTIR studies, the drug- polymer compatibility was confirmed. Evaluation studies like percentage yield, particle size, entrapment efficiency, drug content, and *in-vitro* dissolution study for formulations were performed. The drug entrapment efficiency was found to be in range of 41.3±0.12 - 83.56±0.25%. The drug content was found to be in the range of 48.59±0.17 - 87.44±0.30%. *In-vitro* drug release varied from 60.11 - 94.84%. The optimized formulation (F10) was further evaluated for SEM, FTIR studies and zeta potential. The optimized formulation (F10) showed good *in-vitro* drug release of 94.84% release at the end of 6th hour. From this study it could be concluded that the nanoparticles formulated using a combination of synthetic and semi-synthetic polymers by nanoprecipitation technique showed good entrapment efficiency, drug content and drug release.

KEYWORDS: Nanoparticles, Ciprofloxacin hydrochloride, Polyvinyl alcohol (PVA), Hydroxypropyl methylcellulose (HPMC), Nanoprecipitation.

INTRODUCTION

One of the most important essential paths in the technical breakthroughs of the top countries, nanotechnology has provided enhanced insights in a field of science and technology that is continually increasing with better ways. There is solid evidence that the use of nanotechnology in the medical area has improved the diagnosis and treatment of several disorders. Some of the drawbacks of traditional therapy can be avoided, and the therapeuticeffectiveness of the drug can be improved, by a well-designed controlled drug delivery system. The use of nanoparticles as drug carriers is one such strategy.[1]

Nanoparticles are defined as particulate dispersion or solid particles within the size range of 10 - 1000nm in which the drug is either dissolved, entrapped, encapsulated or attached to a nanoparticle matrix.[2] Depending on the preparation process used, such as solvent evaporation, nanoprecipitation, solvent diffusion, reverse salting out, ionotropic gelation, interfacial polymerization, emulsion polymerization, and desolvation method, nanospheres or nano capsules can be obtained.

Nanospheres are matrix systems in which the drug is physically and uniformly dispersed, while nano capsules are systems in which the drug is confined to a cavity surrounded by a unique polymeric membrane.[3] Biodegradable polymeric nanoparticles, particularly those coated with hydrophilic polymers have been used as potential drug delivery devices in the recent years because of their ability to circulate for a prolonged period time target a particular organ, as carriers of DNA in gene therapy, and their ability to deliver proteins, peptides, and genes.[4]

Controlling particle size, surface characteristics, and the release of pharmacologically active substances are the main objectives when designing nanoparticles as a delivery system to achieve the drug's site-specific activity at the therapeutically ideal pace and dosing regimen.[5] Solid lipid nanoparticles, metallic nanoparticles, liposomes, polymeric nanoparticles, nanocrystals and nanosuspensions, carbon nanotubes, and other types of nanoparticles are among the various types.[6,7]

MATERIALS AND METHODS

Materials

Ciprofloxacin hydrochloride was received as a gift sample from Pharma French Pvt. Ltd., Tamil Nadu, India. Chitosan, PVA and HPMC were procured from Loba Chemie Pvt. Ltd., Mumbai. Tween 80 was kindly provided by Karnataka Fine Chem., Bengaluru. Acetone was procured from S.D Fine Chemicals Ltd., Mumbai.

Pre-formulation studies of Drug Solubility of Ciprofloxacin hydrochloride

The solubility of Ciprofloxacin hydrochloride was performed in various solvents like water, ethanol, methanol, chloroform, acetone and DMF. Accurately 1mg of drug was transferred in a clean and dry test tube and dissolved in 5ml of the solvents individually and shaken vigorouslyand the solubility of the drug was checked visually.[8]

Infrared Spectroscopy of Drug

The compatibility of the drug and polymers were analyzed using an FTIR spectrophotometer. Infrared spectra of samples were recorded in Bruker. The spectra were recorded by placing the samples on a zinc selenoid crystal plate and screwing the anvel over the sample carefullyand scanning the samples in region of 4000-400 cm^{-1} to determine various functional groups.

