RESEARCH ARTICLE

Polymeric Nanoparticles of Loratadine Betacyclodextrin Inclusion Complex: 3^2 Factorial Design, Optimization and *In-vitro* Evaluation

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ABSTRACT

Loratadine (LOR) a second-generation antihistaminic exhibits low water solubility and high permeability. In the present work an attempt was made to formulate LOR nanoparticles to enhance dissolution rate and to prolong the release for oral delivery. With the objective of enhancing solubility of LOR, Loratadine-Betacyclodextrin inclusion complex (LOD-BCD) was prepared by solvent evaporation method. Later based on 3^2 factorial design 9 LOR-BCD polymeric nano formulations (L1 to L9) was formulated by solvent displacement technique by selecting LOR:BCD and Eudragit RS 100 (ERS) as independent variables. From *in vitro* studies the effect of independent variables on responses was found to agree Quadratic model and formulation LOR 4 was selected as optimized formulation with the particle size of 104.2nm, PDI of 0.274 and zero order *in vitro* drug release of 61.98±0.68%. The study concluded that LOR–BCD polymeric nanoparticles were successfully formulated using a validated factorial design, exhibiting improved dissolution and sustained drug release.

Keywords: Loratadine, Betacyclodextrin, Eudragit RS 100, BCS class II, Nanoparticles, Antihistamine, 3^2 Factorial design

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INTRODUCTION

Loratadine is a tricyclic second-generation antihistamine drug indicated for the symptomatic relief of allergy, such as allergic rhinitis (hay fever), wheal formation, seasonal and perennial allergic rhinitis, urticaria, upper respiratory tract infection, chronic idiopathic urticaria, skin allergies, and ocular allergy[1-3]. Loratadine, due to its low aqueous solubility i.e. 0.00303 mg/mL, and high permeability with log P value of 5[2,4] it is categorized under BCS Class II drugs. It exhibits pH dependent solubility, soluble in acidic pH, which is attributed to the Pyridine nitrogen atom in its chemical structure[5,6]. Reported literature states that oral administration of Loratadine produces side effects such as hepatotoxicity and allergic reactions[5,7,8]. Therefore, pH dependent solubility and its side effects result in poor oral bioavailability and reduced therapeutic efficacy of Loratadine[4,9].

The stated limitations can be mitigated by a nanotechnology approach. Nanoparticles are colloidal solid particles ranging from 1-1000nm (nanometer) in size, which consist of macromolecular materials in which the active ingredient is dissolved, encapsulated, entrapped, adsorbed, or attached. Nanoparticles therefore deal with the increase in drug solubilization, enhance the stability by protecting the drug from degradation until they reach the target site, retention of drug, longer clearance time, dose proportionality, enhance the absorption, and prolong the release of the drug, which enhances the bioavailability[1,4,10].

Eudragit RS 100 is widely used in the formulation of controlled-release oral dosage forms due to its insolubility across a range of physiological pH levels. It is a neutral copolymer composed of ethyl acrylate, methyl methacrylate, and a small proportion of methacrylic acid ester, containing quaternary ammonium groups in the range of 4.5–6.8%. Owing to its low permeability and pH-independent swelling properties, Eudragit RS 100 is considered an ideal polymer for developing sustained-release drug formulations that remain unaffected by pH variations[11-13].

β-Cyclodextrin inclusion Nanoparticles are one of the strategies used in developing nanoparticle drug delivery systems. Cyclodextrins are hydrophilic colloidal cyclic oligosaccharides composed of dextrose units joined through the 1–4 bond with a hydrophilic exterior and a relatively hydrophobic internal cavity. Among the cyclodextrins, β-Cyclodextrin has more potential applications due to its biocompatibility, low toxicity, and greater cavity size with a capacity of holding drug molecules with a molecular weight of 200-800g/mol[7,14-16]. It enhances the solubility of poorly soluble drugs by forming an inclusion complex[17,18]. Literature studies showed that cyclodextrin-based inclusion complexes can improve aqueous solubility and stability of the drugs and are widely used in developing nanoparticles and nanofibers[19-21]. Studies have proved that the solubility of LOD can be enhanced by preparing an LOD inclusion complex with BCD[22,23].

