Journal of Applied Pharmaceutical Research
Volume 12 Issue 4, Year of Publication 2024, Page 21 – 30
DOI: https://doi.org/10.69857/joapr.v12i4.603

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Research Article

JOURNAL OF APPLIED PHARMACEUTICAL RESEARCH | JOAPR
www.japtronline.com ***ISSN: 2348 – 0335***

SOLUBILITY ENHANCEMENT OF ETORICOXIB USING INCLUSION COMPLEXATION WITH CYCLODEXTRINS: FORMULATION OF ORO DISPERSIBLE TABLETS BY QbD APPROACH

Anjan Kumar Mahapatra*, Siddharth Dora, Sanatan Parida, Usharani Bal, Bandana Rani Jena, Madhusmita Lenka

Article Information
Received: 11th February 2024
Revised: 23rd April 2024
Accepted: 15th May 2024
Published: 31st August 2024

Keywords
Inclusion complexes (ICs), etoricoxib, β-cyclodextrins, hydroxy propyl β-cyclodextrin

ABSTRACT
Background: The work was intended to enhance etoricoxib's solubility and dissolution rate and then develop oro-dispersible tablets for faster onset of action. **Methodology:** Inclusion complexes (ICs) of the drug were obtained with β-cyclodextrin (β-CD) and hydroxypropyl β-cyclodextrin (HP β-CD) at ratios of 1:0.125, 1:0.25, 1:0.5, 1:1, and 1:2 (w/w). The selected cyclodextrin at appropriate drug carrier proportion was used to develop oro-dispersible tablets (ODTs) by direct compression, adding crospovidone as a super disintegrant. Phase solubility studies of etoricoxib were carried out by using multiple concentrations of β-cyclodextrin and hydroxypropyl β-cyclodextrin, i.e., 1 %, 2 %, 3 % w/v in distilled water at 37±2°C. Spectroscopic (FT-IR) and thermal analysis (DSC) techniques were employed to identify the drug-carrier interactions. **Result:** It showed that etoricoxib solubility improves with increasing hydrophilic carrier concentration. The Gibbs free energy values (ΔG°_{tr}) are consistently negative, showing the solubility of etoricoxib. Significant drug carrier interaction in spectroscopic or thermal analysis was not found. **Discussion:** The ICs of drugs with β-CD and HP β-CD have successfully addressed the challenges of solubility enhancement and taste masking for etoricoxib. **Conclusions:** It is observed that the inclusion complexes formed by the kneading method using β-cyclodextrin (β-CD) at a 1:1 ratio and hydroxypropyl β-cyclodextrin (HP β-CD) at a 1:2 ratio can be used to improve dissolution. Hence β-CD (at a 1:1 ratio) is selected for the formulation of oro-dispersible tablets. ODTs offer more patient compliance and an alternative to available conventional tablets.

INTRODUCTION

In drug development, high-throughput screening helps identify new drugs with high lipophilicity and poor solubility. Therefore, increasing the solubility of low-soluble drugs can increase their bioavailability by increasing the quantity of dissolved drugs in the gastrointestinal system. Complexing with cyclodextrin derivatives, preparing solid dispersions, or adding surfactants means increasing the solubility and, hence, the dissolution of low-soluble compounds [1,2].

The kneading method is used to formulate ICs to improve the drug solubility and rate of the amount absorbed by BCS type II

*Royal College of Pharmacy and Health Sciences, Berhampur-760002, Odisha, India

***For Correspondence:** **anjanmahapatra@gmail.com**

drugs. The main purpose is to release the therapeutic drug into the targeted site and obtain the drug concentration in the therapeutic region for the desired period. Encapsulating drug molecules within macrocyclic host molecules (typically cyclodextrins) causes the formation of different guest-host complexes that shield the drug molecule from the aqueous environment [3,4]. Etoricoxib (EtR), also known as 5-chloro-6-methyl-3- [4-(methyl sulfonyl) phenyl]-2, 3-bipyridine, is a 2nd-generation cyclooxygenase-2 inhibitors. It is more effective than nonsteroidal anti-inflammatory drugs (NSAID). However, its poor water solubility could cause formulation problems, delaying absorption and onset of action, minimizing its medicinal application [5]. Cyclodextrin may improve the solubility of weakly lipophilic drugs when used as a complexing agent. The EtR structure is given in Figure 1.

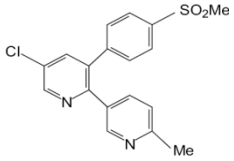

Figure 1: Etoricoxib Structure

Cyclodextrins (CDs) are a prominent excipient that attracts attention and is widely used mainly as a solubilizing complexing agent. CDs, which are cyclic oligosaccharides, possess an outer hydrophilic layer and a slightly lipophilic core. CDs may dissolve lipophilic drugs in aqueous solutions by forming hydrophilic ICs. They have become popular building blocks for various forms of drug administration due to their fascinating toxicological profile and capacity to partially or host bioactive molecules (e.g., medicines) while protecting them from the external environment. Their bond-forming capacity improves when they self-assemble, mix, or copolymerize with other molecules. CDs have a high affinity for specific drug molecules and are passed on to the carrier system, resulting in a distinctive drug delivery mechanism that has increased the soluble concentration, dissolution rate, stability of drugs, and their bioavailability in aqueous media [6]. The work is intended to evaluate the possibility of enhancing etoricoxib solubility by the complexation with cyclodextrins. Geriatric and pediatric patients have experienced dysphagia with conventional tablets. To bypass this limitation, scientists have created a novel approach for drug delivery in the form of oro-dispersible tablets. The European Pharmacopoeia 2002 states that ODTs are tablets placed on the tongue and disintegrate in seconds before swallowing. It can also be called fast melting, dissolving, or disintegrating tablets. The advantages of administration without water anywhere and anytime make it suitable for geriatric or pediatric cases. It can be considered a dosage form choice due to its advantages, such as enhanced bioavailability, rapid action, and better patient compliance [7].

