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Innovative Biodegradable Polymer Hydrogel Beads for Enhanced Controlled Drug Delivery: Formulation and Characterization

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To address this, our research pioneers the development of Cefixime-loaded controlled-release hydrogel beads using biodegradable polymers, an innovative approach designed to optimize antibiotic delivery and combat resistance. This study's novelty lies in utilizing chitosan, a natural, biocompatible polymer, for sustained drug release in the gastric environment. The hydrogel beads were engineered through ionic gelation, with tripolyphosphate (TPP) acting as the crosslinking agent, allowing for a stable, controlled release formulation. Key analyses included FTIR spectroscopy for structural confirmation, drug entrapment efficiency (DEE) for measuring Cefixime retention, and in vitro release studies to assess the extended-release profile. This research contributes to the field of controlled drug delivery systems by offering a practical solution to prolong antibiotic efficacy, particularly in regions facing high rates of bacterial resistance. The application of such a system could revolutionize treatment strategies, minimizing resistance development while ensuring effective drug levels over extended periods. The entrapment efficiency of hydrogel beads with Cefixime trihydrate ranged from 92.17±0.92% to 61.82±0.45%. Among all formulations, F3 demonstrated sufficient drug release in vitro. Kinetic analysis revealed that all formulations had an n (release exponent) value greater than 1, indicating super Case II transport, in which the swelling and erosion of the polymer matrix controlled the drug release rate.

Keywords: Biodegradable drug carriers; Crosslinking in hydrogel formation; Controlled release; Gelation process in hydrogels; Kinetic profile; In-vitro drug release.

The main objective in designing an oral controlled drug delivery system should be to improve the predictability and bioavailability of the medication. In many developing countries, infectious diseases are prevalent, with bacterial pathogens being a significant concern. Cefixime trihydrate is a broad-spectrum antibiotic that targets various bacteria, including *Branhamella catarrhalis, Proteus mirabilis,* and *Proteus vulgaris*. By binding to penicillin-binding proteins that are involved in the biosynthesis of peptidoglycan, a major building block of the cell wall of Gram-positive bacteria. This inhibits bacterial growth by disrupting cell wall formation action. According to The Japan Times,[1,2] cefixime trihydrate is used for the treatment of infections including bronchitis, urinary tract infections and gonorrhoea as well as various forms of ear, throat and tonsil infections. It is also used with other drugs to treat some types of bacterial infections that occur during a cold or flu.[3,4]

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Cefixime trihydrate has limited solubility in water and 0.1 M HCl, but it can dissolve in methanol and 0.1 M NaOH. This limited solubility and narrow absorption window result in low oral bioavailability. Due to its short half-life of approximately three hours, frequent dosing is required to maintain effective antibacterial levels. However, repeated oral doses can lead to dose dumping, which can cause toxicity and serious adverse effects. Additionally, traditional oral solid dosage forms of Cefixime have safety limitations[5,6]. To address the challenges associated with drug administration, the development of a controlled-release drug delivery system utilizing polymeric gel beads presents a promising solution. This innovative approach seeks to enhance the bioavailability of cefixime trihydrate by prolonging its release over an extended duration. By facilitating a more controlled and consistent release profile, such a system not only aims to improve therapeutic outcomes but also seeks to reduce the frequency of dosing, thereby potentially enhancing both the efficacy and safety of the treatment regimen.[7]

MATERIALS AND METHODS

Remedy Labs Pvt. Ltd., located in Gujarat, India, graciously provided cefixime trihydrate as a gift sample. Gellan gum was obtained from Sigma-Aldrich Chemicals Pvt. Ltd. in Bangalore. Additionally, chitosan, potassium dihydrogen orthophosphate, and sodium hydroxide were procured from HiMedia Laboratories Pvt. Ltd. in Mumbai, while all other chemicals and reagents utilized were of chemical grade.

Preparation of Hydrogel beads of Cefixime trihydrate

Cefixime trihydrate, the active pharmaceutical ingredient, was employed to formulate four distinct batches (F1 to F4) utilizing the ionotropic gelation method. Hydrogel beads containing cefixime trihydrate were synthesized using sodium tripolyphosphate (TPP) as the crosslinking agent. The Drug itself was dispersed in water to obtain a homogeneous solution at room temperature with stirring (60 rpm) for 1 h; Next ×=‘Cefixime Trihydrate‘. This gum-drug solution was then dropped through a 21-gauge flat-tipped hypodermic needle into stirred 1.5% sodium tripolyphosphate solution with continuous stirring to form beads that began sinking after about 30 min. These beads were then washed, filtered and dried at 40 °C[8].

Evaluation parameter

FTIR Spectroscopy

Infrared (IR) spectroscopy has established itself as a pivotal analytical technique in the qualitative identification of chemical compounds. This method is particularly effective due to its ability to provide distinctive spectral fingerprints based on molecular vibrations. Each compound exhibits unique absorption peaks, allowing for precise identification and characterization. The application of this technique has become increasingly vital in pharmaceutical research, particularly in the examination of drug formulations where the interaction between drugs and polymers can significantly influence drug efficacy and stability.[9]

Differential Scanning Calorimeter (DSC) Analysis

DSC is a pivotal analytical technique widely employed to characterize the thermal properties of materials, particularly pharmaceuticals and their excipients. In this study, the DSC thermograms of a pure drug, chitosan, and gellan gum, as well as their respective physical mixtures with the Drug, were meticulously recorded

Table 1. Composition of hydrogel beads of Cefixime

No.	Composition(mg)	F1	F2	F3	F4
1	Cefixime trihydrate (mg)	200	200	200	200
2	Chitosan (g)	1	1	1	1
3	Acetic acid (ml)	1	1	1	1
4	Gellan gum (mg)	-	100	50	150
5	Sodium Tripolyphosphate (TPP)(g)	1.5	1.5	1.5	1.5
6	Distilled water (ml)	q.s			

utilizing a Perkin-Elmer Pyris-Diamond TG/DTA instrument, calibrated against indium for accuracy.