Differential Scanning Calorimetry (DSC)

DSC (PerkinElmer-4000 series) experiments were carried out in order to characterize the physical state of the drugs. Sample of Ciprofloxacin hydrochloride were placed in aluminum pans and thermally sealed. The heating rate was 20°C per minute using nitrogen as the purgegas.

X-Ray Diffraction (XRD)

Ciprofloxacin hydrochloride was investigated by XRD (Rigaku model smart lab 3KW Japan). The generator was operated at a 40 –KV tube voltage and 40–mA tube current and used K α lines of copper as the radiation source. The diffraction angle ranged from 0°-80° (2Θ) in the step- scan mode (step width: $1.0°min^{-1}$).

FTIR spectrophotometer

The compatibility of Ciprofloxacin hydrochloride, Chitosan, PVA and HPMC were recorded by placing the samples on a zinc selenoid crystal plate and screwing the anvel over the sample carefully and scanning the samples in the region of 4000-400 cm^{-1} to determine various functional groups.

Formulation of Ciprofloxacin hydrochloride Nanoparticles

Ciprofloxacin hydrochloride Nanoparticles were prepared by Nanoprecipitation method.

Active Pharmaceutical Ingredient (API) and polymers was dissolved in miscible organic solvent such as acetone. The organic phase is supplemented with the aid of a syringe in a series of droplets into the aqueous phase containing a Tween 80 as the surfactant under stirring. The final preparation was continuously stirred in a magnetic stirrer at 1000 rpm to completely evaporate the solvent. The solution was centrifuged for half an hour. The precipitate obtained was then washed with distilled water and thus nanoparticles were obtained.[9]

Table 1: Formulation chart of Ciprofloxacin hydrochloride Nanoparticles.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ciprofloxacin hydrochloride(mg)	500	500	500	500	500	500	500	500	500	500	500	500
Chitosan (%w/v)	0.5	0.7	-	-	-	-	0.25	0.35	-	-	0.25	0.35
PVA (%w/v)	-	-	0.5	0.7	-	-	0.25	0.35	0.25	0.35	-	-
HPMC (%w/v)	-	-	-	-	0.5	0.7	-	-	0.25	0.35	0.25	0.35
Tween 80 (%w/v)	6	6	6	6	6	6	6	6	6	6	6	6
Acetone (ml)	15	15	15	15	15	15	15	15	15	15	15	15

Evaluation of Ciprofloxacin hydrochloride Nanoparticles Percentage Yield Determination

To determine the % yield of nanoparticles, the weight of the drug and polymers utilized and the weight of nanoparticles after drying were determined. The % yield of nanoparticles was calculated using the formula:

$$\%\ Yield = Total\ weight\ of\ nanoparticles\ formed / Total\ weight\ of\ drug\ and\ polymers\ used \times 100$$

Drug entrapment efficiency and Drug content

The entrapment efficiency and drug content of Ciprofloxacin hydrochloride loaded nanoparticles were determined by centrifugation at 1500 rpm for 2 hours using "Ultracentrifuge (Remi Instruments, Mumbai, India)". Then, the samples supernatant was pipetted, appropriately diluted with 0.1N HCl, and then analyzed using a "UV spectrophotometer" at 277nm. All the experimental units were analyzed in triplicates.[10]

The entrapment efficiency was calculated using following equations

$$Entrapment\ efficiency\ (EE)\ \% = (Amount\ of\ total$$

$drug - Amount\ of\ free\ drug)/\ Amount\ of\ total\ drug \times 100$

$Drug\ content\ (\%) = (Amount\ of\ total\ drug - Amount\ of\ free\ drug)/\ Amount\ of\ dry\ nanoparticles \times 100$

In-vitro Dissolution Study

The formulated Ciprofloxacin hydrochloride loaded nanoparticles were filled in capsule and checked for *in-vitro* dissolution study by type I dissolution apparatus by using phosphate buffer (pH 6.8). The dissolution apparatus temperature was maintained at 37°C and 50 rpm speed. Samples were collected in 30 min, 1, 2, 3, 4, 5 and 6th hour intervals. The collected samples were analyzed by UV spectrophotometric technique and %CDR was calculated.[11]

Evaluation of Optimized Formulation (F10)

Scanning Electron Microscopy

The powders were imaged by a scanning electron microscope (SEM) run at an accelerating voltage of 10kV using Hitachi SU 3500. The powder in few µg were fixed on to stub by a double- sided sticky carbon tape and kept inside the SEM chamber and analyzed at different magnification such as 60X, 200X, 500X, 1.10X and 2.50X respectively to obtain better clarity on the particle morphology.