MATERIALS AND METHODS

Materials

Aurobindo Pharma in Hyderabad provided Etoricoxib, β-CD, and HP β-CD as a gift sample. As gift samples, crospovidone, sodium starch glycolate, Ac-di-sol, and PEG 4000 (fine powder) were obtained from Alembic Pharmaceutical Ltd.. Microcrystalline cellulose, pearlitol SD 200, were purchased from Finar Chemicals Ltd. Ahmedabad, Aerosil from Thomas Baker chemicals Pvt. Ltd, Mumbai. Methanol was purchased from Pallav Chemicals and Solvents Pvt. Ltd., Tarapur, Bolsar. All other analytical-grade ingredients were used in the work.

Methods

Linear plot of etoricoxib

50mg of the drug was accurately weighed and taken in a 50 mL volumetric flask. Then, 5 ml of methanol was added to dissolve the drugs. Standard solutions from 5-50ppm were prepared using phosphate buffer pH 7 containing 1% SLS. The linear plot was plotted between absorbance and Concentration using a Shimadzu 1800 UV—Vis Spectrophotometer.

Study on phase or saturation solubility [8-11]

Higuchi and Connors performed the study. The phase or saturation solubility study was conducted using a water bath shaker (Remi Instrument Division, Mumbai) for 72 h at 37±0.5ºC. The values for Gibbs free energy (ΔG_{tr}^{0}) of transfer were calculated from the equation:

$$\Delta G_{tr}^{\circ} = -2.303\ RT\ \log \frac{S_0}{S_s}$$

$S_{o,}$ drug solubility in aqueous solutions of carriers

S_s drug solubility in pure water. Considered in molar ratio

Drug Dissolution study

The dissolution rate test used a USP apparatus type II (Lab India Disso 2000) with 900 mL of phosphate buffer (pH 7) and 1% SLS. The test was carried out on 120 mg of pure EtR. Samples (5 ml) were removed at intervals (5, 10, 20, 30, 45, 60m), and volume was replaced with fresh dissolving media. Absorbance was noted at 234 nm after filtration and suitable dilution for the samples withdrawn (Shimadzu UV-1800, Japan) [13].

Preparation of ICs

Inclusion complexes of etoricoxib with cyclodextrins were prepared by taking the calculated weighed quantities of etoricoxib and respective cyclodextrin in a mortar. A water: methanol mixture at a 1:10 ratio was used as a solvent. The solvent was added to the etoricoxib—cyclodextrin powder mixture by hand mixing for sufficient time to support the complexation of etoricoxib and cyclodextrin. The mixture was dried and passed through a 30 mesh sieve to obtain the mixture as a dry powder, i.e., ICs.

Drug Content Study

Percent drug content was obtained by preparing 20 and 30 µg/mL solutions by taking the drug equivalent to 50 mg from the ICs (treated as test solutions). The absorbance value of these test solutions was compared with the absorbance value of 20 and 30 µg/mL standard solutions obtained by taking the pure drug (values obtained in the preparation of linear plot). The test and standard absorbance ratio were multiplied by a hundred to obtain the percentage of drug content. This estimation ensures drug content uniformity in the ICs [12].

Preparation of Etoricoxib- β-CD ICs

Etoricoxib ICs with β-CD were made using a kneading approach at 1:0.125, 1:0.25, 1:0.5, 1:1, and 1:2 (w/w) ratios. All the preparations were passed through a 30-mesh sieve and placed in a desiccator until use [2].

Dissolution rate of Drug-β- CD ICs

The study was carried out similarly to the dissolution study of drugs. Dissolution media pH 7 phosphate buffer solution was mixed with 1% SLS. Samples containing drugs equivalent to 120 mg were taken from the inclusion complex formulations [14,15].

Dissolution rate of Drug-HP β -CD ICs

The study was carried out similarly to the dissolution study of drugs. Dissolution media pH 7 phosphate buffer solution was mixed with 1% SLS. Samples containing drugs equivalent to 120 mg were taken from the inclusion complex formulations.