To conduct this analysis, samples of precisely 2 mg were encapsulated in 50 µl aluminium pans and hermetically sealed to prevent environmental interference. The experiments were executed under a controlled nitrogen atmosphere, set to a flow rate of 20 ml/min, ensuring an inert environment that mitigates oxidation or other thermal degradations. The temperature range for the measurements spanned from 30.00ºC to 440.00ºC, with a consistent heating rate of 10.00ºC per minute.[10]

X-Ray Diffraction Studies

Qualitative X-ray diffraction (XRD) study was conducted utilizing the Ultima III X-ray diffractometer to analyze the crystalline properties of pure Drug, chitosan, and gellan gum. The analysis was performed over a temperature range of 0-50°C, focusing on the diffraction angle of 2è. The experimental conditions were meticulously controlled, employing Ni-filtered Cu-Ká radiation (ë = 1.54 Å) with an operational voltage of 45 kV and a current of 40 mA. The scan speed was set at 5° per minute to ensure precise data collection and resolution.[11,12]

Bead Size Analysis

Accurate measurement of particle size in pharmaceutical formulations is critical for ensuring the efficacy and safety of drug delivery systems. In this study, the diameter of dried drug-loaded beads was evaluated using an optical microscope (Olympus Model HB, India) to ensure precision and reliability.

To begin the process, the optical system was calibrated using a standard stage micrometer, which formed the basis for subsequent measurements. Calibration of the eyepiece micrometer is paramount, as it allows for the conversion of the marked divisions into actual units of measurement, thereby enhancing the accuracy of the diameter readings. Following calibration, the dried beads were carefully placed on a glass slide for analysis. Notably, a hundred beads were randomly selected from each formulation to account for potential variability in size within and between batches. This randomized approach ensures that the resulting data is representative of the entire formulation.[13]

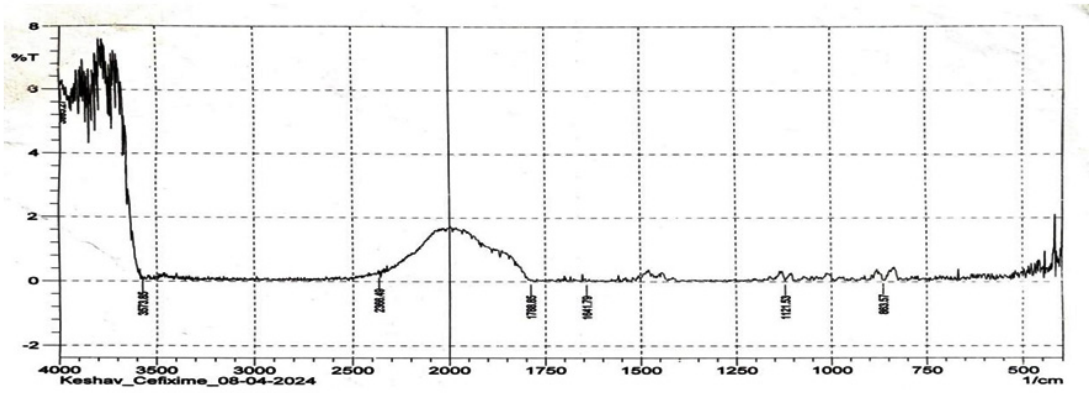

Fig. 1. FTIR Spectra of Cefixime

Table 2. FTIR Interpretation of Cefixime

No.	Functional Group Vibration	Absorption frequency band (Reference)(cm^{-1})	Observed Frequency (cm^{-1})
1	N-H Stretching	3300-3500	3573.85
2	OH Stretching	2500-3300	2366.49
3	CO Stretching	1650-1700	1641.79
4	CC Stretching	1450-1600	1121.53
5	CS Stretching	600-800	863.57

Drug Entrapment Efficiency

A precise quantity of 50 mg of dried drug-loaded beads from each batch was weighed and subsequently introduced into 50 ml of phosphate buffer. This suspension was stirred continuously on a magnetic stirrer for 12 hours. Upon completion of this period, the mixture underwent filtration, and the filtered sample was further diluted to a total volume of 10 ml using phosphate buffer adjusted to pH 7.4. The absorbance of the final solution was then measured at 288 nm using a UV-visible spectrophotometer to evaluate the percentage of entrapment efficiency.[14]

***In-Vitro* Release**

Drug release studies were carried out on the hydrogel beads of each batch by *in vitro* drug release tests using USP dissolution apparatus II (paddle method). Hydrogel beads were soaked in 0.2 M phosphate buffer of pH 7.4 for 500 ml while the time interval taken was fixed as four hours on all days. The first one was maintained under a rotation of 50 rpm and the second one was stabilized at 37 ± 0.5 ºC, an aliquot of 1 ml samples was withdrawn at predetermined time intervals and replaced by an equal volume of fresh buffer to remain constant for the system volume. The quantitation of the drug content was performed with a UV spectrophotometer (UV-1800, Shimadzu, Japan)[15,16].