FTIR spectrophotometer

Ciprofloxacin hydrochloride was recorded by placing the samples on a zinc selenoid crystal plate and screwing the anvel over the sample carefully and scanning the samples in the regionof 4000- 400 cm^{-1} to determine various functional groups. The IR spectra of the sample was checked for any possible drug excipients interaction and confirmed the chemical integrity of the given sample.

Zeta potential

Zeta potential was measured by photon correlation spectroscopy using Zetasizer (Malvern Zetasizer Nano ZS, UK; Malvern Instruments, Worcestershire, UK), which measures the potential range from -120 to +120 V. Zeta potential results of nanoparticles of optimized formulation (F10) was taken after diluting 20 times with buffer pH 1.

Kinetic analysis of *In-vitro* Release rates of Ciprofloxacin hydrochloride nanoparticles

The results of *in-vitro* release profile obtained for all the Ciprofloxacin hydrochloride nanoparticles were plotted in modes of data treatment as follows:

a) Zero-order kinetic model
b) First order kinetic model
c) Higuchi model
d) Korsmeyer equation / Peppas model
e) Hixson-Crowell model

RESULTS AND DISCUSSION

Solubility of Ciprofloxacin hydrochloride

The solubility of Ciprofloxacin hydrochloride showed that it was soluble in water, slightly soluble in ethanol, methanol and insoluble in chloroform, acetone and DMF implying purity of drug.

Infrared Spectroscopy of Drug

It was observed that the functional group peak frequencies were in resemblance to the standard range values of Ciprofloxacin hydrochloride (Figure 1). Thus, the presence of Ciprofloxacin hydrochloride can be confirmed.

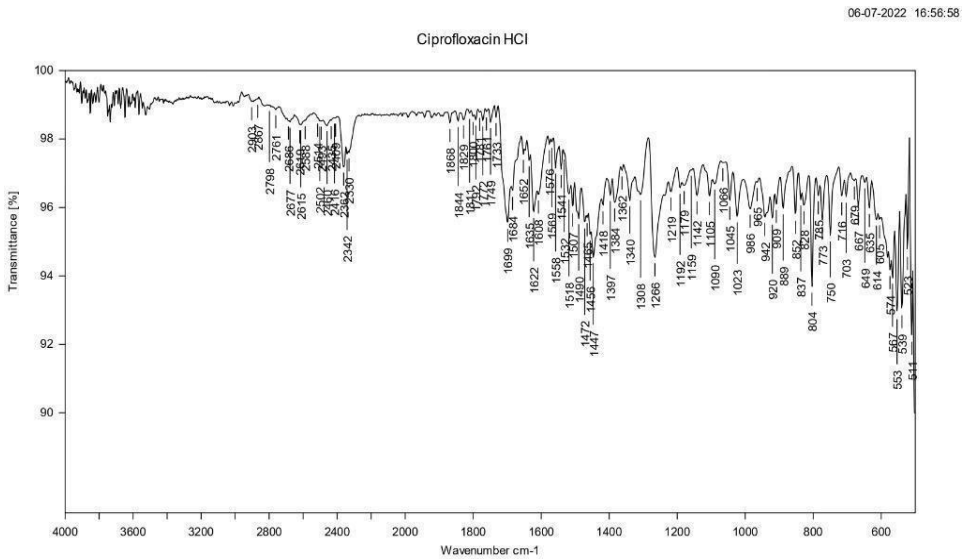

Figure 1: IR Spectra of Ciprofloxacin hydrochloride.

Differential Scanning Calorimetry (DSC)

DSC thermogram showed a sharp endothermic peak at 323ºC which is corresponding to the melting point of the drug (Figure 2). This value was found to be between the standard range of 293 - 323°C. Thus, the presence of Ciprofloxacin hydrochloride was confirmed.

