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"Ketoprofen Loaded B-Cyclodextrin Complexation For Enhancing BCS Class II Drugs Solubility."

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Abstract

Ketoprofen is the most widely used non-steroidal anti-inflammatory drug (NSAID) which comes under BCS Class II, making it effective for relieving pain and inflammation. However, despite its therapeutic benefits, Ketoprofen has low aqueous solubility, which significantly hinders its oral bioavailability. This limitation highlights the need for innovative strategies to improve its absorption in the body. One promising approach involves forming cyclodextrin inclusion complexes, which act as a specialized delivery system for drugs with poor solubility. In our study, we focused on synthesizing Ketoprofen/ β- β-cyclodextrin inclusion complexes using microwave irradiation, with molar ratios of 1:1 and 1:2. The main goal of our research is to investigate how these β-cyclodextrin complexes affect the solubility and bioavailability of Ketoprofen. To thoroughly evaluate the effectiveness of this novel system, we will examine various parameters, including the percentage of practical yield. This will be carried out using exacting laboratory techniques such as *in-vitro* drug dissolution investigations, differential scanning calorimetry (DSC), and Fourier-transform infrared spectroscopy (FTIR). We will also assess drug content uniformity to ensure a comprehensive analysis of how these complexes enhance the properties of ketoprofen.

Keywords: β- Cyclodextrin, Inclusion complex, Ketoprofen, Microwave Irradiation

Introduction:

Drug solubility is an important factor in the invention and development of new drugs and dosage forms. A Biopharmaceutical Classification System (BCS) Class II has low solubility. It requires a prospective dosage form that will aid in achieving the drug's solubility and, in comparison, bioavailability goals. Different methods are created to increase their solubility. The most sophisticated drug carriers, cyclodextrin inclusion complexes, can enhance the bioavailability through oral routes of administration and dissolution properties of drug substances that are not very water-soluble. This research aims to combine β-cyclodextrin and ketoprofen to improve the drug's water solubility. This study aims to create a complex of β-cyclodextrin and Ketoprofen to enhance the drug's solubility in water. Since Ketoprofen is a weakly water-soluble drug, this complex could significantly improve its aqueous solubility. Ketoprofen, also known as α-(3-benzoyl phenyl) propionic acid, is a popular non-steroidal anti-inflammatory medication that has antipyretic and analgesic effects. It is utilized to treat acute and chronic inflammatory conditions. This drug is crystalline and exhibits poor water solubility [1, 2]. Ketoprofen functions by inhibiting the enzymes phospholipase A, cyclooxygenase, and prostaglandin synthase. Additionally, it can induce central analgesia by acting at a supraspinal level. Following oral administration, Ketoprofen reaches peak plasma concentration in less than one hour. According to the BCS, Ketoprofen is categorized as a weak acid due to its poor water solubility (0.13 mg/mL) [3-6]. In this carrier system, cyclodextrin (CD), a cyclic oligosaccharide molecule made up of a macrocyclic ring of glucopyranose subunits connected by α-1, 4-glycosidic bonds plays an important role. It features a unique cavity structure, with hydrophobic properties in the inner cavity and hydrophilic properties in the outer cavity. The conical truncated structure of CDs allows them to encapsulate hydrophobic molecules in the cavity, thereby enhancing their water solubility [7]. Cyclodextrins are categorized into natural cyclodextrins and derived cyclodextrins. Different ionic, lipophilic, and hydrophilic and the use of derivatives have been created to improve the biopharmaceutical and physicochemical properties of drugs and enhance the entrapment capacity of natural cyclodextrins [8,9]. Natural cyclodextrins are further classified based on the number of glucopyranose units as α, β, and γ, which are composed of 6, 7, and 8 units respectively & properties of α, β, γ cyclodextrin [10]. Hydroxypropyl- β-cyclodextrin (HP- β- CD), sulfobutyl ether- β- cyclodextrin (SBE- β- CD), and randomly methylated- β-cyclodextrin (RM- β- CD) are widely used derivatives of cyclodextrin for drug complexation [11, 12].

The administration of medications of BCS classes II and IV that are poorly soluble in water through different routes presents a major challenge. Although techniques such as solubilization [13,14], co-solvency [15,16], and solid dispersion [17] may improve drug absorption, dissolution, and solubility characteristics, they have drawbacks such as poor drug loading and more doses. In contrast, cyclodextrin complexation offers an alternative method to enhance biopharmaceutical and physicochemical characteristics [18, 19]. β-Cyclodextrin is the most commonly used type of cyclodextrin because of its larger cavity size, which makes it more appropriate than other cyclodextrins to encapsulate a wide range of molecules. The outer layer of β-cyclodextrin is hydrophilic, allowing it to form hydrogen bonds with different molecules and dissolve in water [20]. Advantages of β-cyclodextrin such as Improving Solubility and Dissolution Rate**,** Bioavailability enhancement, Higher stability against hydrolysis and thermal, Thermal stability, Chemical Stability, Storage stability, Photostability, Reduced odor and taste, and Permeability enhancement proving it is an advanced and promising drug carrier system for drugs with low solubility [21].