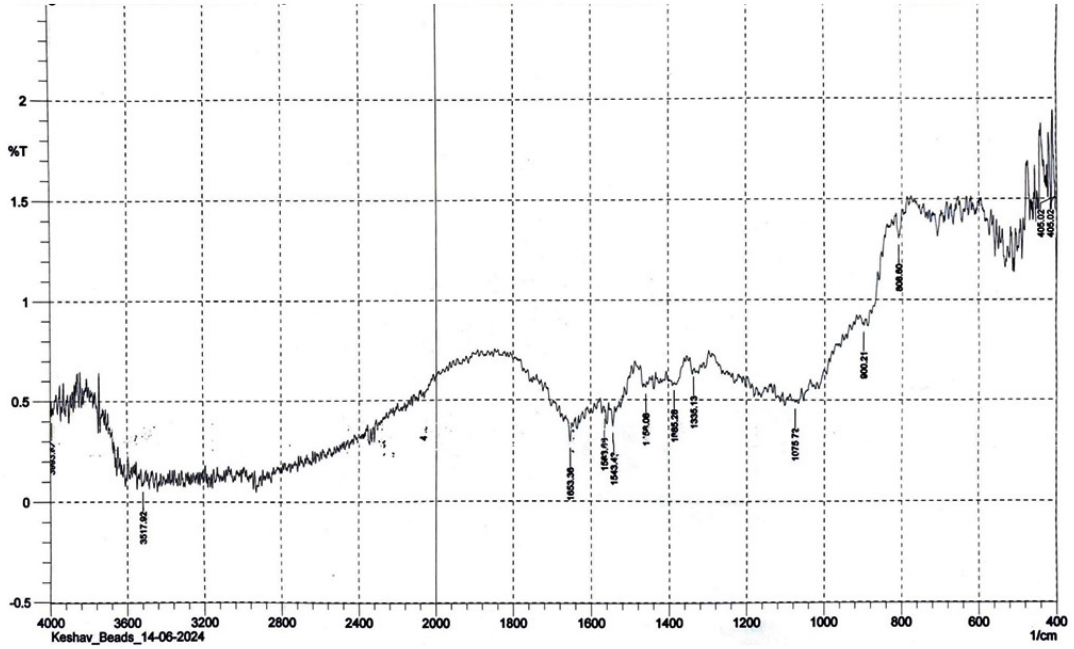

Fig. 2. FTIR Spectrum of Physical Mixture of Formulation (F3)

Table 3. FTIR Interpretation of hydrogel beads (F3)

No.	Functional Group Vibration	Observed Frequency (cm^{-1}) drug	Observed peaks (cm^{-1}) Formulation
1	N-H Stretching	3573.85	3517.92
2	OH Stretching	2366.49	2380.76
3	CO Stretching	1641.79	1653.36
4	CC Stretching	1121.53	1075.72
5	CS Stretching	863.57	808.6

RESULT AND DISCUSSION

FTIR Spectroscopy of Cefixime Trihydrate

The exact peaks are directly shown in Fig. 1 and fully described in Table No.2. The baseline was corrected using dried KBr and about 1-2 mg of sample were analyzed in each case. We conducted the study of a mixture spectrum, which consisted of drug and potassium bromide, essential functional groups were well identified in this range

