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PHASE SOLUBILITY STUDIES OF IBUPROFEN WITH β-CYCLODEXTRIN AND HYDROXY PROPYL-β CYCLODEXTRIN IN DIFFERENT BUFFER MEDIA

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Abstract:

An oral route of drug administration is the most common and preferred method of delivery due to its convenience and ease of ingestion, but for many of drugs it can be hard way due to poor solubility. As the therapeutic activity of drugs is related to their solubility in water, in case of poorly water-soluble drugs, dissolution is the rate-limiting step in the process of drug absorption hence will lead to low bioavailability. To overcome the problems related with oral absorption and bioavailability issue, several strategies have been utilized including hydrotrpes, complexation, microcapsulation, use of surfactants, permeation enhancers, micronization, salt formation, Cyclodextrins, nanoparticles, solid dispersions, self emulsifying drug delivery system. By the early 1950s the basic physicochemical characteristics of cyclodextrins had been discovered and are widely used for the solubilization of poorly soluble drugs in the formulations. The versatile pharmaceutical material cyclodextrins (CDs) are classified into hydrophilic, hydrophobic, and ionic derivatives. Ibuprofen is a non steroidal anti-inflammatory drug and it is used as an analgesic, antipyretic and anti-inflammatory in the treatment of pain. It is very slightly soluble in water (<1 mg/ml, BCS class II) and its absorption could be a prerequisite for the quick onset of its action. In the present study solubility of ibuprofen was studied in presence of β- cyclodextrin and Hydroxypropyl- β- cyclodextrin at different p^H. The stability constant (K_c) for ibuprofen in presence of β- cyclodextrin at 7.4, 7.2 and 6.8 were 1368.03, 56.7525 and 74.2418 respectively. Similarly, stability constant (K_c) in presence of hydroxy propyl-β-cyclodextrin at 7.4, 7.2 and 6.8 were 790.095, 143.684 and 372.055 respectively. The solubility of ibuprofen in presence of Hydroxypropyl-β-cyclodextrin was found more than and β- cyclodextrin at p^H 7.2.

Keywords: *Ibuprofen, Inclusion Complex, Phase Solubility, β- Cyclodextrin, Hdroxyl Propyl β- Cyclodextrin.*

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INTRODUCTION:

Oral route of drug administration is the most common and preferred method of delivery due to its convenience and ease of ingestion, but for many of the drugs it can be hard way due to poor solubility, hence will lead to low bioavailability [1]. Solubility is the measure of its saturation to remain undissolved while adding solute upon the solvent and it is fundamentally depends on the solvent used, temperature and pressure [2]. According to the Noyes-Whitney equation, solubility of drug substance is directly proportional to the dissolution rate and hence the therapeutic effectiveness of a drug depends upon the dissolution, bioavailability and ultimately upon the solubility of drug molecules. Thus solubility is one of the influential ways to achieve desired concentration of drug in systemic circulation. It can be defined in quantitative term, as the concentration of solute in a saturated solution at a certain temperature and in qualitative terms, as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. [3] According to the BCS classification about 8% of new drugs have both high solubility and permeability [1]. In case of poorly water-soluble drugs, dissolution is the rate-limiting step in the process of drug absorption. The potential bioavailability problems are prevalent/ regnant with extremely hydrophobic drugs (aqueous solubility less than 0.1 mg/ml at 37°C), due to erratic or incomplete absorption from GIT **[4]**.

Ibuprofen is a non steroidal anti-inflammatory drug and it is used as an analgesic, antipyretic and anti-inflammatory in the treatment of pain [5] and chemically is 2-(4 isobutyl phenyl) propionic acid. The empirical formula for Ibuprofen is $C_{13}H_{18}O_2$ and its molecular weight is 206.29 g/mol [6]. It is white powder that is very slightly soluble in water (<1 mg/ml) and readily soluble in organic solvent such as ethanol and acetone [7]. Ibuprofen is a BCS class II drug; its absorption could be a prerequisite for the quick onset of its action [8]. Its oral bioavailability is about 87-100%, with a mean peak plasma concentration of 25-35µg/ml at about 2 hours after of one 400 mg oral dose [9]. It is extensively bound to plasma proteins (99%), and has a relatively short elimination half - life (2-4 hrs). Ibuprofen has pKa of 4.7-4.8 [10]. Enhancing solubility and dissolution rate of poorly water-soluble drug is one of the striking areas of research in pharmaceutical field [11].