Formulation of oro-dispersible tablets

Oro dispersible tablets (ODTs)are designed to break and disperse in seconds in the oral cavity without using water, offering an effective and convenient suspension for patients with swallowing difficulties (dysphagia), such as pediatric, geriatric, and psychiatric patients [16,19]. The development of ODTs addresses several critical issues associated with conventional oral dosage forms. From a pharmaceutical perspective, the formulation of ODTs involves sophisticated techniques to ensure quick disintegration and a pleasant taste with adequate stability [20]. Different techniques have been employed, including freeze-drying (lyophilization), direct compression, and sublimation, each with unique advantages and challenges. The choice of excipients is important in optimizing the disintegration time, mouthfeel, and overall patient feeling [21]. Ensuring mechanical strength to endure handling with packaging while preserving quick disintegration properties requires a delicate balance. Additionally, achieving taste masking, especially for bitter drugs, is essential to ensure patient acceptability [22]. Oro-dispersible tablets of etoricoxib were made using an equivalent amount of the drug (120 mg) in the ICs of β-CD. All the ingredients were weighed, passed through a 40 mesh sieve, and mixed to get a homogeneous mixture (except lubricants), which were added in the last step and mixed roughly. The tablets were compressed by direct compression. The formulation table is given in Table 1.

Evaluation tests for tablets [23]

Hardness

The hardness of the tablets is a critical parameter in the formulation of ODTs. The hardness will affect the dispersion time, and less hardness may not withstand the mechanical stress during shipping and handling. Hence, the hardness was maintained between 2.5–3kg/cm^2

Friability

Friability was tested using Roche friability. Twenty-five tablets were taken and rotated for four minutes, and the weight loss was determined.

Disintegration test

The disintegration test for tablets was performed by taking 6 tablets in a disintegrating test apparatus and running the DT apparatus to note the tablets' DT.

Test for Dispersion

The dispersion test is an important evaluation parameter for ODTs. The same two tablets were in a beaker containing 100 mL of water. When required, the contents were stirred gently at the top and waited for 3 minutes. After 3 minutes, the content was

poured through a 710 µm sieve (22 mesh), and no residue remained over the sieve, indicating the tablet passed the test.

Differential Scanning Colorimetry

The thermal behavior of the drug carrier used in the inclusion complexes was studied using a differential scanning calorimeter (DSC 4000, Perkin Elmer, USA). A sample of 5 mg was kept in an Al pan and sealed. The isothermal study process was kept at 40°C/m and a flow rate of 25 ml/m at a temperature range of (5-300°C) in an atmosphere of N_2 as a purge gas.

FT-IR Studies

An interaction study used FT-IR spectroscopy (Shimadzu, Japan, FTIR-8400S). The spectra were obtained for both the drug carrier and etoricoxib. Samples were made using KBr discs and scanning from 400-4000 cm^{-1}.

Table 1: Formulation of etoricoxib oro-dispersible tablets

S.No.	Ingredients (in mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Etoricoxib ICs (equivalent to 120 mg of drug)	240	240	240	240	240	240	240	240	240
2.	Crospovidone	12	24	36	-	-	-	-	-	-
3.	Sodium starch glycolate	-	-	-	12	24	36	-	-	-
4.	Croscarmellose sodium (ac-Di-Sol)	-	-	-	-	-	-	12	24	36
5.	Pearlitol SD 200	40	40	40	40	40	40	40	40	40
6.	Microcrystalline cellulose	34	22	10	34	22	10	34	22	10
7.	PEG 4000 (Fine Powder)	2	2	2	2	2	2	2	2	2
8.	Aerosil	2	2	2	2	2	2	2	2	2
	Total weight	330	330	330	330	330	330	330	330	330

RESULTS

Figure 2 shows the linear plot for etoricoxib, the R^2 value, and the regression equation.

Table 2: Showing the values of Gibbs free energy

Concentration of carrier in water (% w/v)	ΔG_{tr}^0 (J/mol)	
	β- CD	HP β- CD
1%	– 1520.45	– 1430.45
2%	– 2212.10	– 2172.10
3%	– 4637.26	– 4537.26

Study on phase or saturation solubility

An increase in Gibbs free energy (ΔG°tr) values in negative indicates the spontaneous nature of drug solubilisation with an increase in carrier concentration. The result is shown in Table 2.

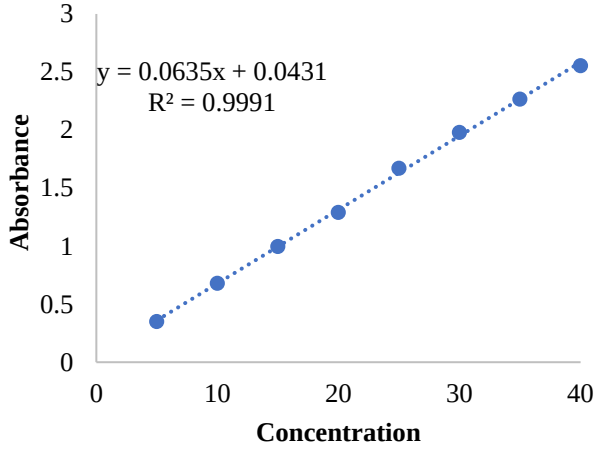

Figure 2: Linear Plot for etoricoxib

Drug Release of Etoricoxib (%)

Table 3: Showing percentage drug release of etoricoxib

Time (min)	Distilled Water	Distilled water + 1% SLS	Phosphate buffer with 1% SLS
0	0	0	0
5	28.09%	31.98%	35.05%
10	34.92%	47.63%	48.95%
20	41.44%	54.95%	57.28%
30	57.49%	62.28%	64.14%
45	67.66%	68.82%	71.07%
60	78.79%	76.08%	79.68%