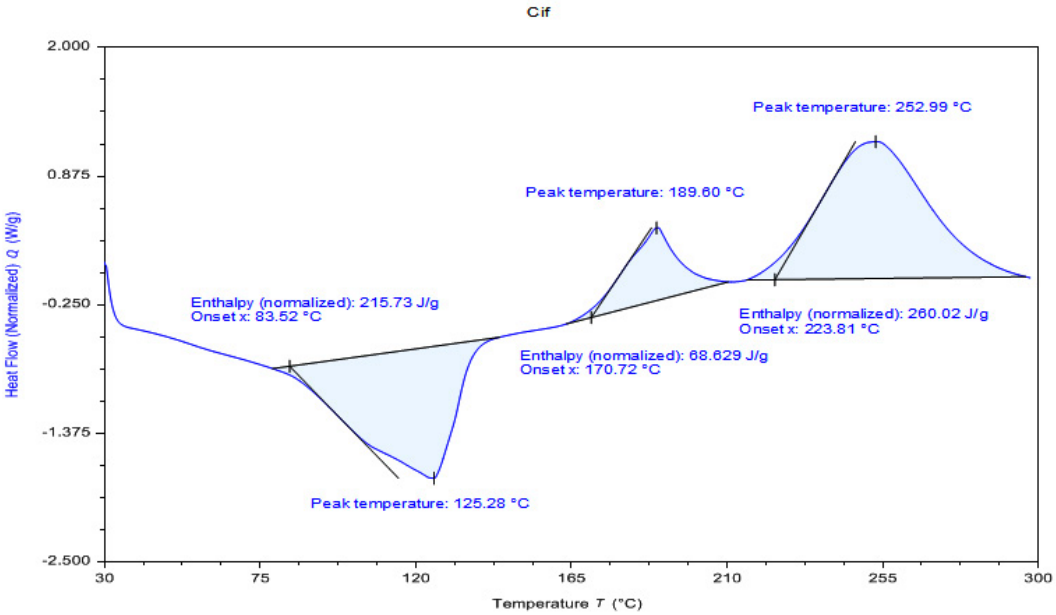

Fig. 3. DSC Thermogram of Drug

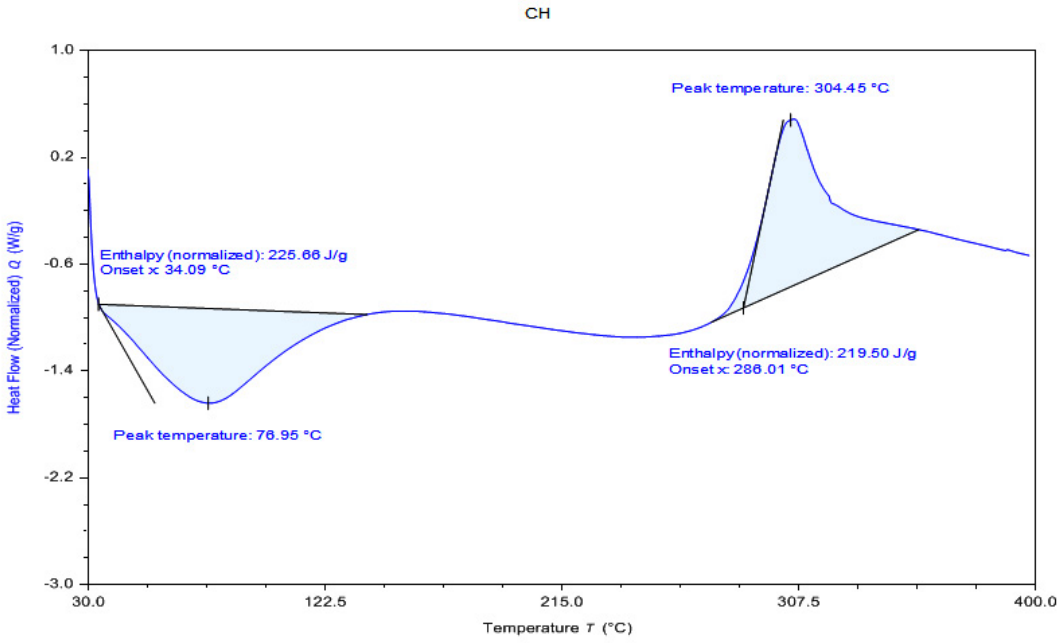

Fig. 4. DSC Thermogram of Polymer (Chitosan)

in agreement with the reported FT-IR values and confirming on presence of cefixime trihydrate.

FTIR Spectroscopy Drug-Loaded Hydrogel Beads

Infrared (IR) spectroscopic analyses were performed on the synthesized beads to evaluate the preservation of Cefixime trihydrate within the formulation. The spectra obtained from the drug-loaded hydrogel beads displayed peaks that aligned with those identified in the spectrum of pure Cefixime trihydrate, though minor shifts were noted. These spectral peaks are represented in Figure 2 and comprehensively detailed in Table No. 3. The findings from the FTIR spectroscopy indicate the absence of significant interactions between Cefixime trihydrate and the polymer, ensuring the integrity of the drug within the matrix.

Differential Scanning Calorimeter (DSC) Study

DSC is a pivotal technique utilized to evaluate the heat differential required to

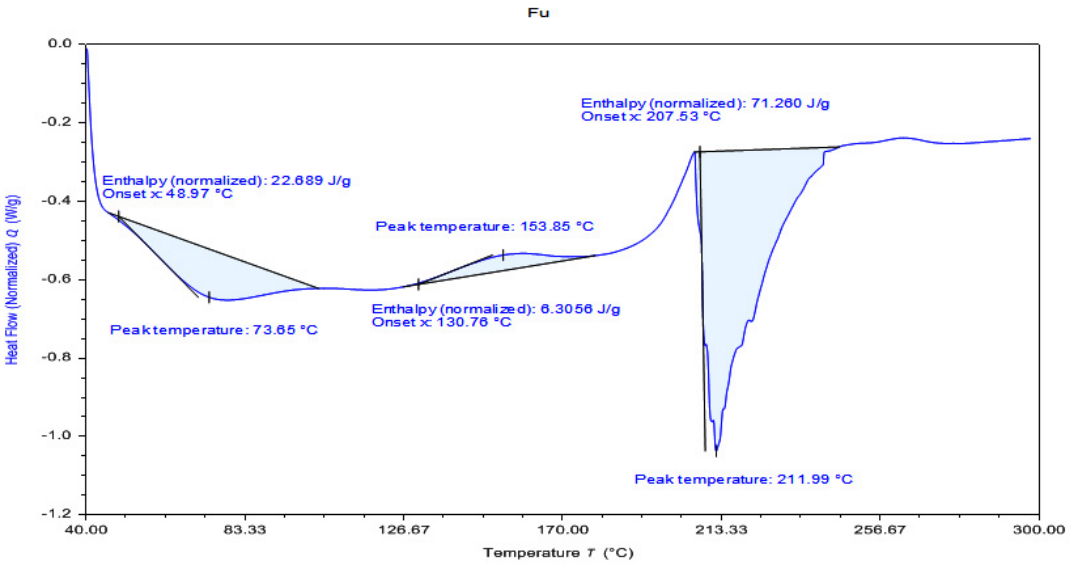

Fig. 5. DSC Thermogram of Drug loaded beads (F3)