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Table 1: Formulation table of LOR:BCD complex nanoparticles

Variables	Formulation code								
	LOR 1	LOR 2	LOR 3	LOR 4	LOR 5	LOR 6	LOR 7	LOR 8	LOR 9
LOR:BCD complex (mg)	10:0 (-1)	10:0 (-1)	10:0 (-1)	10:30 (0)	10:30 (0)	10:30 (0)	10:60 (+1)	10:60 (+1)	10:60 (+1)
ERS (mg)	250 (-1)	500 (0)	750 (+1)	250 (-1)	500 (0)	750 (+1)	250 (-1)	500 (0)	750 (+1)
Acetone (ml)	05	05	05	05	05	05	05	05	05
Water (ml)	05	05	05	05	05	05	05	05	05

Table 2: %Y and %EE of LOD-BCD complex Nanoparticles

Formulations	LOR1	LOR 2	LOR 3	LOR 4	LOR 5	LOR 6	LOR 7	LOR 8	LOR 9
%Y	83.7 ± 0.41	85.5 ± 0.24	89.0 ± 0.05	92.1 ± 0.11	94.7 ± 0.31	95.7 ± 0.29	80.4 ± 0.19	82.8 ± 0.21	87.1 ± 0.04
%EE	62.5 ± 0.23	57.9 ± 0.05	57.0 ± 0.02	56.4 ± 0.13	89.3 ± 0.06	87.5 ± 0.19	85.8 ± 0 .32	67.0 ± 0.08	64.7 ± 0.37

Hence, in the present research work, LOD conjugated β-Cyclodextrin-polymeric nanoparticles were prepared using polymer Eudragit RS 100 by applying 3^2 factorial design to enhance solubility and to achieve sustained drug delivery. Later, nanoparticles were characterized for *in vitro* performance, and an optimized formulation was identified by using software Design Expert.

MATERIALS AND METHODOLOGY

Loratadine was kindly gifted by Apotex Research Pvt Ltd, Bengaluru, Batacyclodextrin by SDFC Pvt. Ltd., Mumbai, Eudragit RS 100 by Evonik industries, Germany, Membrane filter by HiMedia Lab Pvt Ltd., Mumbai, and all the other chemicals used are from Sisco Laboratories Pvt Ltd., Mumbai.

Phase Solubility Studies

LOR phase solubility in BCD was studied using the Higuchi and Connors (1965) method. BCD solutions (4–30 mM) were prepared in pH 6.8 phosphate buffer, and 10 mL of each was placed in glass vials. Excess LOR was added and shaken at room temperature for 72 hours. After centrifugation, supernatants were filtered (0.45 µm) and analyzed at 246 nm using a UV spectrophotometer. A phase solubility diagram was plotted, and the apparent stability constant (K) was calculated using the Higuchi and Connors equation[17,24,25].

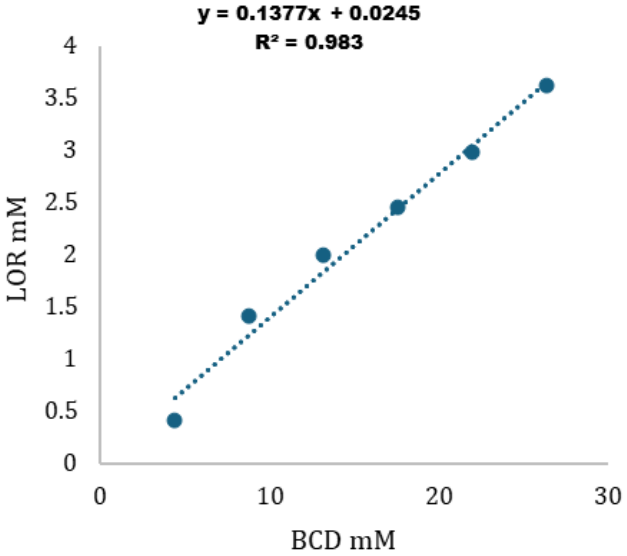

Figure 1: Phase solubility curve of LOR in BCD

$$K \frac{Slope}{Intercept\ (1-Slope)} \quad \text{Eq…1}$$

Preparation of LOR:BCD Inclusion Complex

The LOR–BCD inclusion complex was prepared by the solvent evaporation technique. LOR was dissolved in 10 mL of ethanol and added to 6 mL of the aqueous BCD solution. The mixture was stirred for 24 hours, then the ethanol was evaporated at room temperature. After filtration (0.45 µm) to remove insoluble drug, the clear solution was vacuum-dried at room temperature to obtain the solid LOR:BCD complex[16,26].