To overcome the problems related with oral absorption and bioavailability issue, several approaches have been utilized including hydrotrpes [3] , complexation [12] , microcapsulation [13], use of surfactants, permeation enhancers, micronization, salt formation, cyclodextrins, nanoparticles, solid dispersions, self emulsifying drug delivery system etc [14,15].

The therapeutic activity of drugs is related to their solubility in water [16].In the case of poorly water-soluble drugs, dissolution is the rate-limiting step in the process of drug absorption.[17] Cyclodextrins are widely used for the solubilization of poorly soluble drugs in the formulations. [18]The versatile pharmaceutical material cyclodextrins (CDs) are classified into hydrophilic, hydrophobic, and ionic derivatives. By the early 1950s the basic physicochemical characteristics of cyclodextrins had been discovered, since than their use is a practical and economical way to improve the physicochemical and pharmaceutical properties such as solubility, stability, and bioavailability of administered drug molecules.[19] *Sudipta Das* and *et al*, prepared complexes of ibuprofen with cyclodextrin in molar ratio by co-precipitation method and inclusion complexes were further formulated into tables by direct compression technique using superdisintegrants in order to increase the solubility of ibuprofen for improvement of dissolution rate and bioavailability. [20] *Stiliyana P and et al* used modified method for ibuprofen and β-cyclodextrin complex formation. Modified method based on ball milling under controlled conditions was developed and its efficiency with respect to the drug encapsulation yield was compared with the kneading and solid dispersion methods for inclusion complexes. [21] *Qifang W* and et al were prepared solid state of the co-ground complex to investigate the possibility of improving the dissolution and stabilization of Ibuprofen, a poorly water-soluble drug, by grinding in a high energy mill with β-cyclodextrin (β-CD). The dissolution rate of solid state of the co-ground complex was determined according to the dispersed amount method.[22] *Iwata M* and et al investigated the enhancement of the solubility of glimepiride (GLM), a poorly water soluble antidiabetes drug, by cogrinding it with various cyclodextrins (CDs) using a ball mill. The phase solubility profiles of glimepiride with β-CD and its derivatives were classified as A_L-type, indicating the formation of a 1:1 stoichiometric water-soluble complex. When GLM crystals were cogrounded with β-CD using a ball mill for 48 h, the aqueous solubility of GLM increased to approximately 250 mg/ml. [23]

The present research work aimed to study the solubility of ibuprofen at different p^H in presence of β- cyclodextrin and hydroxypropyl- β- cyclodextrin and hence to make improvement in dissolution rate and bioavailability.

MATERIALS AND METHODS:

Materials

Ibuprofen was obtained as gift sample from the Unicure Remedies Pvt. Ltd. Vadodara (Gujarat, India). B-cyclodextrin (β-CD) and Hydroxypropyl- β-cyclodextrin (HP-β-CD) were purchased from Yarrow Chem. Products Mumbai. All other ingredients used were of analytical grade.

Method

Preparation of Calibration curve of Ibuprofen

Accurately weighed Ibuprofen (100mg) was and transferred to 100 ml volumetric flask and dissolved in phosphate buffer solution (p^H 6.8, 7.2 or 7.4). The final volume was adjusted up to 100 ml with the respective phosphate buffer solution to get first stock solution (FSS). One milliliter of FSS (1000 mcg/ml) was transferred to another volumetric flask and diluted with respective buffer solution up to 100 ml to get second stock solution (SSS). Further, 1 ml,2 ml,3 ml,4 ml,…..9 ml of second stock solution diluted up to 10 ml to get the solutions corresponding to 1 µg/ml, 2 µg/ml,3 µg/ml,4 µg/ml …..9 µg/ml and the absorbance were recorded at 221 nm by spectrophotometrically using respective buffer solution as blank (Shimadzu Double Beam Spectrophotometer-Model- UV 1700). The calibration curve was plotted using absorbance verses concentration and regression coefficient was calculated from the straight line equation. [24-26]

Phase solubility studies

Phase solubility studies were carried according to the method reported by Higuchi and Connors [27]. An excess amount of drug (Ibuprofen, 200mg) was added to glass containers (10 ml), containing ß-cyclodextrin (β-CD) and hydroxypropyl- ß-cyclodextrin (HP-β-CD) in buffer media of different p^H like 6.8, 7.2, 7.4. The concentration of ß-cyclodextrin (β-CD) and hydroxypropyl- ß-cyclodextrin (HP-β-CD) in solution were ranging from 0 to 0.01 mol. The glass containers were sealed and rotated for 48 hrs at 30 rpm. After 48 hours, sample solutions were filtered suitably diluted and ibuprofen content was determined by UV method at 221 mm.