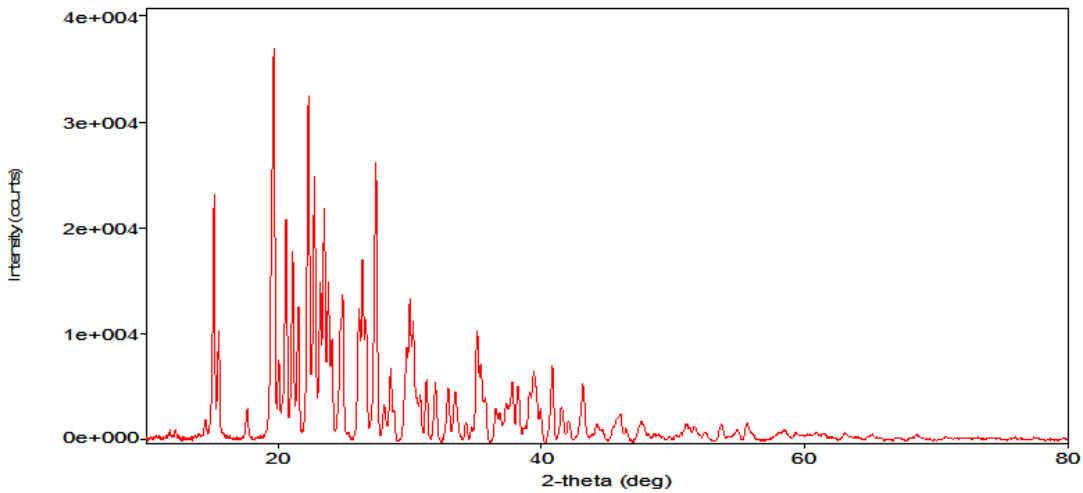

Fig. 6. X-ray Diffractogram of Drug

elevate the temperature of a sample relative to a reference across various temperatures. This method is instrumental in identifying melting points, observing shifts in crystalline structures, and examining potential interactions between pharmaceuticals and their carriers. Figures 3 through the DSC analysis for cefixime trihydrate, chitosan, and drug-loaded hydrogel beads. Notably, the DSC thermogram for cefixime trihydrate Figure 3 revealed a clear endothermic peak at 252.99°C, signifying its melting behavior.

In the DSC thermogram of chitosan, the endothermic peaks were observed around 76.95°C, and an exothermic peak was observed at 304.45°C. (Figure 4).

The DSC thermogram of the drug-loaded beads (Fig. 5) exhibited an endothermic peak at 211.99°C, indicating a slight reduction in the melting temperature after drug incorporation. The absence of the characteristic peak of pure Cefixime suggests a uniform dispersion of the drug within the polymer matrix. Additionally, an exothermic peak was observed at 153.85°C, further confirming the structural integration of the drug in the hydrogel beads.

X-Ray Diffraction (XRD) Study

X-ray diffraction (XRD) is a non-destructive technique used to analyze crystalline materials, providing valuable insights into their phases, structural characteristics, preferred orientations, and lattice parameters. In the case of Cefixime trihydrate, the XRD analysis revealed distinct, sharp peaks, confirming its crystalline structure. However, the XRD patterns of the

Table 4. Size of Prepared Beads Formulation

No.	Formulation Code	Arithmetic mean diameter(µm)± SD
1	F_1	314.2± 0.14
2	F_2	377.04± 0.22
3	F_3	251.36± 0.27
4	F_4	408.46± 0.12

Table 5. Drug entrapment efficiency (DEE) of prepared bead formulation

No.	Formulation Code	Drug entrapment Efficiency (%)
1	F1	61.82± 0.45
2	F2	74.47± 0.56
3	F3	92.17± 0.92
4	F4	67.03± 0.80

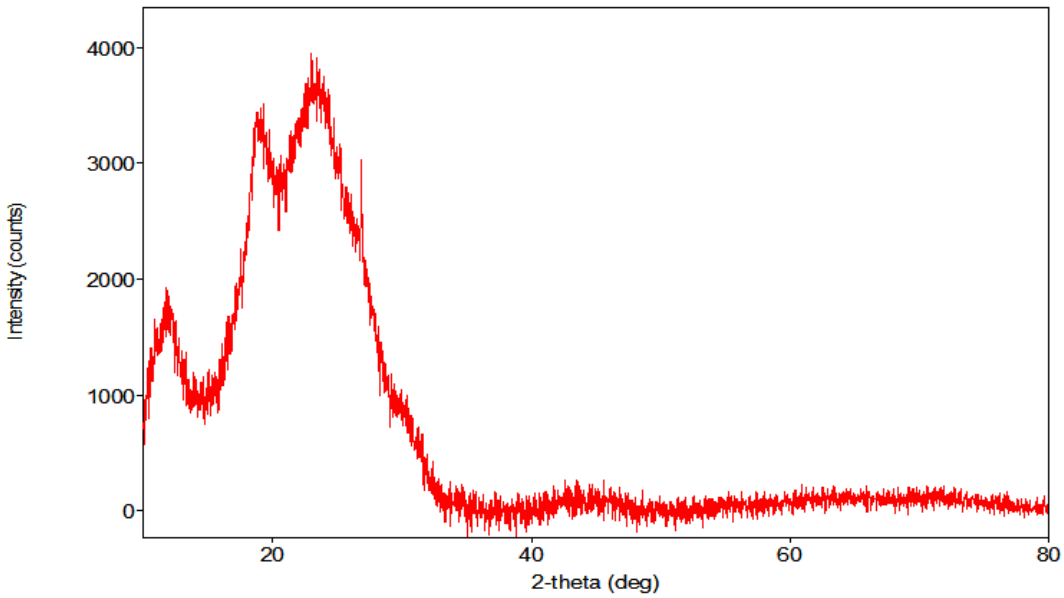

Fig. 7. X-ray Diffractogram of Drug loaded beads (F3)