Design of Experiment According to 3^2 Factorial Design

LOR:BCD complex nanoparticles were formulated using a 3^2 full factorial design. The independent variables were the LOR:BCD ratio (A) and Eudragit RS 100 concentration (B), while the responses were % yield (Y1), % encapsulation efficiency (Y2), and % drug release at 8 hours (Y3). Table 1 shows the coded levels of variables: +1 (high), 0 (medium), and 1 (low), and details of nine formulations (LOR1 to LOR9) developed based on the design[27,28].

Preparation of LOR:BCD Complex Nanoparticles

LOR, either as pure drug or BCD complex (1:1 or 1:2), was encapsulated in Eudragit RS 100 via solvent displacement. The complex was dispersed in acetone containing dissolved Eudragit and stirred for 30 min at 25°C. Then, 5 mL of water was added, and the mixture was homogenized at 15,000 rpm for 10 min to form nanoparticles. The solvent was removed using a rotary evaporator at 45°C, and nanoparticles were collected by centrifugation (15,000 rpm), re-suspended, and freeze-dried[24,26].

Physicochemical Characterization of LOR:BCD Complex Nanoparticles

Percentage Yield and Percentage Entrapment Efficiency

Percentage yield of LOR:BCD nanoparticles was calculated using the product weight and total polymer weight (Equation 2).

Entrapment efficiency was determined by dispersing a known amount of nanoparticles in methanol, followed by centrifugation at 10,000 rpm for 30 minutes. Free LOR in the supernatant was measured using a UV

Table 3: Fit model summary statistics of responses

Response	Model	p-value *	SD	R^2	AR^2	PR^2
Y1	Quadratic	0.0024	1.03	0.9862	0.9632	0.8579
Y2	Quadratic	< 0.0001	0.4714	0.9996	0.9988	0.9954
Y3	Quadratic	0.0347	0.5545	0.9996	0.9990	0.9954

*p-value less than 0.05 indicates significance; AR^2 – Adjusted R^2; PR^2 – Predicted R^2

Table 4: Coefficients and ANOVA for the Quadratic model of all the responses

Factors	Y1			Y2			Y3		
	CE	F-value	P-value	CE	F-value	P-value	CE	F-value	P-value
A	-1.32	9.73	0.0525	3.82	393.31	0.0003*	19.62	7513.65	< 0.0001*
B	2.60	37.93	0.0086*	-1.62	70.57	0.0035*	-3.73	270.31	0.0005*
AB	0.3500	0.4583	0.5470	-0.7000	8.82	0.0591	-1.15	17.36	0.0252*
A^2	-9.42	165.86	0.0010*	-26.55	6344.12	< 0.0001*	1.99	25.20	0.0152*
B^2	0.3333	0.2078	0.6795	0.1500	0.2025	0.6832	-0.0633	0.0174	0.9035

CE-Coefficient Estimate; *P Value <0.05 indicates significance

Table 5: confirmation analysis of the optimized formulation LOR 4 with prediction values

Response	Predicted Mean	LOR 4 Observed	SD	n	SE Pred	95% PI low	Average data of 3 formulations	95% PI high
% Yield	91.67	92.1	1.03	3.00	0.97	88.57	90.56	94.78
% Encapsulation	89.13	89.3	0.47	3.00	0.44	87.71	88.6	90.54
% Drug release	60.40	61. 8	0.54	3.00	0.51	58.77	62.8	62.03

spectrophotometer, and entrapment efficiency was calculated using Equation 3[29-31].

$$\%\,Yield = \frac{Actual\ weight\ of\ product}{Total\ weight\ of\ Drug\ and\ Polymer} X100 \ldots Eq\ 2$$

$$\%\,EE = \frac{Amount\ of\ Initial\ drug - Amount\ of\ Free\ drug}{Amount\ of\ Initial\ drug} X100 \ldots Eq\ 3$$

Particle Size, Polydispersity Index (PDI), and Zeta Potential

LOR:BCD nanoparticles were dispersed in distilled water and mixed for 5 minutes to obtain a uniform suspension. Particle size, polydispersity index (PDI), and zeta potential were measured using dynamic light scattering (Malvern Zetasizer) at 25 °C under an electric field of 23 V/cm[15,32].