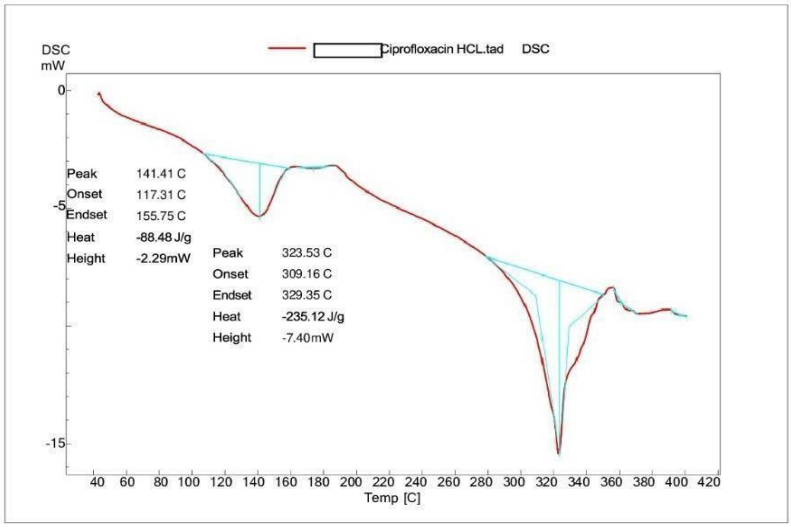

Figure 2: DSC of Ciprofloxacin hydrochloride.

X-Ray diffraction (XRD)

XRD graph is shown in Figure 3.

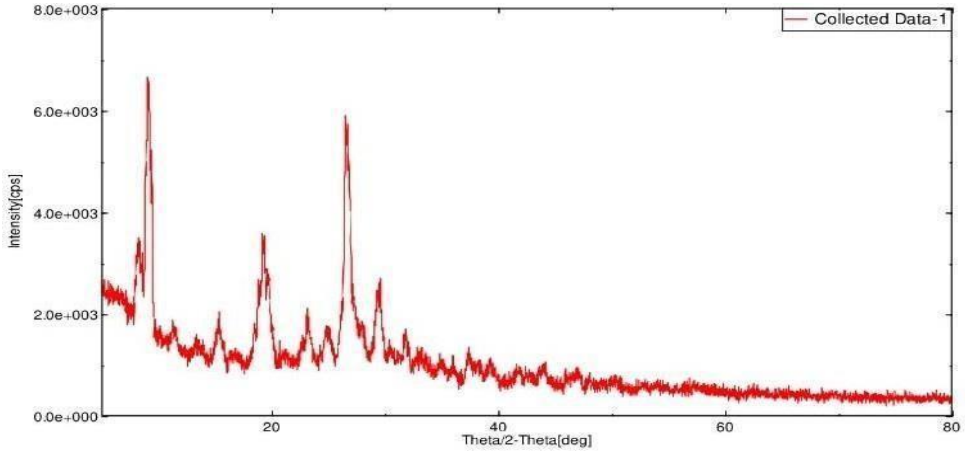

Figure 3: X-Ray diffraction of Ciprofloxacin hydrochloride.

FTIR spectrophotometer of combinations

The IR spectrum of Ciprofloxacin hydrochloride was compared with the polymers such as Chitosan, PVA and HPMC to check for any interaction as shown in Figure 4. These values were found to be between the standard range. Thus, they were compatible with each other.