2. MATERIALS AND METHOD

2.1 Material used:

Ketoprofen serves as the active pharmaceutical ingredient provided by Arti Pharma Medicinal Products. To improve its solubility and stability, the formulation includes β-Cyclodextrin and ethanol as excipients which are sourced by Cydex Pharmaceuticals in Lawrence, Kansas, and Research Lab Fine Chem Industries in Mumbai. This combination creates a well-formulated and effective medication.

2.2 Method used: The microwave irradiation method was implemented to synthesize the ketoprofen-loaded β -cyclodextrin complex.

In this method, Ketoprofen and β-cyclodextrin were combined in the ratios of 1:1 and 1:2, then combined with a 1:1 v/v water-ethanol combination. The resultant paste was then microwaved at a temperature of 60°C for 90 seconds using an Electrolux microwave oven. After the completion of the reaction, additional solvents were added to wash the residual β-cyclodextrin and Ketoprofen. The precipitate was then filtered, and the resulting product was dried. The formula for developing the inclusion complex is mentioned in Table 1. The microwave irradiation method is displayed in Fig_1 & developed batches of β-cyclodextrin and Ketoprofen complex are shown in Fig_2 [21-23].

Table 1 Ingredients for Inclusion Complex Formulation

Sr. No.	Ingredients	Role of Ingredients
1.	Ketoprofen	NSAID
2.	β-cyclodextrin	Solubility enhancer
3.	Ethanol	Solvent
4.	Distilled water	Solvent

Fig_1 The microwave irradiation method

Fig_2 Ketoprofen- cyclodextrin complexes

2.3 Preformulation studies:

These are carried out on Ketoprofen (Active Pharmaceutical Ingredient) and mainly involve assessing organoleptic properties, determining the melting point, conducting FTIR and DSC analyses, establishing λ-max, and preparing a calibration curve [24].

1. Organoleptic Properties

Organoleptic properties such as the color and odor of Ketoprofen were determined.

2. Determination of melting point

It is determined using the open capillary method using Thiel's tube as shown in Fig_3 [24].

Fig_3 Melting point determination

3. FTIR analysis for identification

The FTIR absorption spectrum of Ketoprofen was obtained using a Shimadzu-FTIR spectrophotometer. In this process, 1- 2 mg of the sample was combined with potassium bromide (K- Br) and kept in a sample holder. The mixture was then compressed into discs for 5 minutes using a hydraulic press, and the IR spectrum was recorded.

4. Identification by using DSC analysis

DSC of Ketoprofen was conducted to generate a thermograph. A small sample of approximately 1-5 mg was analyzed using DSC on a Setline instrument. A sealed aluminum pan was used, and the temperature ranged from 40 ℃ to 300 ℃. At a flow rate of 20 mL/min, nitrogen gas was employed as the purge gas [24].

5. Determination of λ-max

A 10 mL solution with a concentration of 1000 µg/mL was created by dissolving 10 mg of ketoprofen in 2 mL of ethanol and diluting it with 8 mL of distilled water, 100 µg/mL was the concentration of a stock solution. Created by taking 1 mL of this solution and diluting it with 9 mL of distilled water. Between 200 and 400 nm was the range where the resultant solution's highest absorbance was found [24].

6. Preparation of calibration curve

From the stock solution, dilutions of concentrations 4 µg/ mL, 8 µg/ mL, 12 µg/ mL, 16µg/ mL, and 20µg/mL were prepared. The calibration curve of absorbance vs concentration was plotted [24].

2.4 Evaluation of Inclusion Complex

1 Percentage Practical Yield

The total amount of inclusion complexes was weighed and evaluated for the percentage yield (g/mL) of each formulation, then the yield was determined:

$$\text{Practical yield} = \frac{\textbf{Practical mass inclusion complex}}{\textbf{Theoretical mass (Drug+carrier)}} \times \mathbf{100}$$

2 Fourier- transform infrared- spectroscopy (FTIR)

It was recorded by using a Shimadzu- FTIR spectrophotometer where 1-2 mg of the sample was added with potassium bromide (K-Br) and kept in a sample holder, comprised into discs for 5 minutes in a hydraulic press, and the IR spectrum was recorded.

3 Differential Scanning Calorimetry (DSC)

Complexes prepared were subjected to DSC studies on a Setline instrument using a sealed aluminum pan over temperatures ranging from 40°C to 300°C. Approximately 1 mg sample was used where nitrogen gas was used as purge gas at a flow rate of 20 mL/ min.

4 *In- vitro* dissolution study

This was carried out at 50 rpm and 37 ± 0.5℃ with a USP paddle device and 0.1 N HCL (900mL) as the dissolve media. At appropriate intervals of 5, 10, 15, 20, 30, 45, and 60 minutes, the samples were periodically removed, and the volume was replaced with an equivalent volume of plain dissolving media. After diluting the samples, a UV spectrophotometer was used to measure the absorbances of the resultant solutions at 260 nm. The *In- vitro* dissolution study of Ketoprofen - β- cyclodextrin is shown in Fig_4.