drug-loaded hydrogel beads showed significantly weakened peak intensities, indicating the loss of Cefixime trihydrate's crystalline nature. This reduction in crystallinity suggests that the drug is uniformly dispersed within the polymer matrix, rather than existing in a crystalline form, which is a key indication of its successful integration into the hydrogel system

Determination of bead size

The hydrogel beads exhibited sizes ranging from 408.46 ± 0.12 µm to 251 ± 0.27 µm, as presented in **Table 4.** Notably, the dimensions of the beads were affected by both the polymer ratio and the concentration of the crosslinker. An increase in chitosan content within the polymer blend correlated with larger bead sizes, whereas a higher concentration of the crosslinker induced a reduction in bead size.

Drug Entrapment Efficiency

The drug entrapment efficiency (DEE) of cefixime-loaded beads was observed to range from 61.82±0.45% to 92.17±0.92%, as presented in **Table 5.** The polymer ratio and the concentration of the crosslinker significantly impact this efficiency. An increase in chitosan content is observed to correlate with a decrease in drug entrapment efficiency. This reduction is likely due to the higher solubility of chitosan, which can destabilize the

Table 6. Drug release of Hydrogel beads in phosphate buffer (pH 7.4) for 8 hrs

S.No.	Time (Min)	Cumulative Percent Drug Release F1	F2	F3	F4
1	60	4.69784768±0.02	4.8220198±0.01	4.5736754±0.03	4.7806291±0.09
2	120	9.7268211±0.05	11.134105±0.07	9.8096026±0.06	10.513245±0.12
3	180	15.542218±0.7	17.984271±0.6	15.749172±0.9	16.866721±0.38
4	240	22.516556±0.42	25.496688±0.45	22.144039±0.32	23.592715±0.51
5	300	32.015728±0.63	33.919701±0.72	29.490894±0.56	32.429635±0.78
6	360	42.549668±0.31	45.405629±0.48	38.700331±0.67	43.667218±0.21
7	420	55.484271±0.87	57.222682±0.73	49.772350±0.81	57.595198±0.89
8	480	69.991721±0.93	69.536423±0.92	62.872516±0.97	72.971854±0.91

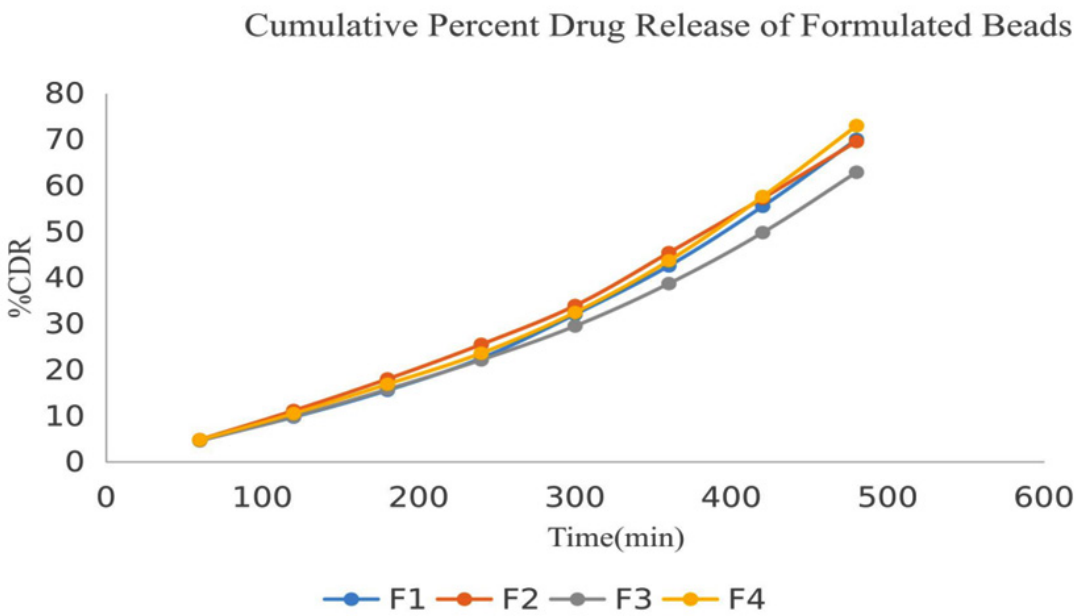

Fig. 7. Interpretation of Cumulative Percent Drug Release Graph

polymer matrix and enhance the swelling behavior of the hydrogel beads. The excessive swelling may result in greater diffusion of the drug out of the matrix during the formulation process, thereby reducing the overall entrapment efficiency. Consequently, during the gelation process in the crosslinker solution, some drug particles may be lost from the polymer network, further diminishing entrapment efficiency. Conversely, a higher concentration of the crosslinking agent was determined to enhance drug entrapment efficiency.