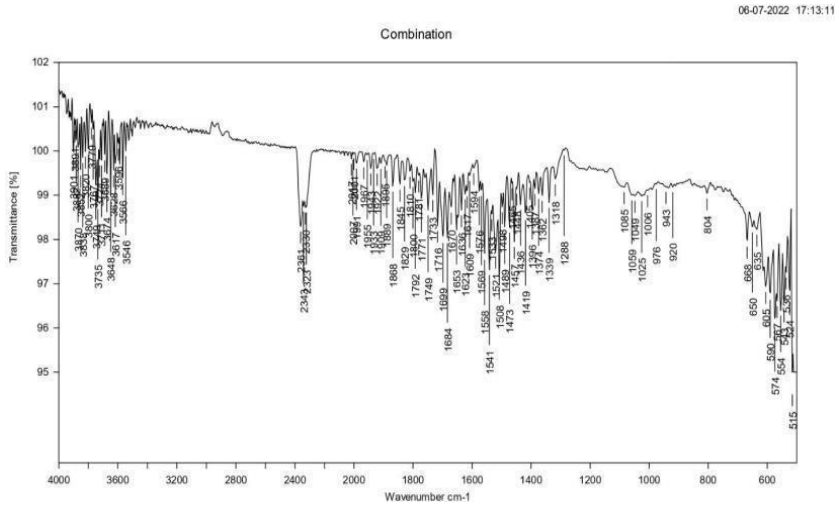

Figure 4: IR Spectra of Drug + Chitosan + PVA + HPMC.

Evaluation of Ciprofloxacin hydrochloride Nanoparticles

Percentage Yield Determination

The percentage yield of prepared Nanoparticles of Ciprofloxacin hydrochloride was found to be in the range of 52.64±0.02 - 74.30±0.04%.

Drug Entrapment Efficiency and Drug Content

The entrapment efficiency and drug content of Ciprofloxacin hydrochloride loaded nanoparticles were determined by centrifugation and was found to be in the range of 41.33±0.12 - 83.56±0.25% and 48.59±0.17 - 87.44±0.30% respectively.

***In-vitro* Dissolution Study**

In-vitro dissolution studies were carried out in pH 6.8 buffer for Ciprofloxacin hydrochloride nanoparticles containing different polymers such as Chitosan, PVA, HPMC and its combinations. The effect of polymers on drug release was observed. From the observation it was found that formulation of F1-F12 has shown drug release which ranged from 60.11%, 63.69%, 87.5%, 90.87%, 76.19%, 78.37%, 80.15%, 84.92%, 92.26%, 94.84%, 68.65%, 71.82% respectively (Figure 5) at the end of 6th hour.

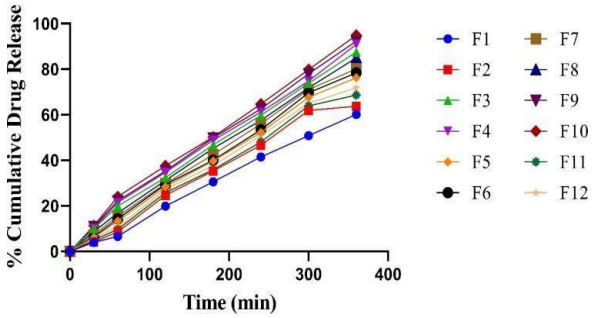

Figure 5: Percentage *in-vitro* drug release of API and formulation (F1-F12).

Evaluation of Optimized Formulation (F10)

Scanning Electron Microscopy (SEM) of optimized formulation (F10)

Nanoparticles of Ciprofloxacin hydrochloride were scanned using Scanning Electron Microscopy at different resolutions (shown in Figure 6).

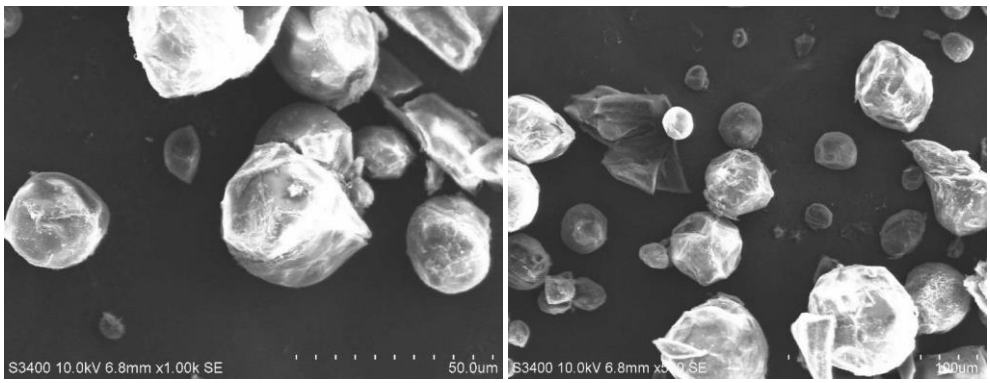

Figure 6: SEM images of optimized formulation (F10).