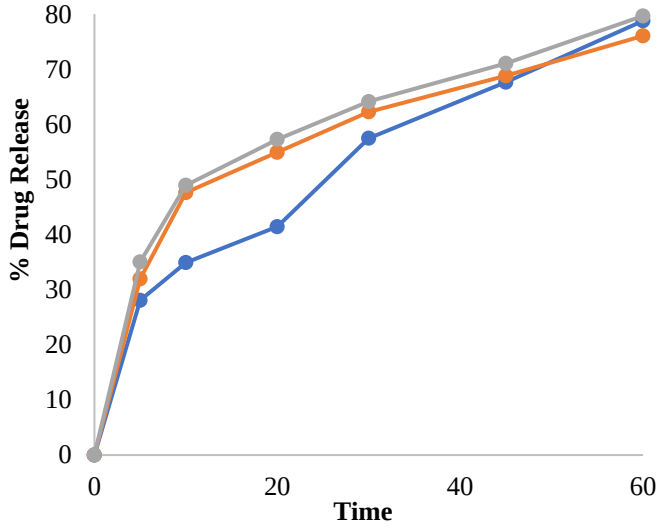

Figure 3: Percentage of drug release of etoricoxib

Drug content

The percentage drug content in inclusion complexes was found to be between 98-100 %.

Hardness

The tablets' hardness was between 2.5 to 3 kg/cm^2.

Disintegration time (DT)

The DT of F2 formulations showed 25-30 seconds, showing satisfactory results with crospovidone, whose mechanism involves swelling and burst releasing.

Friability

The tablets' friability was less than 1 %, indicating that the test passed. The dispersion test was passed as per IP, as the dispersion time was less than 3 minutes.

Dissolution rate of Drug-β- CD ICs

Table 4: Rate of dissolution of etoricoxib ICs by kneading technique using β-CD

Time (min)	F_1 (%)	F_2 (%)	F_3 (%)	F_4 (%)	F_5 (%)
0	0	0	0	0	0
5	34.87	35.78	39.21	44.2	42.5
10	45.42	49.50	56.32	64.92	62.12
20	58.15	62.17	71.03	75.6	71.76
30	69.43	71.19	80.26	83.66	77.34
45	79.43	84.30	88.53	92.36	87.44
60	82.07	85.58	91.41	96.42	91.05

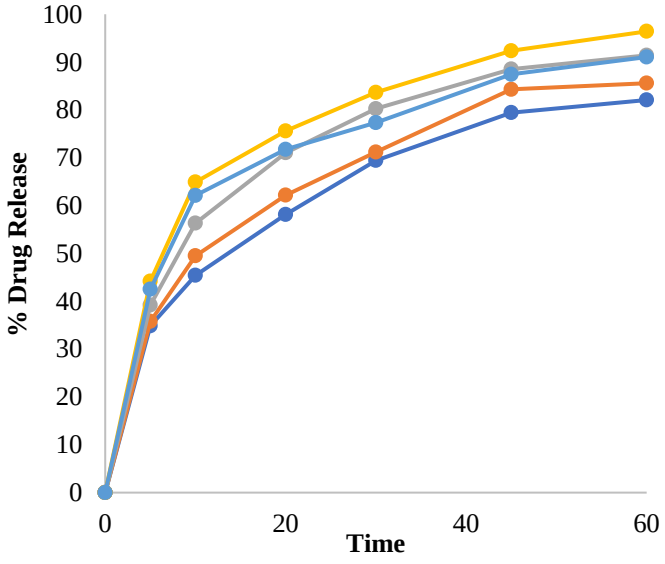

Figure 4: Drug percentage release of EtR SDs using β-CD

Dissolution rate of Drug-HP β -CD ICs

Table 5: Dissolution rate of etoricoxib ICs by kneading technique using HP β-CD

Time (min)	F_1 (%)	F_2 (%)	F_3 (%)	F_4 (%)	F_5 (%)
0	0	0	0	0	0
5	33.62	41.76	34.55	38.96	40.96
10	45.95	59.47	53.58	60.72	61.32
20	56.62	64.85	65.40	66.34	76.4
30	62.21	67.27	71.20	72.90	81.45
45	71.07	71.43	74.5	79.46	91.16
60	78.46	84.99	87.41	89.56	93.52

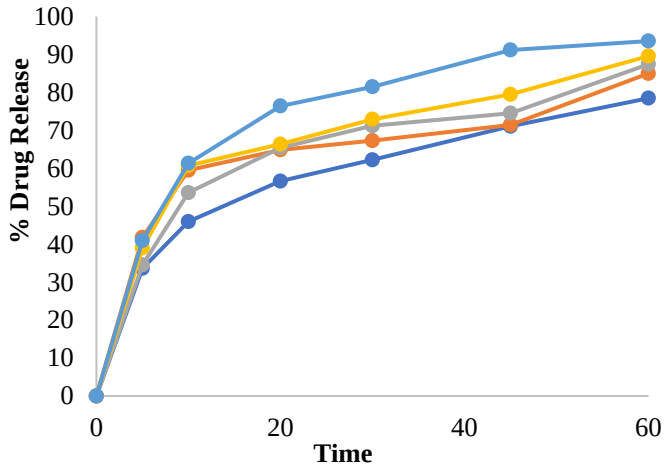

Figure 5: % Drug release of etoricoxib ICs using HP β-CD

Dissolution: The study observed that F2 formulations fulfill the objectives of working at the optimum concentration of super disintegrant and other ingredients. A more than 76 % release in 30 minutes and more than 87% of the drug was calculated, indicating that the formulations fulfill the dissolution criteria.