The phase solubility diagram was constructed by plotting the dissolved ibuprofen against respective concentration of ß-CD. The binding constant K_a was calculated from phase solubility diagram using its slope and intercept values using equation

$K_c = Slope/S_o(1-Slope)$

Where, K_a is apparent stability constant, So is solubility of drug without cyclodextrin, M is molar concentration 22,24.

The solubility data of ibuprofen in presence of β-CD and HP-β-CD was analyzed statistically (Student t test) to evaluate the effect of host (β-CD and HP-β-CD) and pH of the media.

RESULT AND DISCUSSION:

Calibration curve of Ibuprofen

The calibration curve of ibuprofen in different buffers was prepared by measuring the absorbance in phosphate buffers p^H 6.8, p^H 7.2, and p^H 7.4 and showed the linearity over the concentration range of 1 - 10 µg/ml, which follows the Beer and Lamberts law. The absorbance of the solutions measured at the wavelength 221.0 nm. The results of standard curve are shown in Table and Figure. The regression coefficients (R^2) for straight line were found to be 0.998, 0.980 and 0.996 for phosphate buffers p^H 6.8, p^H 7.2, and p^H 7.4 respectively.

Table 1: Absorbance of Ibuprofen at 221 nm in phosphate buffer

Sr. No.	Concentration of Ibuprofen (mcg/ml)	Absorbance at 221 nm		
		p^H 6.8	p^H 7.2	p^H 7.4
1	0	0	0	0
2	1	0.063	0.038	0.064
3	2	0.104	0.085	0.103
4	3	0.134	0.121	0.144
5	4	0.178	0.105	0.182
6	5	0.222	0.200	0.229
7	6	0.269	0.255	0.29
8	7	0.308	0.295	0.318
9	8	0.342	0.332	0.366
10	9	0.386	0.358	0.404
11	10	0.433	0.430	0.473
Regression coefficient		**0.998**	**0.980**	**0.996**