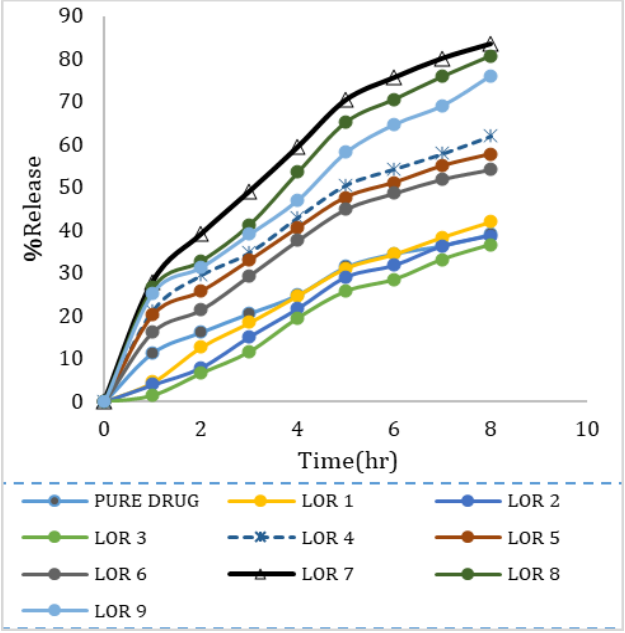

Figure 2: *In vitro* drug release of LOR-BCD complex nanoparticles

Fourier Transform Infrared Spectroscopy (FTIR)

Pure drug, Solid dispersion, the physical mixture of the drug with excipients, and the optimized formulation LOR 4 were subjected to FTIR (Jasco 460 plus FTIR Spectrophotometer), DSC (Shimadzu DSC 60), and XRD, and analysed as per the standard procedure[24,29,30,33].

In-vitro Drug Release

Drug release from LOR:BCD nanoparticles and pure LOR was evaluated using USP Apparatus II (paddle type) in 900 mL of pH 6.8 phosphate buffer at 37 ± 0.5 °C and 50 rpm. Samples were withdrawn at predetermined intervals over 8 hours, filtered (0.45 µm), and replaced with fresh medium. Drug content was analyzed using a UV–Visible spectrophotometer at 246 nm[9,34,35].

Release Kinetics

The *in vitro* drug release profile of LOR:BCD complex nanoparticles were analyzed by various kinetic models, including First-order, Zero-order, Higuchi, and Korsmeyer–Peppas models, to analyse the drug release mechanism.

Interpretation of the results was done based on the correlation coefficient (r^2) and the 'n' value, with the highest r^2 indicating the predominant release mechanism[36].

Model Validation Statistical Analysis

The results from the *in vitro* evaluation were analyzed statistically and validated using Design Expert version 12.0.

RESULTS AND DISCUSSION

Phase Solubility Studies

As shown in Figure 1, LOR solubility increased linearly with BCD concentration (r = 0.9818), indicating an AL-type phase solubility curve per Higuchi and Connors. The slope <1 suggests a 1:1 molar complex formation between LOR and BCD [37]. The intrinsic solubility of LOR was 0.024 mM, and the apparent stability constant was $4.853 \times 10^3\ M^{-1}$, indicating sufficient complex stability with effective drug release in solution[38].

Optimization and Model Validation

Using a 3^2 factorial design, nine runs (Table 2) were conducted to study the effects of two independent variables- LOR:BCD complex ratio (A) and Eudragit RS 100 concentration (B)—on the responses: % yield (Y1), % encapsulation efficiency (Y2), and % *in vitro* release at 12 h (Y3). Results are presented in Table 2 and Figure 2.

From multiple linear regression analysis (Table 3 and 4), it was observed that all responses fit a quadratic model and statistically significant and model suitability was confirmed by difference of less than 0.2 between Predicted R^2 and Adjusted R^2. The coded quadratic equations for responses are:

$Y1=+93.94 -1.31 A +2.60 B +0.35 AB -9.41 A^2 +0.33 B^2$

$Y2=+87.36 +3.81 A -1.61 B -0.10 AB -26.55 A^2 +0.15 B^2$

$Y3= +56.75 +19.62 A -3.72 B -1.15 AB +1.96 A^2 -0.05 B^2$

Statistical significance of factors was evaluated by ANOVA (Table 4), where a P-value < 0.05 and higher F-value denote significant model terms[27,39]. The coded coefficients are detailed in Table 4.

Effect of LOR:BCD and ERS on % Y (Y1), %EE (Y2) and %DR (Y3)

From the quadratic model, LOR:BCD ratio showed no significant effect on % yield (%Y) but had a significant positive impact on encapsulation efficiency (%EE) and drug release (% DR). The increase in %EE with a higher LOR:BCD ratio is likely due to the larger cavity size of BCD, enhancing drug encapsulation and stronger binding with LOR[40,41]. Similarly, % DR increased with LOR:BCD ratio, reflecting improved LOR solubility in the presence of BCD[40,42].