IR Analysis: The result of the peaks observed are discussed as follows: in the IR spectra of etoricoxib, the peaks at 3059.10 are due to aromatic C-H stretching SP2, 2920.23 may be due to Alkane C-H stretching SP3, 1869.02 is due to C=O stretching, 1597.06 is due to aromatic C=C stretching, 1138.00 may be due to C-F stretching, 1065.92 is due to C-O stretching ether, 775.38 is due to C-Cl stretching. Similarly, for the drug-polymer mixture, i.e., etoricoxib and β-CD, the peaks at 3647.39 are due to O-H stretching alcohol, 1429.25 may be due to C=C stretching, 1296.16 is due to C-F stretching, 844.82 may be due to C-Cl stretching. Similarly, in Drug polymer mixture, i.e., etoricoxib and HP-β-CD the peaks at 3664.75 is due to O-H

stretching, 1604.77 may be due to C=C stretching, 1300.02 is due to C-F stretching, 850.61 may be due to C-Cl stretching. Though there is a shift in peak values due to the formation of bonds for drug cyclodextrin complexes, these important peak values for the drug are still retained, indicating no significant interaction. The IR spectrum is given below for all those required.

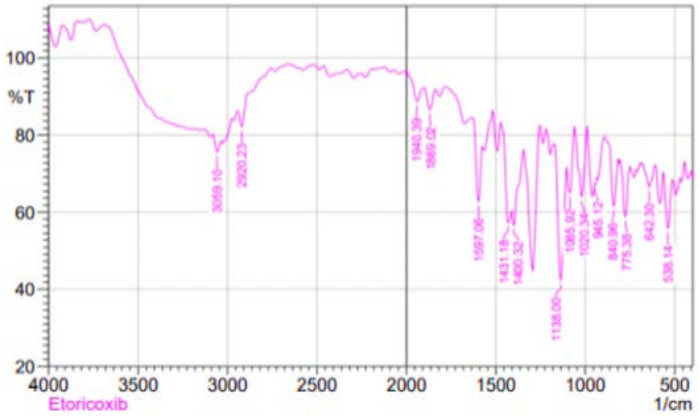

Figure 6: Spectrum for etoricoxib

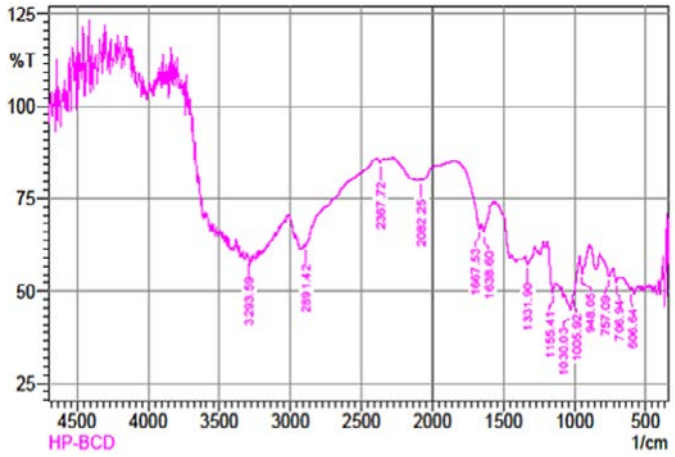

Figure 7: Spectrum for HP-β-CD

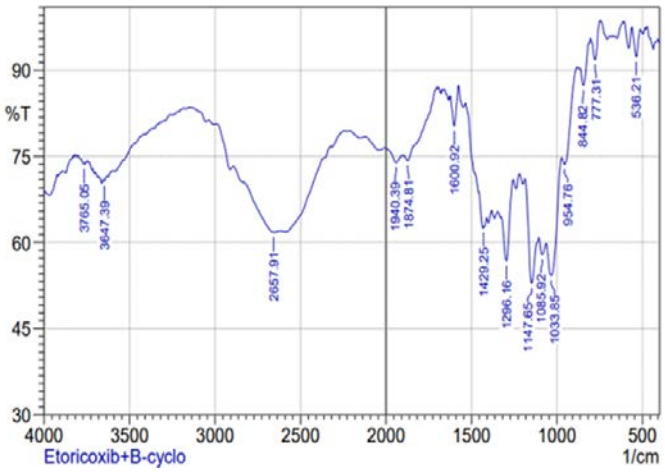

Figure 8: Spectrum for etoricoxib with β-CD

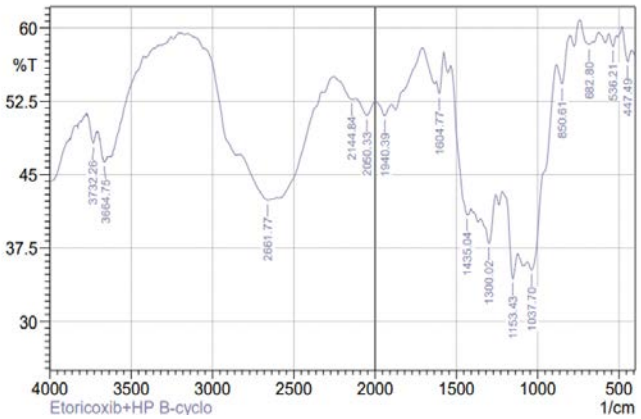

Figure 9: Spectrum for etoricoxib with HP-β-CD

DSC