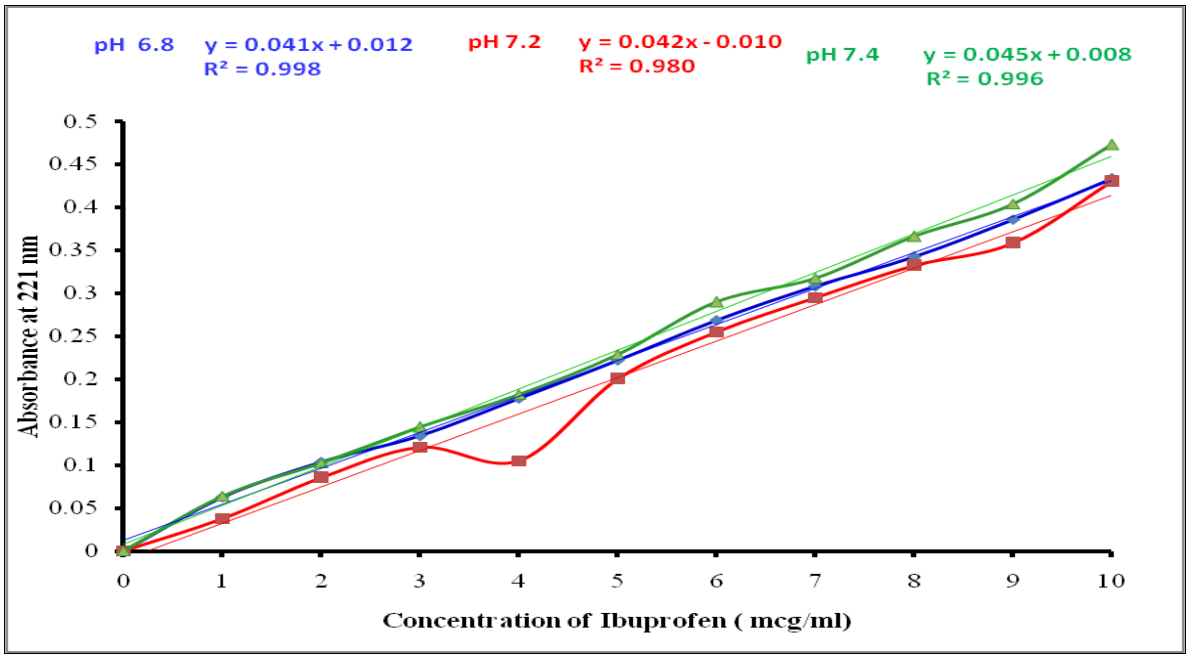

Fig 1: Calibration Curve of Ibuprofen in Phosphate buffer solutions

Phase solubility study

The solubility of ibuprofen in phosphate buffers p^H 6.8, p^H 7.2 and p^H 7.4 were studied in presence of β-CD and HP-β-CD. The phase solubility diagrams were obtained by plotting the graph amount of ibuprofen solubilized verses concentration of respective cyclodextrin. The apparent stability constant (K_c) and complexation efficiency (CE) was calculated from the linear plot of the phase solubility diagram and according to the equation...

$$Kc = \frac{Slope}{So(1-Slope)} \quad (1)$$

$$CE = \frac{Slope}{(1-Slope)} \quad (2)$$

Where, S_o = solubility of the drug in absence of β-CD and HP-β-CD.

The results of solubility of ibuprofen in phosphate buffers p^H 7.4, p^H 7.2 and p^H 6.8 in presence of β-CD are shown in table 2 and 3 and figure 2 and 3**.** The result showed that, maximum solubility of ibuprofen in presence of β-CD and HP-β-CD was found to be 0.00429 mcg/ml and 0.00518 mcg/ml respectively at p^H 7.2. In all p^H range, the aqueous solubility was increased linearly with β-CD and HP-β-CD concentration. All phase solubility diagrams are classified as type A_L according to Higuchi and Connors. The slope values were found to be less than unity in each case indicating the formation of 1:1 stoichiometric complexes

Table No 2: Solubility study of ibuprofen in different p^H with β-CD

Sr. No.	β-cyclodextrin concentration (Mol)	Solubility of Ibuprofen (mg/ml) in different p^H		
		p^H 6.8	**p^H 7.2**	**p^H 7.4**
1	0	0.00148	0.00275	0.000433
2	0.001	0.00156	0.00265	0.00026
3	0.002	0.00174	0.00303	0.00044
4	0.003	0.0019	0.00316	0.00073
5	0.004	0.002	0.00326	0.00112
6	0.005	0.00202	0.00328	0.00153
7	0.006	0.00215	0.00335	0.00176
8	0.007	0.00226	0.00341	0.00265
9	0.008	0.00231	0.00363	0.00276
10	0.009	0.0024	0.00386	0.00325
11	0.01	0.00249	0.00429	0.00323