Fig_4 *In-vitro* dissolution study

3. RESULTS AND DISCUSSION

3.1 Preformulation Study of Drug:

3.1.1 Properties of organoleptic:

The drug was white, odorless, and powder in nature which meets the specifications mentioned in I.P.2014.

3.1.2 Measurement of melting point (M. P):

It was found that pure ketoprofen has a melting point of 94 ℃, which is within the stated melting point range. Ketoprofen's melting point is shown in Table 2.

Table 2 Melting Point of Ketoprofen

Name	M.P. Observed	M.P. Reported
Ketoprofen	94°C	93-96°C

3.1.3 FTIR Analysis:

This study indicates characteristic peaks because of vibrations of principle functional groups at specific wave numbers which were compared with standard functional group frequencies. FTIR Spectrum for Pure Ketoprofen

FTIR Interpretation

The FTIR spectrum analysis of Ketoprofen indicates that it belongs to propionic acid derivatives. Figure_ 5 and Table 3 display the major functional groups present in Ketoprofen.

Table 3 FTIR Spectrum Interpretation for Ketoprofen

Functional Group	Observed Vibrational Frequencies (cm^{-1})	Standard Vibrational Frequencies (cm^{-1})
-C-C-(Stretching)	968.27	1000-800
-C-O-(Stretching)	1226.73	1350-1000
O-H (Bending)	1307.74	1500-1200
C-H (Bend in plane)	1435.04	1500-1300
C=C (Aromatic)	1583.56	1600-1400
C=O (Stretching)	1656.85	1900-1600

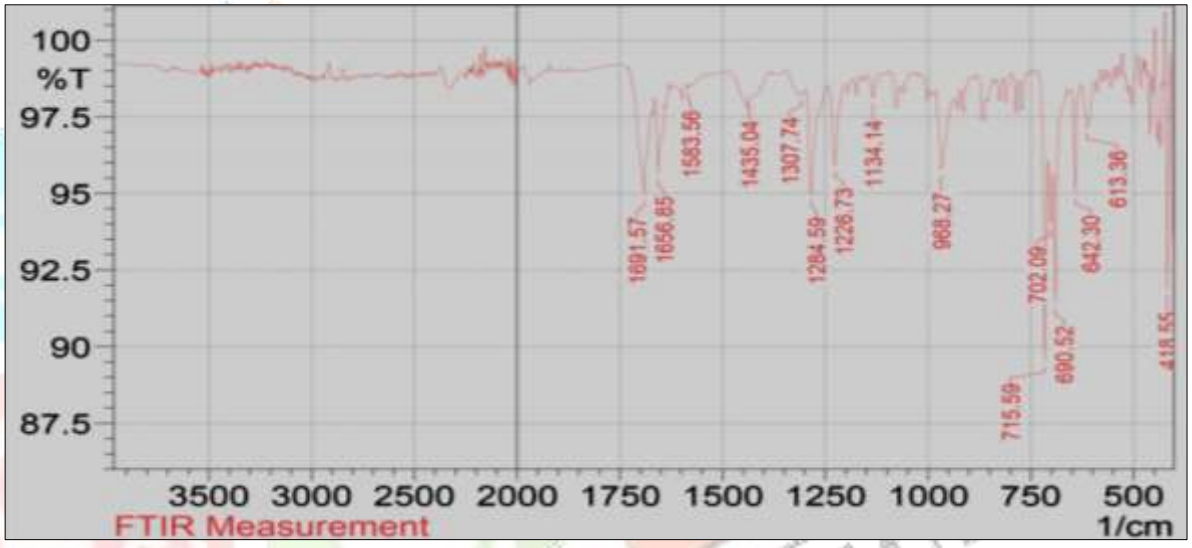

Fig_5 FTIR Interpretation of Ketoprofen

3.1.4 Differential Scanning Calorimetry

Ketoprofen's DSC thermogram revealed a strong endothermal peak at 96.49℃, which is the drug's stated melting point. Fig_6 shows the DSC of pure ketoprofen.