The DSC analysis reveals the sharp endothermic (down) peak for etoricoxib at 141, corresponding to its melting point and indicating its crystalline nature. However, there is no sharp peak in the drug's ICs; it is a broad peak with retention of melting points for the drug and cyclodextrins, indicating compatibility. This indicates the drug's homogeneous distribution in CDs. The thermograms are given below.

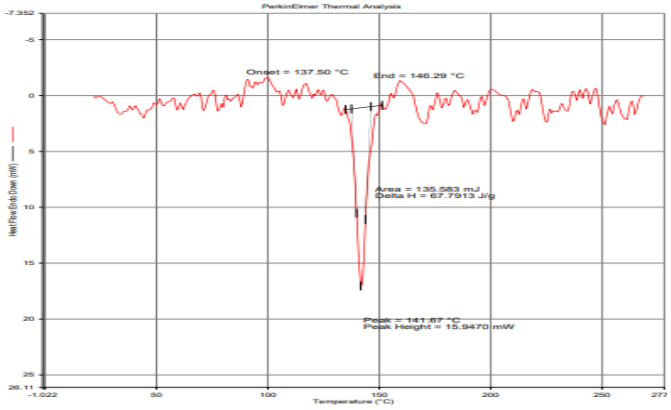

Figure 10: DSC for etoricoxib

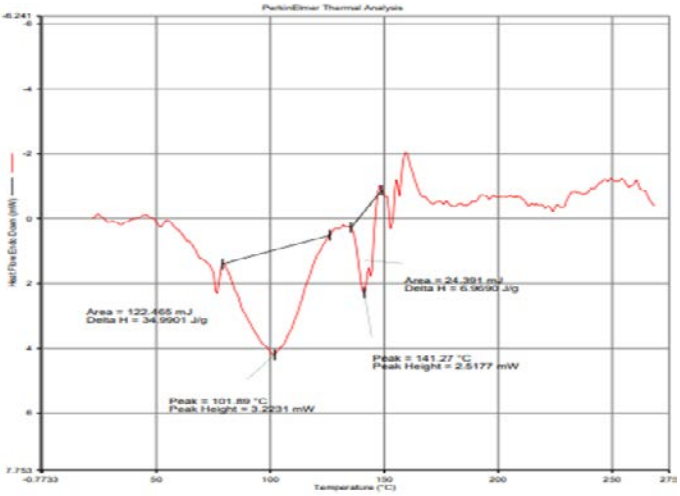

Figure 11: DSC for etoricoxib + β-CD

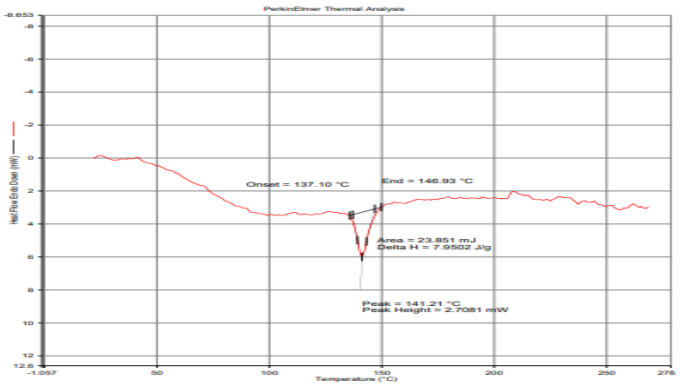

Figure 14: DSC for etoricoxib + HP-β-CD

ANOVA for selected factorial model

Table 6: Showing 2^2 factorial 2-level design

Std.	Run	Factor 1	Factor 2	Response 1
		A: β-CD	B: Crospovidone	R1
4	1	240	36	91.05
1	2	60	12	91.41
5	3	120	24	96.42
3	4	60	36	88.23
2	5	240	12	87.42

Table 7: Showing Response 1: % Drug Release

Source	SS	df	SM	F-value	p-value
Model	0.0000	0		2.53	0.0121
Residual	49.99	4	12.50		
Cor Total	49.99	4			

SS–Sum of square, SM–Square of Mean Factor coding is Coded. Sum of squares is **Type III – Partial**

A P-value less than 5% indicates that model terms are significant. Hence, there are no significant model terms here. The experiment's design is a two-factorial two-level fractional design. The P value found was 0.0121, which is less than 0.05, which indicates that the strategy is significant at the ratio of ICs of drug—β-CD (1:1w/w) with the optimized formulation.

Table 8: Showing Fit Statistics

S.D.	3.54	R^2	0.998
Mean	90.91	Adjusted R^2	0.997
C.V. %	3.89	Predicted R^2	-0.5625
		Adeq. Precision	NA(1)

Adequate Precision measures the signal-to-noise ratio. A ratio of 3.67 indicates an inadequate signal, and this model need not be used to navigate the design space.