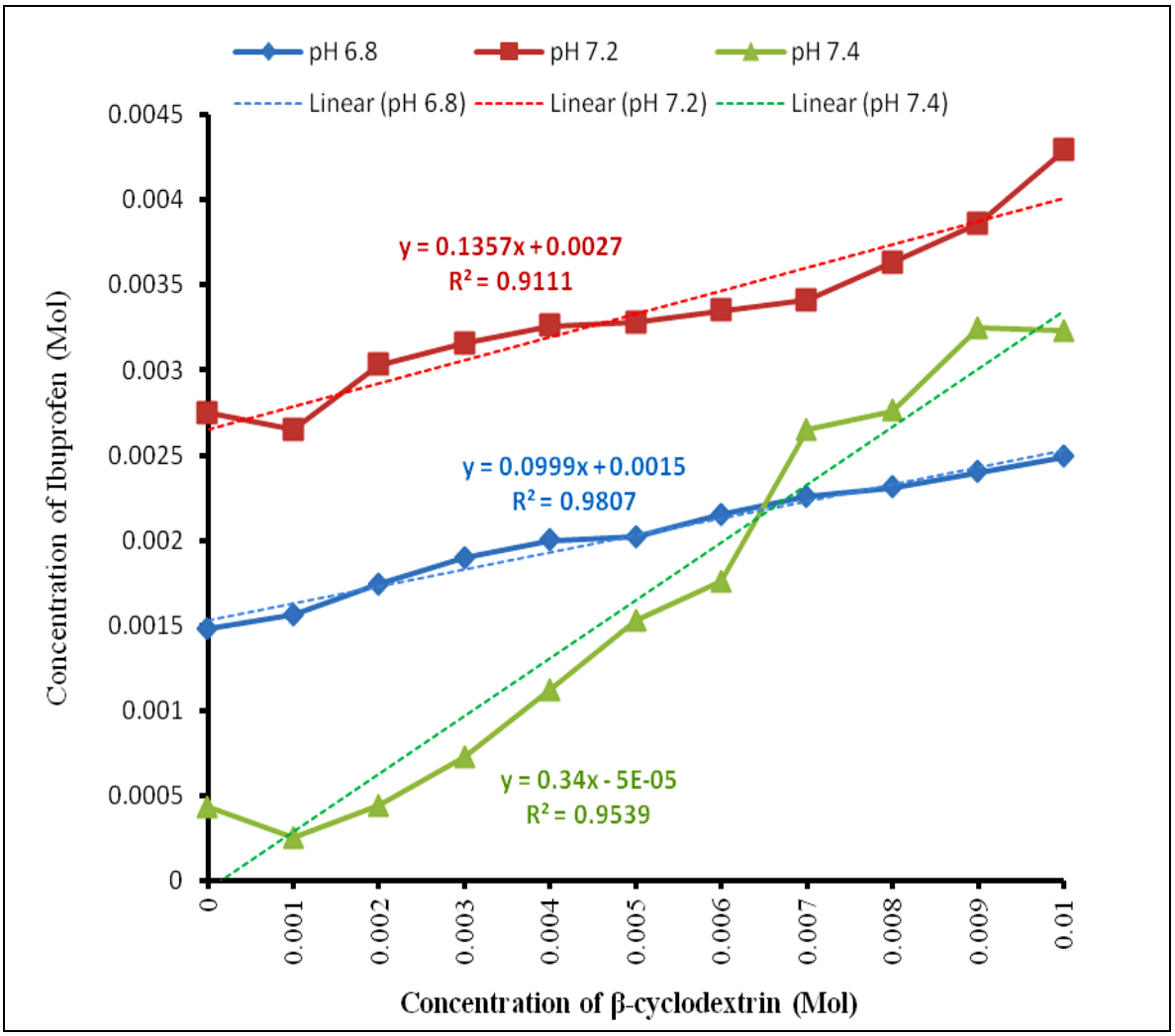

Fig 2: Phase solubility studies of ibuprofen with β-CD

Table 3: Solubility study of ibuprofen in different p^H with HP-β-CD

Sr. No.	Hydroxy propyl β-Cyclodextrin concentration(M)	Solubility of Ibuprofen (mg/ml) in different p^H		
		p^H 6.8	p^H 7.2	p^H 7.4
1	0	0.00059	0.00272	0.000522
2	0.001	0.000597	0.00259	0.000542
3	0.002	0.00069	0.00284	0.000737
4	0.003	0.00076	0.00304	0.001044
5	0.004	0.00098	0.00331	0.001306
6	0.005	0.00135	0.00357	0.001564
7	0.006	0.001356	0.00384	0.001946
8	0.007	0.00149	0.0045	0.00222
9	0.008	0.00183	0.00471	0.00265
10	0.009	0.00202	0.005	0.00298
11	0.01	0.00238	0.00518	0.003266