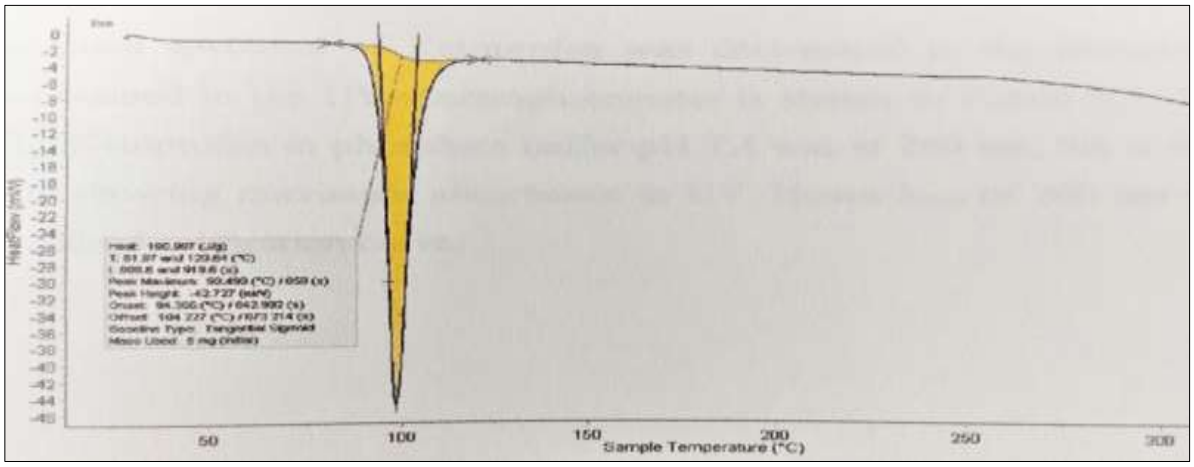

Fig_6 DSC thermogram of Ketoprofen

2.1.5 Identification of absorbance (λ max):

The UV absorption spectrum of Ketoprofen was determined in ethanol and distilled water. The scan obtained in the UV-spectrophotometer is shown in Figure_7. The maximum absorbance shown by Ketoprofen was at 260nm.

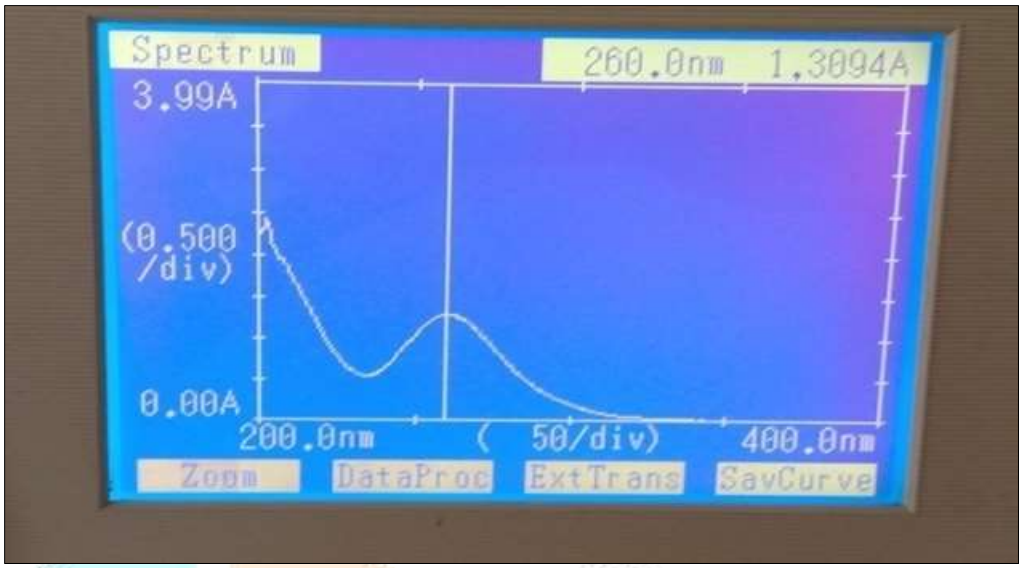

Fig_7 Absorbance by using UV-visible spectrophotometer

3.1.6 Preparation of calibration curve:

The Ketoprofen calibration curve, conducted in ethanol and distilled water, was shown to be linear within the concentration range of 4–20 µg/ mL. A calibration curve is shown in Fig_8 and Table 4.

Table 4 Calibration curve data of Ketoprofen

Drug	Ketoprofen
Solvent	Ethanol + Distilled water
λ-max (nm)	260
Equation	y = 0.048x + 0.034
Correlation factor (R^2)	0.999