***In-vitro* Drug Release Study**

Hydrogel beads were employed to investigate the release profile of the drug over four hours in alkaline media, specifically a phosphate buffer at pH 7.4. The data, illustrated in Figure

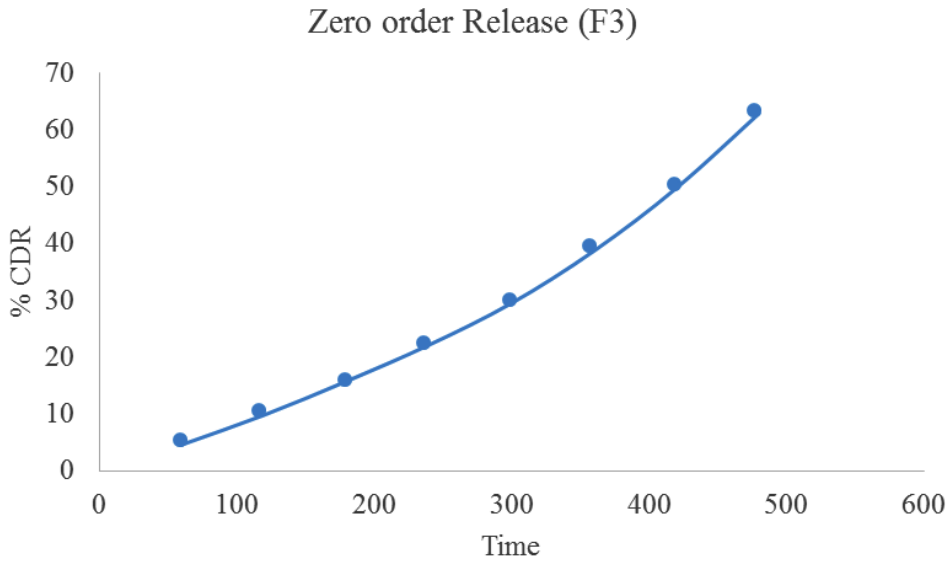

Fig. 8. Interpretation of Zero Order Release Graph

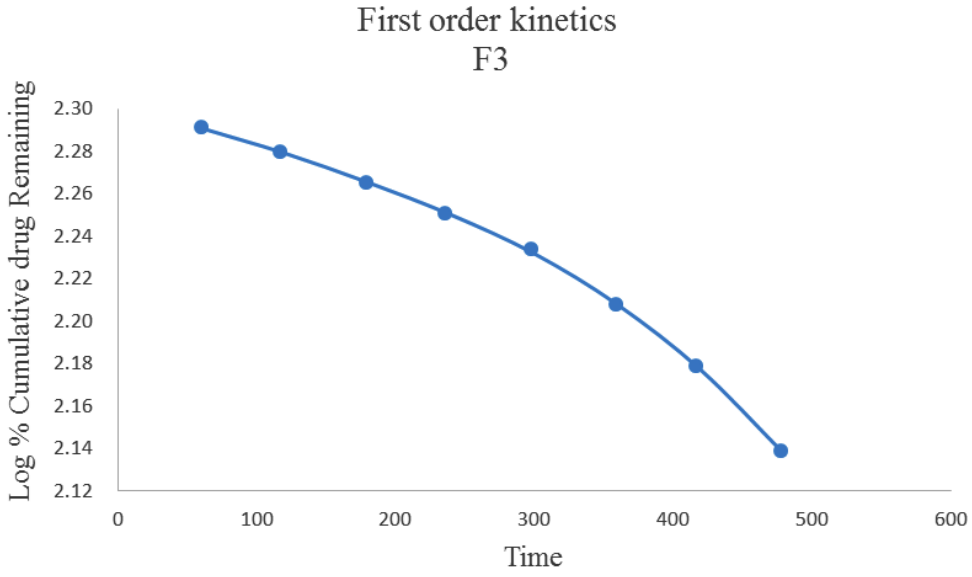

Fig. 9. Interpretation of First Order Drug Release Graph

7, demonstrates a notable increase in cumulative drug release percentage as time progressed. Furthermore, the results indicate that as the pH of the medium rose to 7.4, there was a significant enhancement in the drug release from the hydrogel beads, underscoring the influence of pH on drug availability.[17]

Formulation F3 was identified as the optimized formulation based on drug release and entrapment efficiency. The kinetic modelling formulation F3 plotted results are shown below.