Table 9: Showing Coefficients in Terms of Coded Factors

Factor	Coefficient estimate	df	Std. Error	95% CI Low	95% CI High
Intercept	83.75	1	3.50	72.62	94.88
Ctr Pt 1	16.24	1	7.82		

Normal and Half-Normal plot: The Half-Normal plot is a graphical tool used to help identify which experiment factors have significant effects on the response, and the normal plot explains how to assess whether a data set is approximately normally distributed.

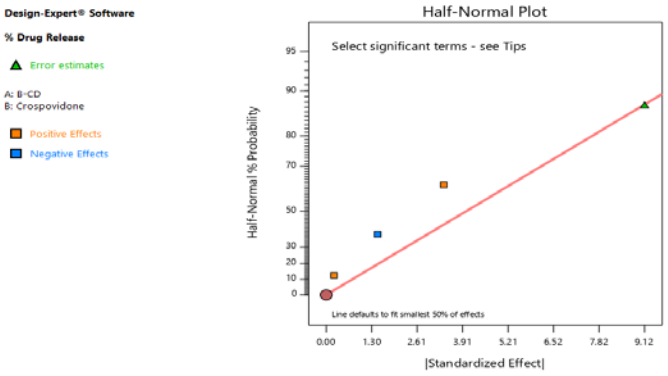

Figure 12: Half-Normal plot showing % DR

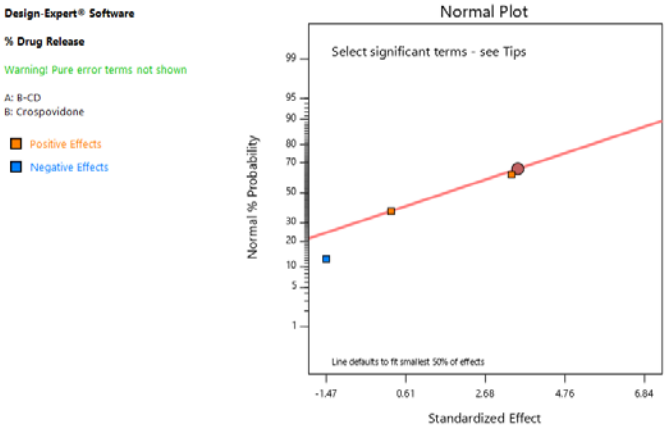

Figure 13: Normal plot showing % DR

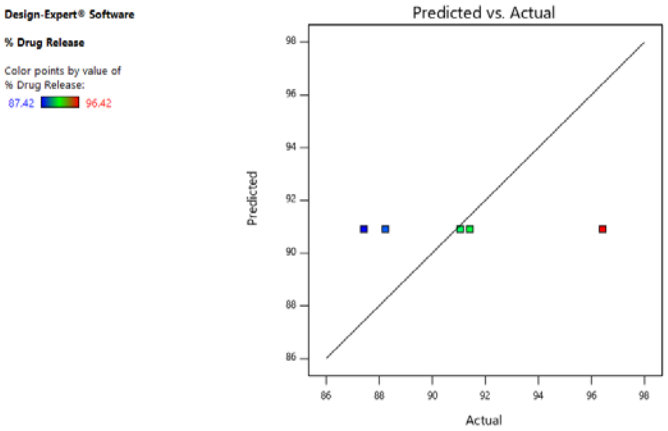

Figure 14: Showing Predicted Vs Actual % DR

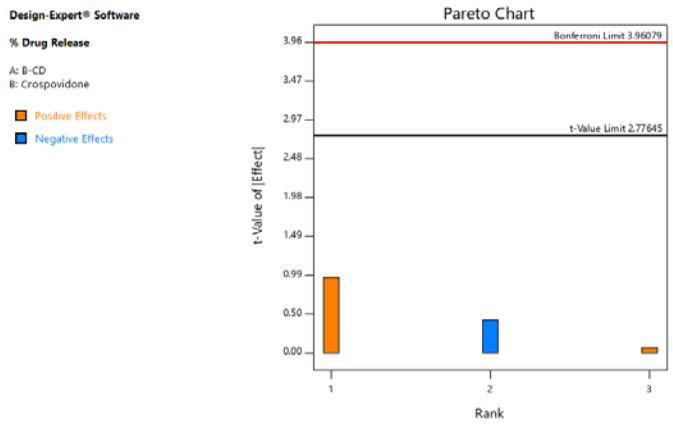

Figure 15: Showing Pareto Chart for % DR

3D Response

The 3D response curve and the predicted response curve in the design space show a positive response to the optimized formulation with a higher predicted value of % drug release. Hence, β-CD can be used to enhance the solubility of etoricoxib, and the ICs of drug-β-CD can be used to design etoricoxib DTs successfully.