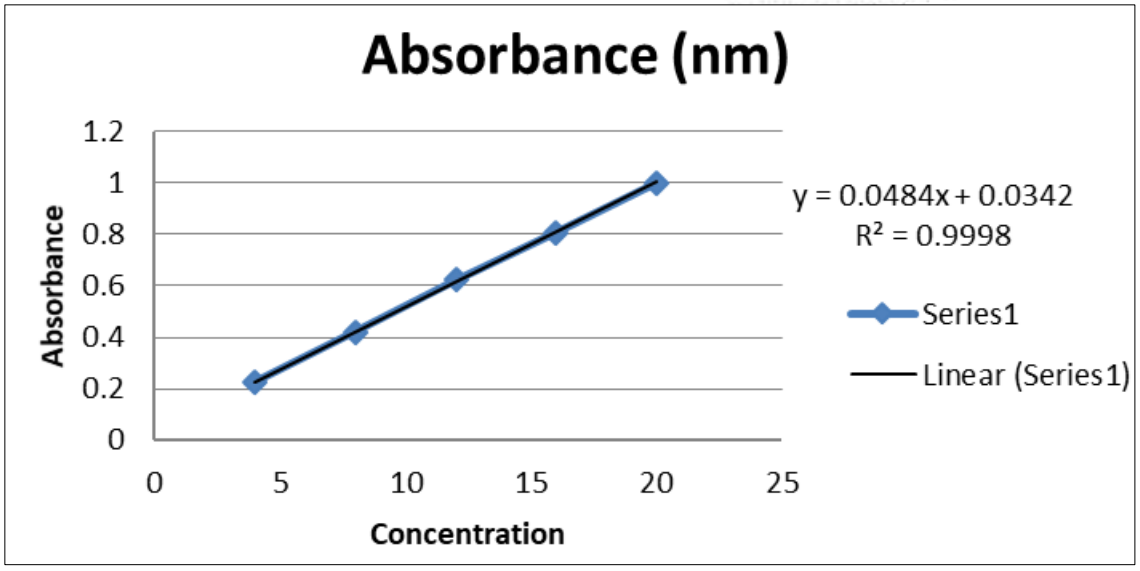

Fig_8 Calibration curve of Ketoprofen

5.2 Evaluation Parameters for Inclusion Complex:

5.2.1 Percentage Yield of Cyclodextrin Complex:

The percentage yield of the Cyclodextrin complex is shown in Table 5.

Table 5 Percentage Yield of Cyclodextrin Complex

Sr. No.	Formulation Code	Theoretical Yield	Practical Yield	% Practical Yield
1.	F1	500	310	62
2.	F2	750	482	64.27

5.2.2 FTIR Analysis of Formulations:

1. F1 formulation

In the FTIR analysis of the F1 formulation, the characteristic peaks were observed at the following wavenumbers: 1442.75 cm^{-1} (C- H bending in the plane), 968.27 cm^{-1} (C- O stretching), 1654.92 cm^{-1}(C-C stretching), 184.59 cm^{-1} (O- H bending), 1693.5 cm^{-1} (C= O stretching), and 2337.72 cm^{-1} (c= c stretching) as illustrated in Fig_9 and Table 6. These results show the presence of all the characteristic IR bands of the drug in the F1 formulation batch.

Table 6 FTIR Spectrum Interpretation for F1 Formulation

Functional Group	**Observed Vibrational Frequencies (cm^{-1})**	**Standard Vibrational Frequencies (cm^{-1})**
C-H (Bend in plane)	1442.75	1300-1500
C-O (Stretch)	968.27	900-1300
C-C (Stretch)	1654.92	1600-1700
O-H (Bending)	1284.59	1200-1500
C=O (Stretch)	1693.5	1600-1900
C=C (Stretch)	2337.72	2100-2400

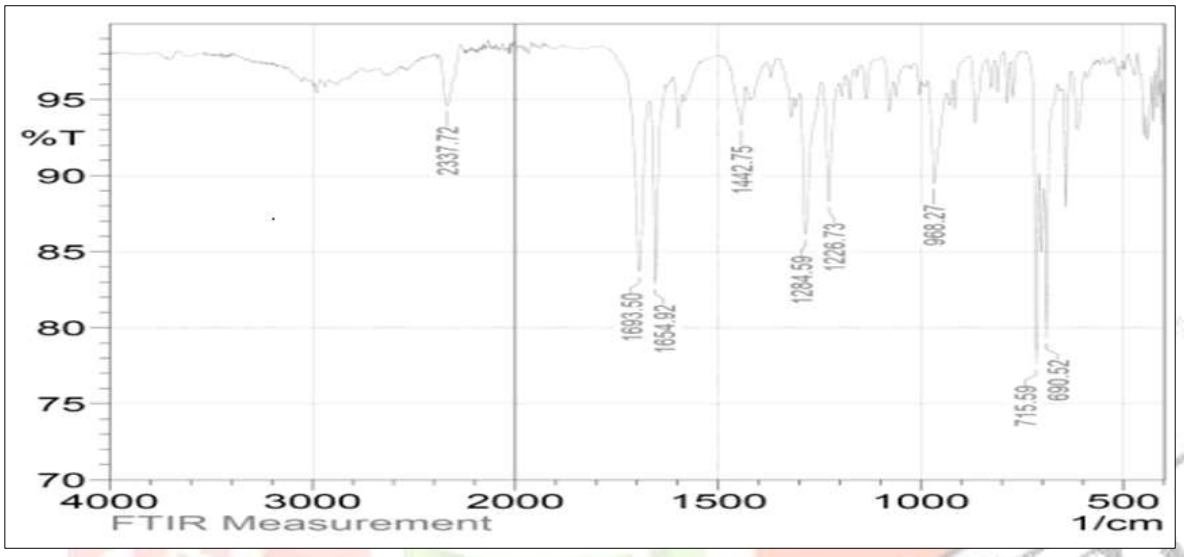

Fig_9 FTIR spectrum of F1 formulation

2. F2 formulation

The FTIR analysis of formulation batch F2 revealed characteristic peaks at specific wavenumbers: 690. 52cm^{-1}

For C- H (rocking), 866.04 cm^{-1} for C- C (stretching), 1319.31 cm^{-1} for O- H (bending), 2337.72 cm^{-1} for C= C (stretching), 1695.43 cm^{-1} for C= O (stretching) and 966.34 cm^{-1} for C- O (stretching) as shown in Fig_10 and Table 7. These peaks are indicative of the presence of the drug in the formulation F2.