Kinetic modelling indicated that the latter half of release is controlled by the Korsmeyer-Peppas model in the case of the optimized

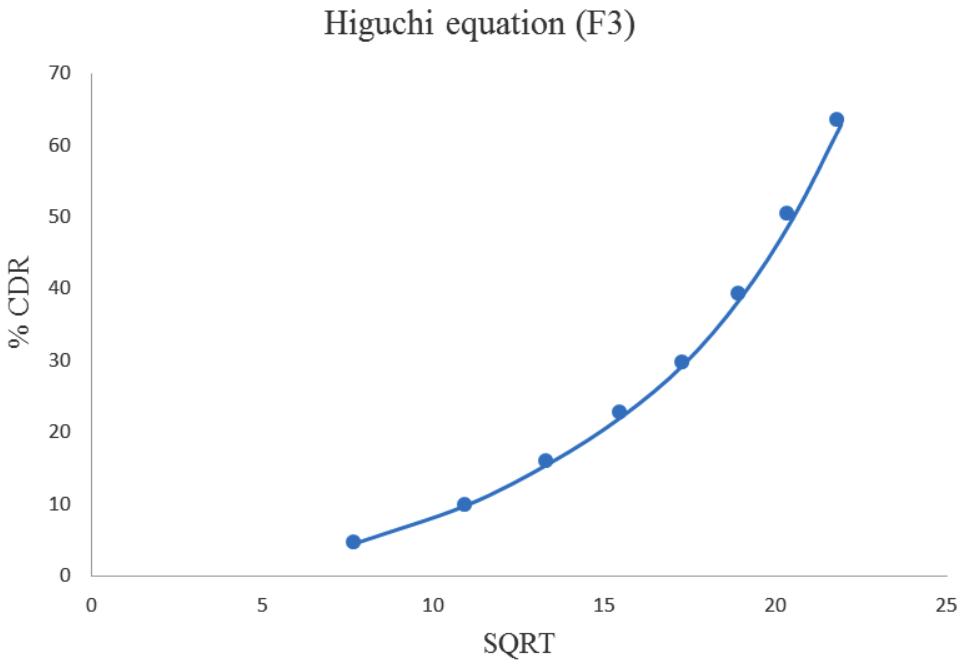

Fig. 10. Interpretation of Higuchi Model Release Graph

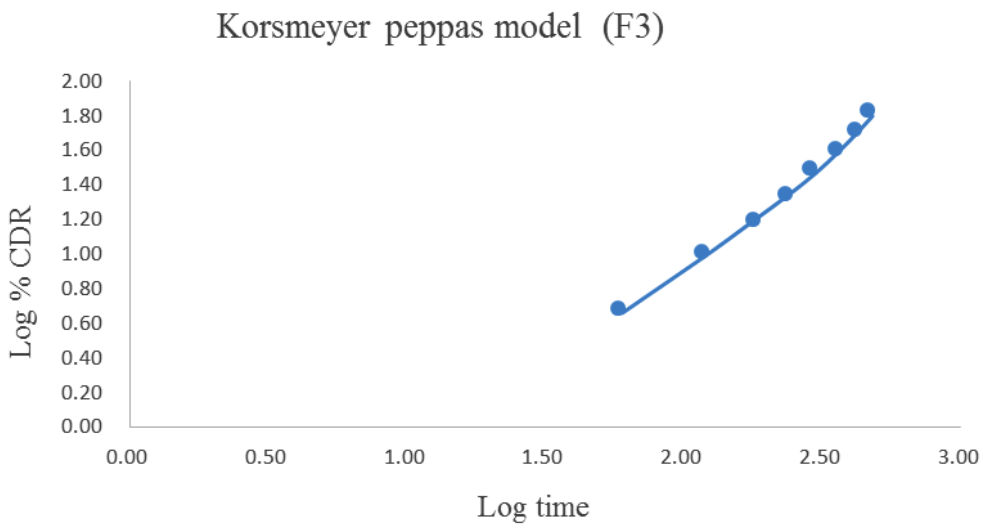

Fig. 11. Interpretation of Korsmeyer Peppas Model

Table 7. Plot of kinetic modeling of drug release data of formulation (F4)

No.	Formulation	Zero Order	First Order	Higuchi Kinetic	Korsmeyer-Peppas	
1		R^2	R^2	R	R^2	n
	F3	0.9738	0.9554	0.9164	0.994	1.2455

formulation. In this kinetic model, the release exponent (n) >1 indicated a super Case II transport mechanism in which both the swelling and erosion of the polymer matrix are the main factors controlling its release rate.[18] Therefore, this discovery has proven that the release of the drug is diffusion-controlled as expected in a sustained-release formulation.

CONCLUSION

Infectious diseases are becoming increasingly prevalent worldwide, particularly in developing countries, with the misuse of antibiotics driving the rise in bacterial resistance. To address this issue, the present study developed Cefixime trihydrate-loaded controlled-release hydrogel beads using biodegradable polymers to prolong drug release in the stomach. Chitosan was employed as the polymer, and the hydrogel beads were synthesized through ionic gelation with tripolyphosphate (TPP) serving as the crosslinking agent. Fourier Transform Infrared (FTIR) analysis confirmed the absence of significant interactions between Cefixime trihydrate and the polymers, preserving the drug's structural integrity. The drug entrapment efficiency ranged from 92.17±0.92% to 61.82±0.45%, depending on the formulation. In vitro release studies indicated that formulation F3 exhibited the slowest release rate among the formulations tested. Kinetic analysis of the drug release profiles revealed an n value greater than 1 for all formulations, suggesting a super Case II transport mechanism. This indicates that drug release is predominantly governed by the swelling and erosion of the polymer matrix, consistent with a diffusion-controlled, sustained-release system. These findings validate the effectiveness of the formulated hydrogel beads in providing a controlled and extended drug release profile.

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Conflict of Interest

The authors do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Author Contributions

Pawan Singh: – Conceptualization, Writing Paper; Keshav Raj: Methodology development; Alankar Shrivastav: Analysis Result; Vijay Sharma: visualization, Supervision the all research work.

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