FTIR Spectrophotometer of optimized formulation (F10)

The IR spectrum of Ciprofloxacin hydrochloride was compared with the optimized formulation (F10) of nanoparticles as shown in Figure 7. These values were found to be between the standard range.

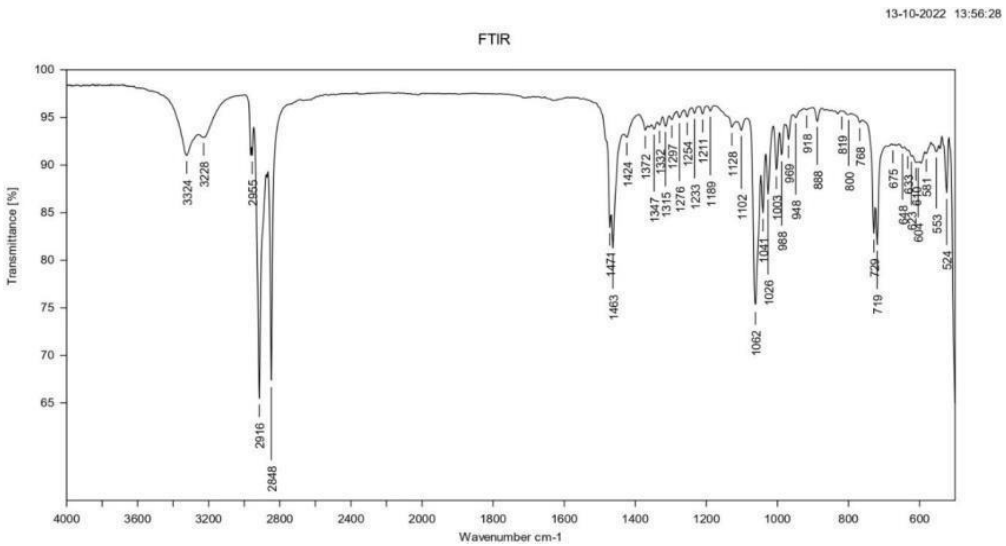

Figure 7: FTIR spectral data of optimized formulation (F10).

Zeta potential measurement of optimized formulation (F10)

The Zeta potential of Ciprofloxacin hydrochloride nanoparticles was carried out for the optimized formulation (F10) and the value observed was found to be – 19.5 (millivolts) whichindicates the prepared formulation was stable (Figure 8).

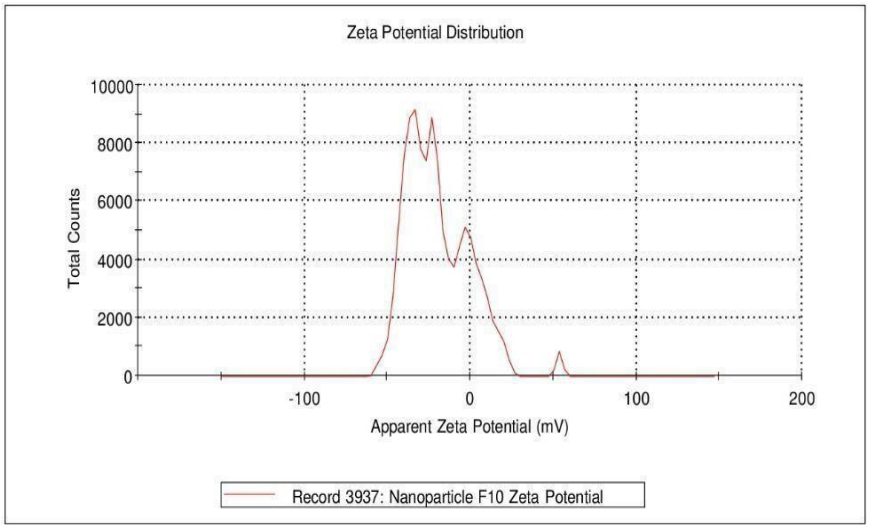

Figure 8: Zeta potential analysis by intensity of optimized formulation (F10).