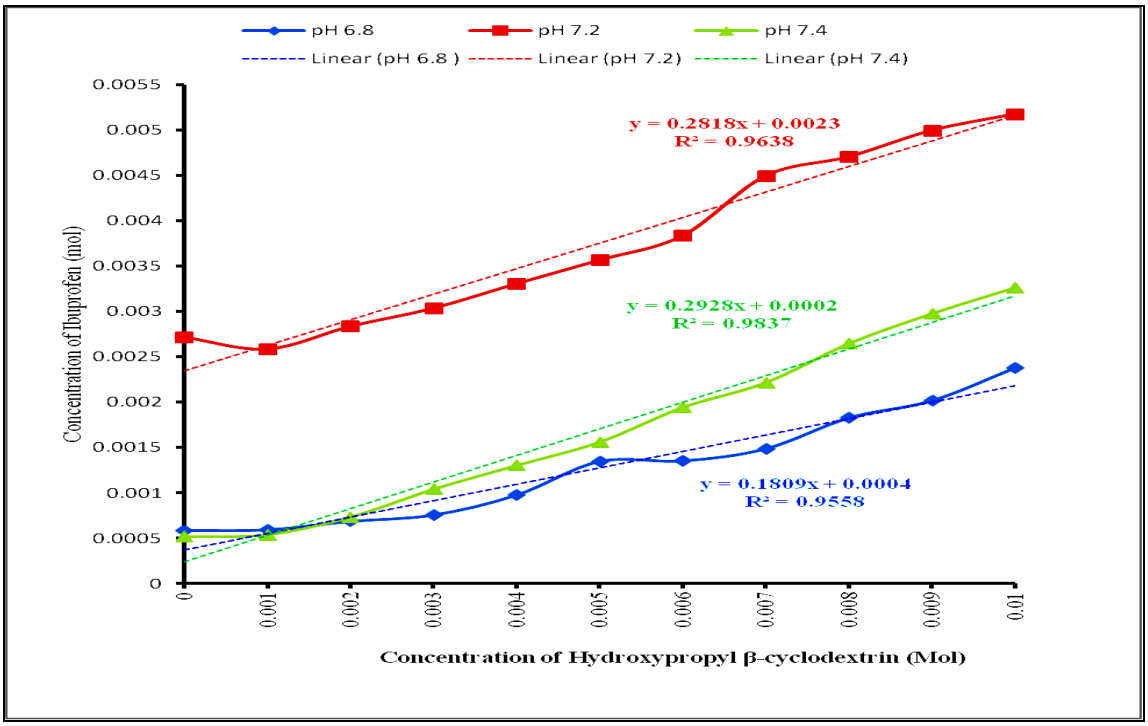

Fig 3: Phase solubility studies of ibuprofen with HP-β-CD

Table 4: Solubility study of Ibuprofen in different p^H

Sr. No.	p^H of media	Solubility of Ibuprofen in different p^H with β-Cyclodextrin		Solubility of Ibuprofen in different p^H with HP- β-Cyclodextrin	
		K_C	CE	K_C	CE
1	7.4	1368.03	0.59236	790.095	0.41243
2	7.2	**56.7525**	0.15607	**143.684**	0.39082
3	6.8	74.2418	0.10988	372.055	0.21951

K_c values in the range of 100-1000M-1 indicated stronger interactions between the guest molecules (drug) and host molecules (β-CD and HP-β-CD) and greater stability of the complex formed**. [28]**The value of stability constants complexes formed between drug-β-CD and drug-HP-β-CD are quite stable in all cases.

The solubility of drug increases with increase in host concentration and phase solubility study showed A_L type of graph using β-CD and HP-β-CD (0.001 to 0.1M) in p^H 6.8, p^H 7.2 and p^H 7.4, buffer media. The apparent stability constant values of inclusion complexes at pH 7.2 in presence of β-CD and HP-β-CD were found to 56.7525 M^{-1} and 143.684 M^{-1} respectively.

The solubility data of ibuprofen in presence of β-CD and HP-β-CD was analyzed statistically to evaluate the effect of host (β-CD and HP-β-CD) and pH of the media. The solubility of ibuprofen was found to be greater in presence of HP-β-CD s than β-CD. (*P* values for pH 6.8, 7.2 and 7.4 were 1.388 x 10^{-5}, 0.02 and 0.457 respectively). It showed that there has been remarkable increase in solubility at pH 6.8 and 7.2, but no significant increase at pH 7.4. The maximum solubility of Ibuprofen was found maximum in p^H 7.2 buffer media with HP-β-CD as well as β-CD.

CONCLUSION:

The aqueous solubility of ibuprofen can increase by the inclusion complexation with β- cyclodextrin and hydroxypropyl β-cyclodextrin. The complexes formed were stable and maximum solubility of ibuprofen was found maximum in p^H 7.2 buffer media in presence of hydroxypropyl β-Cyclodextrin.

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