Conversely, Eudragit RS (ERS) significantly increased %Y due to its hydrophobic nature and swelling properties, which promote efficient nanoparticle precipitation[43]. However, ERS had a significant negative effect on %EE and %DR. Despite this, ERS aids encapsulation by forming a less porous surface, contributing to sustained drug release[44].

Response surface and interaction plots (Figures 3 & 4) revealed a significant negative interaction effect (AB) on %

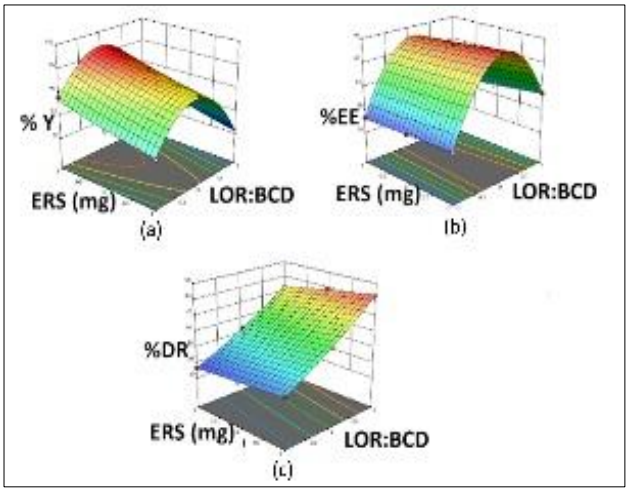

Figure 3: Surface response plot: Effect of LOR:BCD and ERS on (a) %Y; (b) %EE; (c) %DR

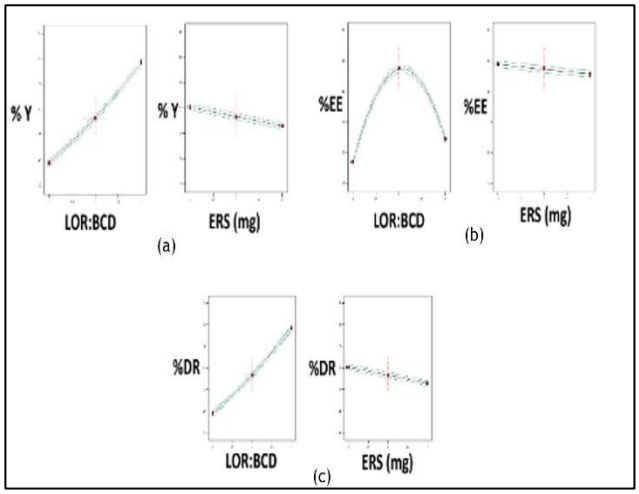

Figure 4: Interaction Effect of LOR:BCD and ERS on (a) %Y; (b) %EE; (c) %DR

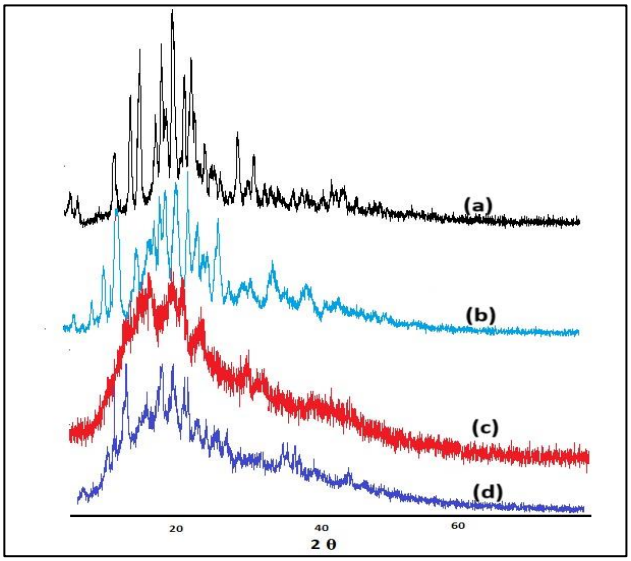

Figure 5: XRD spectra of (a) drug; (b) LOR:BCD solid dispersion; (c) Physical mixture of LOR and ERS; (d) LOR 4