Table 7 FTIR Spectrum Interpretation for F2 Formulation

Functional Group	**Observed Vibrational Frequencies (cm^{-1})**	**Standard Vibrational Frequencies (cm^{-1})**
C-H (Rocking)	690.52	600-900
C-C (Stretch)	866.04 1654.92	800-1200 1600-1700
O-H (Bending)	1319.31	1200-1500
C=C (Stretch)	2337.72	2100-2400
C=O (Stretch)	1695.43	1600-1900
C-O (Stretch)	966.34	900-1300

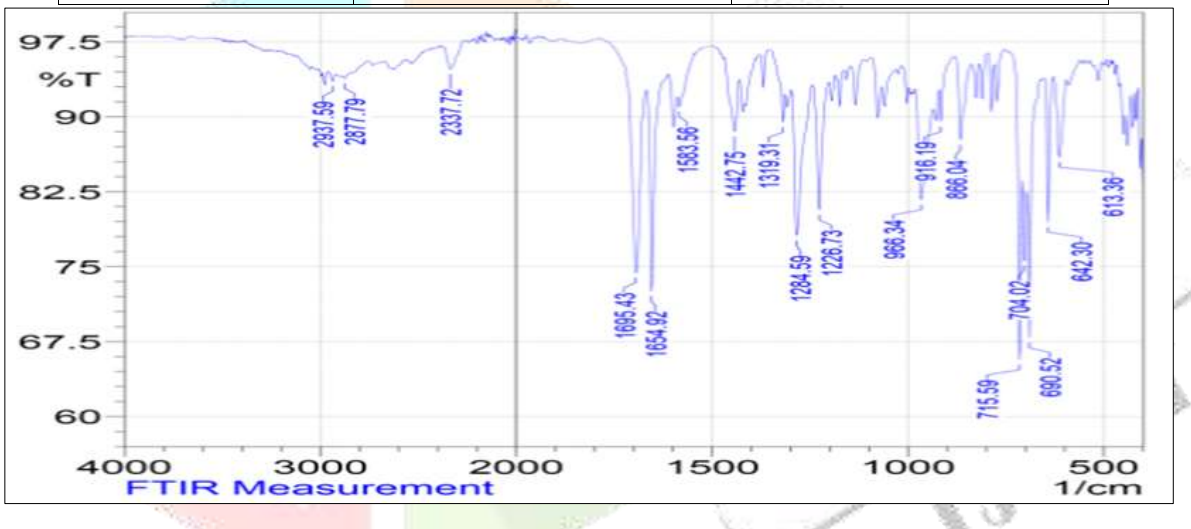

Fig_10 FTIR spectrum of F2 formulation

3.2.3 DSC Analysis:

1. F1 formulation

The DSC thermogram of the F1 formulation displayed two endothermic peaks at 93.9°C, indicating the presence of Ketoprofen, as illustrated in Fig_11. Additionally, a complex peak was noted around 375°C, likely due to the interaction between the drug and β-cyclodextrin. This suggests that the drug has been effectively entrapped within the cyclodextrin cavity.