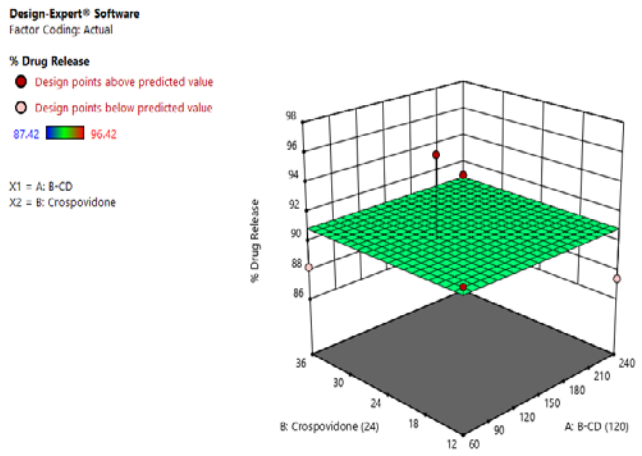

Figure 16: Showing 3D Response of % DR

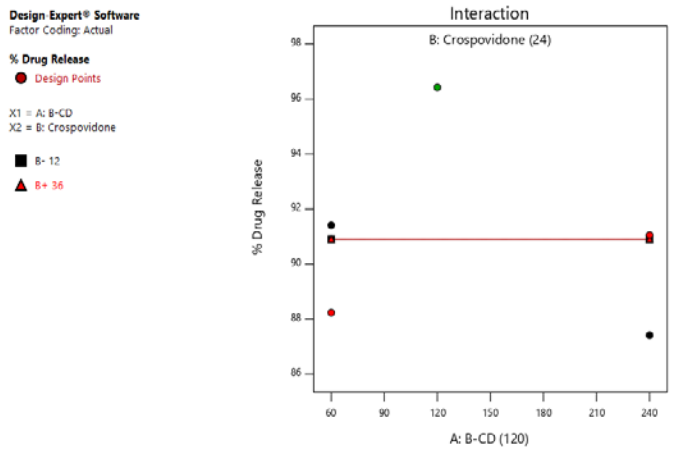

Figure 17: Showing Interaction of % DR

Phosphate buffers at pH 7 with 1% SLS were utilized as a medium for the dissolution testing of etoricoxib. From the UV spectroscopic analysis, the λmax value observed for the drug corresponds to many reported values. From the saturation solubility study and Gibbs free energy values, it is observed that an increase in the concentration of CDs increases the solubility of the drug. The drug content study revealed no drug or carrier loss in the ICs and found nearly 98-100%. The ODTs passed the dispersion test, and the friability in all the formulations was less than 1%. The disintegration time for the selected tablets (F2) was 25-30 seconds, showing satisfactory results with crospovidone, whose mechanism involves swelling and burst to release. The water solubility of cyclodextrins and their abilities for amorphization, solubilization, and complex formation enhanced the drug's solubility. The drug-ICs demonstrated increased dissolution rates. The study observed that F2 formulations are fulfilling the objectives of working at an optimum concentration of super disintegrant and other ingredients. A release of more than 76 % in 30 minutes and more than 87% of the drug was calculated, indicating fulfillment of the dissolution criteria. Cyclodextrin derivatives, with their lipophilic inner cavity and hydrophilic outer, increase solubility by lowering the interfacial tension between hydrophobic substances and the solvent system, thereby enhancing the drug's solubility, stability, and bioavailability. Studies of DSC and IR confirmed that the drug is compatible with cyclodextrins, as characteristic peaks for the drug were retained in the mixture analysis. The ANOVA design is a level two factorial fractional design with single response % drug release. The P value is less than 0.05%, which indicates the model is significant, and the R2 value was found to be 0.998. Adequate Precision measures the signal-to-noise ratio where there is no adequate precision, which means the model is adequate and there is no error.

CONCLUSION

In the current investigations, HP β-CD and β-CD- ICs of etoricoxib were formulated. The solubility and dissolution rate of etoricoxib can be enhanced by formulating its ICs with β-CD. A qbD approach was used for optimization and response surface plots, contour plots were drawn, and a statistical approach was used to select optimum formulations. The promising results of this study suggest that the preparation of inclusion complexes is an important strategy for improving solubility. The study result showed that β-CD is preferred to HP β-CD for enhancing the solubility of etoricoxib at a (1:1w/w) ratio. ODT formulation

(F_2) was selected as an optimized one containing 7% crospovidone as a super disintegrant. The combination of β-CD and PEG 4000 in the ODTs exhibited a synergistic effect on the responses. Such an approach can be exploited to improve the dissolution rate of other low water-soluble drugs. A critical limitation of the ODTs is that they may not withstand mechanical stress during handling and shipment because the tablets have less hardness. Moreover, the super disintegrants used in the formulation of ODTS are hygroscopic, and particularly crospovidone is highly hygroscopic. Hence, proper packaging, selection of container system, and storage should be rationally selected so as not to affect the disintegration time, dissolution rate, and stability of the tablets.

ACKNOWLEDGMENT
We acknowledge RCPHS for availing of the required facilities and conducting IR and DSC studies.

FINANCIAL ASSISTANCE
Nil

CONFLICT OF INTEREST
The authors declare no conflict of interest

AUTHOR CONTRIBUTION
Anjan Kumar Mahapatra designed the study and planned the work with its aim and objectives, reviewed the manuscript, and edited the article. Siddharth Dora Sanatan Parida, Usharani Bal, Bandana Rani Jena, and Madhusmita Lenka performed the work, collected data, and wrote the manuscript.

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