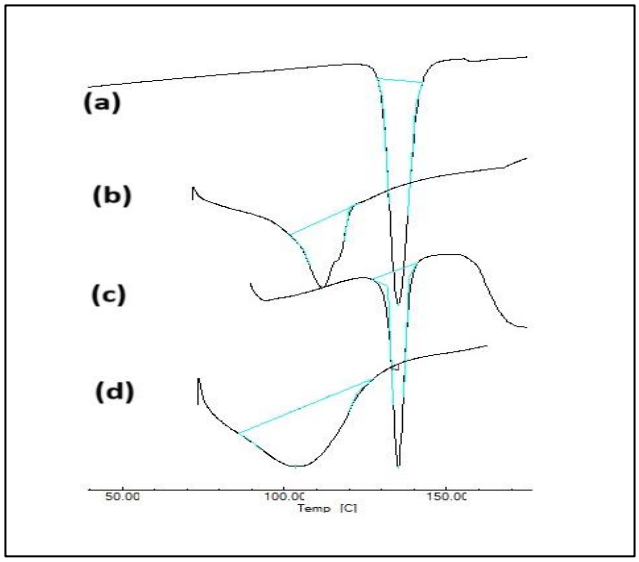

Figure 6: DSC thermogram of (a) drug; (b) LOR:BCD solid dispersion; (c) Physical mixture of LOR and ERS; (d) LOR 4

DR, while the quadratic term A^2 had a positive effect on % DR—doubling the LOR:BCD ratio increased drug release. However, doubling this ratio negatively affected %Y and %EE.

Optimization

Numerical optimization was performed by setting acceptable ranges for independent and dependent variables: % Y (85-95 %), % EE (80-90%), and % DR (60-70%). Formulation LOR 4 was selected as optimal and predicted values from the quadratic model were validated by confirmation analysis, showing that observed responses fell within the prediction intervals, confirming the model's accuracy and reliability[27,45]. Predicted and experimental results with statistics are summarized in Table 5.

Characterization of Nanoparticles

XRD and DSC

From XRPD (Figures 5), it was observed that retention of sharp peaks in LOR:BCD solid dispersion (Figure 5b) confirms the crystalline nature of LOR after complex formation with BCD, and the sharp peak of LOR was absent in the physical mixture of LOR and polymer (Figure 5c), which may be due to dilution of LOR in ERS[46]. In the diffractogram of optimized formulation LOR 4 (Figure 5d) the intensity of LOR peak was reduced, which may be due to encapsulation of the drug in polymer and Formation of an inclusion complex with BCD[46,47]. These results were in consistency with DSC results, which established the amorphous nature of LOR due to complexation with BCD.

The pure LOR showed a characteristic sharp endothermic peak at 140.6°C, confirming its crystalline nature (Figure 6a) (46).

DSC analysis of the LOR:BCD solid dispersion (Figure 6b) revealed the disappearance of LOR's sharp peak and a shift to lower temperatures, indicating inclusion complex formation[5,17]. In contrast, the drug-polymer physical mixture (Figure 6c) retained the sharp drug peak, suggesting no interaction between drug and polymer. The optimized formulation LOR 4 (Figure 6c) exhibited a significant peak shift to lower temperatures, reflecting LOR's amorphous state and enhanced complexation[41,47].

Zeta Potential, Particle Size, and PDI

Particle size reduction enhances solubility by increasing surface area, improving drug dissolution and targeting. Polydispersity index (PDI) reflects the size distribution uniformity, with values below 0.1 indicating a monodispersed system. The optimized formulation LOR 4 showed a particle

size of 104.2 nm and a PDI of 0.274, indicating a nano-range size but a broader size distribution, likely due to BCD complex self-assembly and agglomeration[46,48]. The zeta potential was measured at –18.6 mV, reflecting a negatively charged surface attributed to hydroxyl groups of BCD oriented outward. Although below the ideal ±30 mV range for stability, this hydrophilic surface contributes to enhanced LOR dissolution[15].

Release Kinetics

The drug release profile of the optimized formulation LOR 4 was evaluated using Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models. The release best fit the Zero-order model with a regression coefficient (r) of 0.9979. The Korsmeyer–Peppas model yielded an 'n' value of 0.38, indicating a non-Fickian diffusion release mechanism[36,49].

AUTHOR CONTRIBUTIONS

Dr.Preethi G.B contributed to the article's conception, design, data analysis, interpretation and Manuscript editing. Ms Ayushi P Jain involved in literature review, performing experiments, data collection and manuscript writing.

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