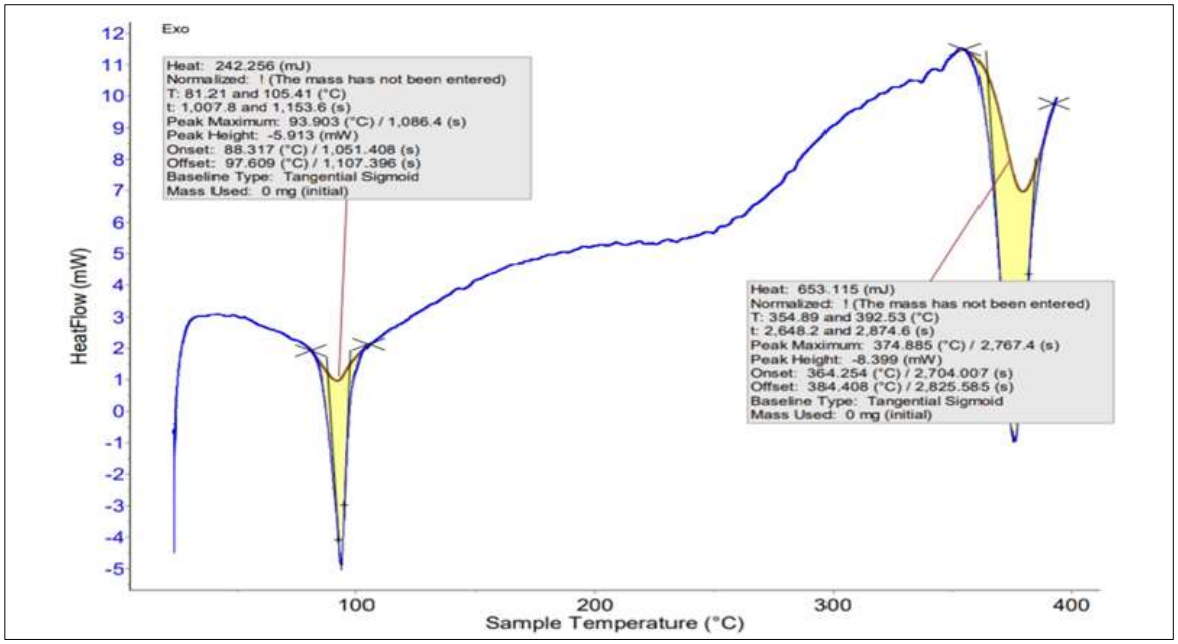

Fig_12 DSC thermogram of F1 formulation

2. F2 formulation

Three endothermic peaks were visible in the F2 formulation's DSC thermogram, as illustrated in Fig_12. The first peak occurs at 94.25°C, corresponding to Ketoprofen. The second peak, around 371.4°C, indicates a complexation between the drug and β-cyclodextrin, suggesting that the drug has been entrapped in the cyclodextrin cavity.

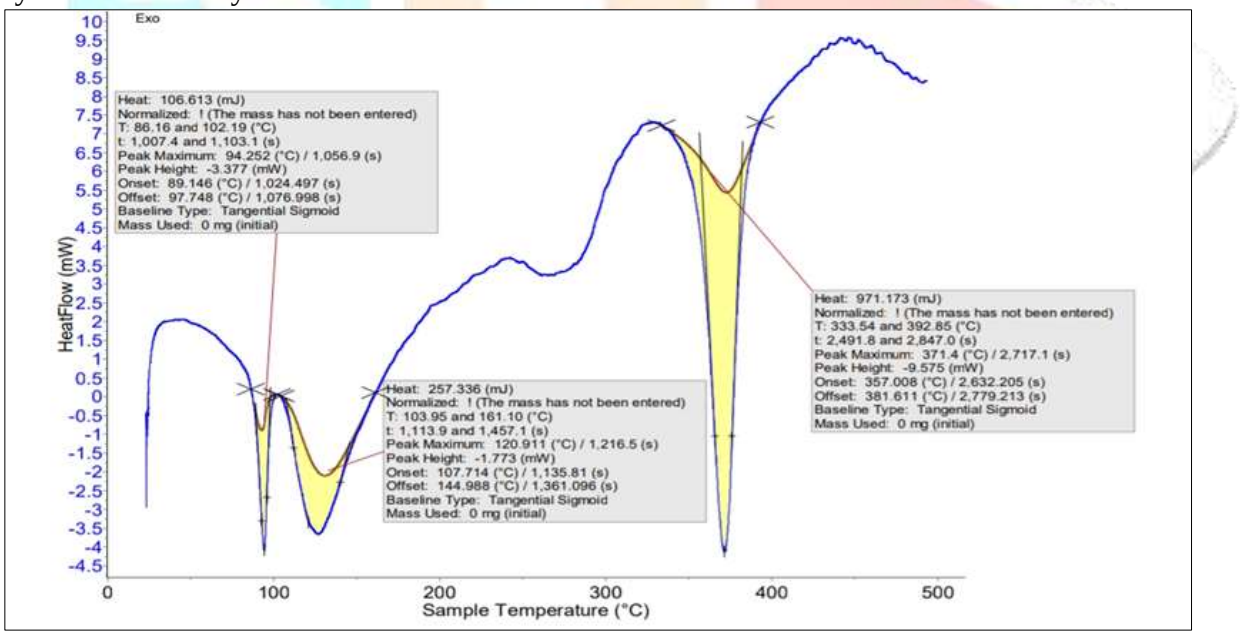

Fig_12 DSC thermogram of F2 formulation

3.2.4 In vitro drug dissolution study:

The dissolution data of Ketoprofen is illustrated in Table 8. Out of the two batches of cyclodextrin inclusion complexes, formulation F1 exhibited a higher cumulative % drug release. The pure drug demonstrated a 51.26% release within 1 hour. It was observed that formulation F1 achieved a 91.8% release within 1 hour, outperforming the other batches as shown in Table 9. In comparison, formulation F2 showed an 87.95% release within 1 hour, which was lower than that of F1 formulation, as shown in Figure_13 and Table 10. This figure depicts the comparative study of the drug release profile of Ketoprofen, F1 formulation, and F2 formulation.

Table 8 Dissolution data of Ketoprofen

Time (min)	Absorbance (nm)	Concentration (µg/ml)	% CDR
0	0	0	0
5	0.0867	1.0979	9.87
10	0.1153	1.6937	14.85
15	0.1337	2.077	18.69
20	0.1563	2.5479	22,89
30	0.2075	3.614	32.52
45	0.2682	4.8791	43.91
60	0.3074	5.6958	51.26

Table 9 Dissolution data of F1 formulation

Time (min)	Absorbance (nm)	Concentration (µg/ml)	% CDR
0	0	0	0
5	0.0995	1.3645	12.28
10	0.1763	2.9645	26.68
15	0.2471	4.4395	39.95
20	0.3012	5.5667	50.10
30	0.3915	7.4479	67.03
45	0.4820	9.333	83.99
60	0.5236	10.2	91.80

The pure drug Ketoprofen exhibited the slowest release rate, with only 51% of the drug being released within 60 minutes.