Kinetic data of optimized formulation (F10)

The graphical representation of the Zero Order, First Order, Higuchi and Korsmeyer-Peppas plot for optimized formulation (F10) is illustrated in Figure 9 and the r^2 data is given in Table 2. From the r^2 values obtained we can project that the formulation follows Zero order kinetics. r^2 value of Higuchi plot was near to 0.9518. So, it was found that Higuchi model followed diffusion pattern of drug release which perfectly fits to describe drug release from Ciprofloxacin hydrochloride nanoparticles. The results of *in-vitro* release data were fit to Korsmeyer-Peppas equation, the n value obtained was 0.81 which helps us to predict that the formulation doesn't follow Fickian release.

Table 2: Kinetics studies of optimized formulation (F10) (r^2).

Formulation	Zero Order	First Order	Higuchi Plot	Korsmeyer-Peppas
	r^2	r^2	r^2	r^2
Optimized formulation F10)	0.9938	0.6731	0.9518	0.9974

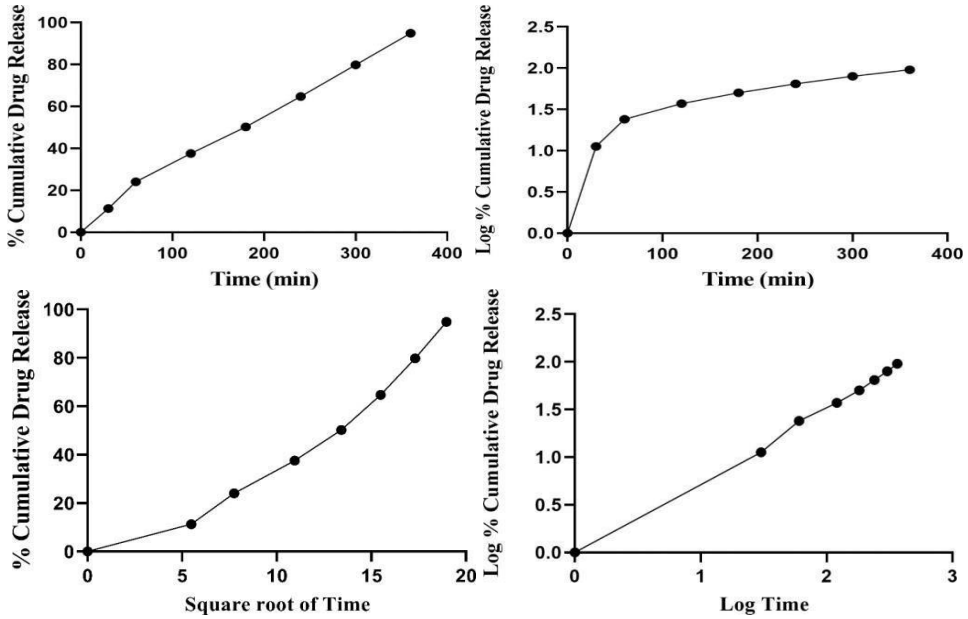

Figure 9: Kinetic study of a) Zero order plot b) First order plot c) Higuchi plot d) Korsmeyer-Peppas plot of optimized formulation (F10).

CONCLUSION

Ciprofloxacin hydrochloride nanoparticles were successfully prepared in the present work using nanoprecipitation method. The newly formed nanoparticles were characterized for several parameters like morphological characters, percentage practical yield, entrapment efficiency, drug content, *in-vitro* release study. The Nanoparticles prepared with a combination of natural, semi-synthetic and synthetic polymers showed an increase in the drug release when compared to the nanoparticles prepared with a single polymer and was selected as the optimized formulation (F10). The optimized formulation (F10) was further evaluated for Scanning electron microscopy (SEM), FTIR, Zeta potential analysis and kinetic studies. Hence, from the above obtained data it can be summarized that it is possibleto formulate Ciprofloxacin hydrochloride nanoparticles using different polymers (natural, synthetic and semi-synthetic) and its combinations by nanoprecipitation technique.

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