Formulation batch F1 demonstrated a 91.80% release of Ketoprofen within 60 minutes, indicating increased dissolution through complex preparation with β-Cyclodextrin.

The formulation batch F2 exhibited 87.95% drug release of Ketoprofen within 60 minutes, which was lower than that of formulation batch F1.

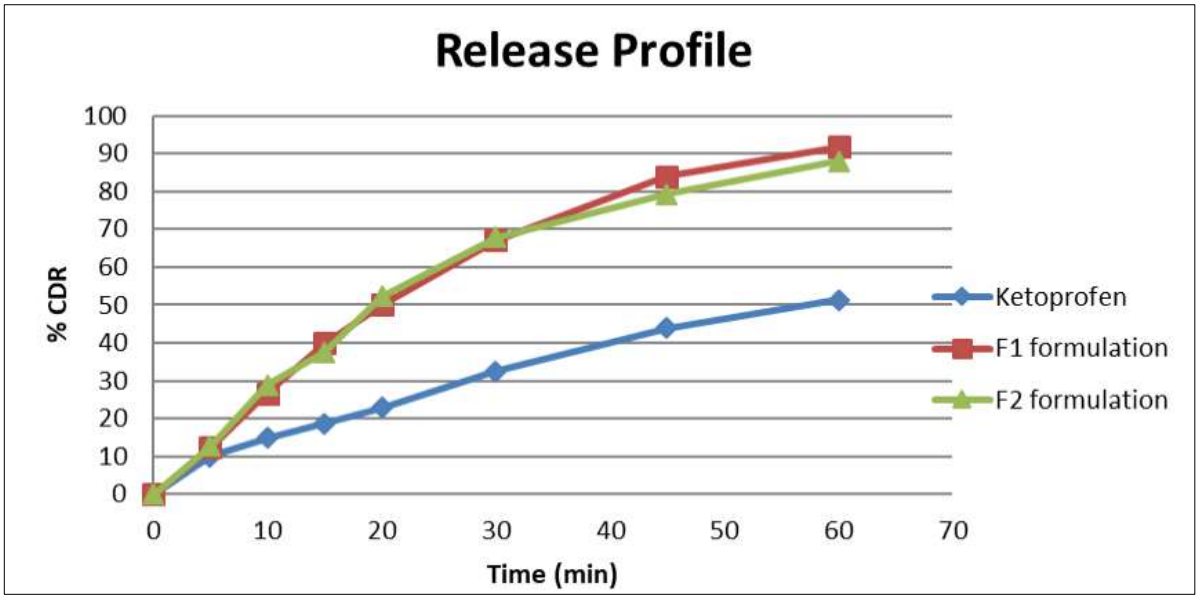

Fig_13 Comparative study of release profile between Ketoprofen, F1 & F2 formulation

Table 10 Dissolution data of F2 formulation

Time (min)	Absorbance (nm)	Concentration (µg/ml)	% CDR
0	0	0	0
5	0.1019	1.4145	12.73
10	0.1879	3.2062	28.85
15	0.2343	4.1729	37.55
20	0.3122	5.7958	52.16
30	0.3954	7.5291	67.76
45	0.4569	8.8104	79.29
60	0.5031	9.7729	87.95

5.2.5 Drug Content Uniformity

F1 formulation exhibited the highest drug content at 82.28%, as indicated in Table 11. Table Drug content of F1 & F2 formulations.

Table 11 Drug content of F1 & F2 formulations

Formulation Code	% Drug Content
F1	82.28
F2	56.45

Conclusion

Ketoprofen forms an inclusion complex with β-cyclodextrin was made with the microwave irradiation method in the ratios of 1:1 and 1:2. This method requires minimal solvents and a short duration for complexation compared to other methods. Formulation F1 exhibited a dissolution rate of 91.80% and a drug content uniformity of 82.28% in comparison to formulation F2. The research concluded that formulation batch 1 yielded the best results.

Abbreviations:

CD: Cyclodextrin

NSAID: Non-steroidal anti-inflammatory drugs

β- CD: Beta cyclodextrin

HP- β- CD: Hydroxypropyl beta cyclodextrin

BCS: Biopharmaceutical Classification System

RM- β- CD: Randomly Methylated – β- cyclodextrin

SBE- β- CD: Sulfobutyl ether- β- cyclodextrin

M.P: Melting point

FTIR: Fourier Transfer Infra-Red Spectroscopy

DSC: Differential Scanning Calorimetry

TGA: Thermal Gravimetric Analysis

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Author's contribution:

Mitali Doshi- Selection of topic, data collection, experimental work, and writing an original

draft.

Prajakta Kakade- Experimental work, Writing an original draft.

Kiran Mali- Review and edit the manuscript.

Ravikumar Gandhi- Review and edit the manuscript.

Dr. T. V. Deshmukh- Monitoring and analysis of data with review and interpretation.

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