Vol 5 | Issue 2 | 2015 | 72-80.

e-ISSN 2249 – 7706
print-ISSN 2249– 7714

International Journal of
Advanced Pharmaceutics
www.ijapjournal.com

DETERMINATION OF EFFECT OF POLYMERS ON SOLUBILITY OF POORLY WATER SOULBLE DRUG

Noor Ahmed VH[1]*, Saleem Malik V[1], Rafi B [1], Venkaiah A[1], Manohar[1], Jameerullah[1], Veeranjeneyulu[1], Naga Sri ND[2], Soheib Afroz [3], Zinab Parvez Hussain[4]

[1]Department of Pharmaceutics, Sree Vidyanikethan College of Pharmacy, Rangampet, Tirupati, Andhra Pradesh, India.
[2] Lydia College of Pharmacy, Ethakota, Ravula palem, Andhra Pradesh, India.
[3]Vaagdevi College of Pharmacy, Hanumkonda, Warangal, Telangana, India.
[4] Mallareddy College of Pharmacy, Misammaguda, Hyderabad, Telangana, India.

ABSTRACT

Ibuprofen is a widely used non-steroidal anti-inflammatory drug [NSAID] and well-tolerated analgesic. According to BCS classification Ibuprofen belongs to class – II having low solubility and high permeability. To enhance the solubility of poorly water soluble drugs various techniques are already in practices. Among those micronisation and crystillisation techniques are the finest solubility enhancement techniques. The scope of present research work is preparation and evaluation of micro crystals of ibuprofen by using different excipients to enhance the solubility of the drug molecule there by improved bioavailability is of major thing. Hence, here we use the technique of micronisation to enhance the solubility by reducing the size of the drug molecules upon usage of different excipients. The reduction of particle size leads to a significant increase in the dissolution rate of the API, which in turn can lead to substantial increases in bioavailability. Prepared crystals are characterized by FTIR, DSC and SEM studies. No interaction between ingredients was confirmed by FTIR, DSC. And also crystals are evaluated for solubility studies, drug content, and *Invitro* dissolution studies. The overall results indicate that prepared crystals had enhanced solubility compared to ibuprofen pure drug. Crystals prepared with Beta-CD had shown appreciable enhancement of solubility.

Keywords: Ibuprofen, COX-1, COX-2, Beta-CD, NSAID, Treated Crystal, Microcrystillisation, *In-Vitro* Release, SLS.

INTRODUCTION

According to BCS classification Ibuprofen belongs to class – II having low solubility and high permeability. Ibuprofen is a non-steroidal anti-inflammatory drug and it is most widely used and well-tolerated analgesic [1]. Ibuprofen is a non-selective cyclooxygenase (COX) inhibitor it inhibits COX-1 and COX-2 forms, its antipyretic, analgesic, and anti-inflammatory activities are achieved principally through COX-2 inhibition [2]. The poor aqueous solubility of Ibuprofen poses several difficulties in formulation process. With the most analgesics, including ibuprofen, the initial rise in plasma concentration following oral administration is a main factor in determining the time to onset of pain relief [3]. Ibuprofen is instantaneously absorbed, and both peak plasma concentrations and maximal analgesic onset are achieved within 1.5-2 hours after oral administration [4]. The crystal form of a drug has been found to be very important variable in pharmaceutical manufacturing. Various crystal forms of a particular drug possess different planes and thus varies not only in their surface area, but also free surface energy. Therefore, they may exhibit various physicomechanical properties [5]. Properties such as, flow properties , dissolution rate and compressibility, which can vary for different habits of the same drug [6–7]. Attempts to change the morphology and the workability of drugs using alternative crystallization procedures include modification of the crystal habits of drugs such as hexamethylmelamine, paracetamol and nitrofurantoin [7-10]. The oral route of drug administration is well established that the drug in a solid dosage form should undergo dissolution before it is available for absorption

Corresponding Author:- **Noor Ahmed VH** Email:- noor.pharmacon@gmail.com

from the G.I.T [11]. The poor dissolution of aqueous insoluble drugs is a substantial problem confronting the pharmaceutical industry [12]. The absorption rate of a poorly aqueous -soluble drug, formulated as an orally administered solid dosage form, is controlled by its dissolution rate in the fluid at the absorption site. The dissolution rate is often the rate-determining step in process of drug absorption. Therefore, the solubility and dissolution behaviour of a drug are the key determinants of the oral bioavailability [13]. These two aspects form the basis of the Biopharmaceutical classification system (BCS) [14]. Different approaches have been suggestible to increase aqueous solubility of poorly water soluble drugs, such as conversion of crystalline molecule to its amorphous state [15-17] micronisation, solubilization in surfactants, cyclodextrin complexation, co-solvency, hydrotropic solubilisation [17-22].

MATERIALS AND METHODS

Materials

Ibuprofen was obtained as gift sample from Hetero Drugs Pvt Ltd ,Hyderabad, Beta-Cyclodextrin was obtained as gift sample from Dr. Reddy's Pharmaceuticals Pvt Ltd, Hyderabad. And all other chemicals used in formulations are analytical grade.

FTIR (Fourier Transform Infra-red Spectroscopy) Studies:

Infra red (IR) spectroscopy studies of Ibuprofen and its formulations with β–cyclodextrin and sodium lauryl sulphate were recorded in a FTIR spectrophotometer (Thermo-IR 200) Potassium bromide pellet method was employed and background spectrum was collected under identical conditions. The spectrum for each sample showed the wavelength of absorbed light which is a characteristic of the chemical bonds in the sample. Each spectrum was derived from 16 single average scans collected in the region of 400 - 4000 cm^{-1} at a spectral resolution of 2 cm^{-1}

UV-VIS Absorption spectrum:

20 µg/ml solution of Ibuprofen was prepared in 0.1N HCl, Phosphate buffer pH 6.8, and Distilled water. UV-VIS scan was taken between the wavelengths 200-400nm using UV-VIS spectrophotometer (shimadzu, UV-1700).

Microscopic studies:

A pinch of Ibuprofen was taken on glass slide which is mounted in mineral oil and cover slip is placed on the slide. Observe in microscope at 45X magnifications. Photography was taken.

Solubility Studies:

Excess amount of Ibuprofen was taken in test tube containing 5ml distilled water, 0.1N HCl, phosphate buffer pH 6.8. Then the test tube was shaken frequently using mechanical shaker rpm set at 50 which is thermostatically controlled. Temperature was maintained at $30^0 \pm 1^0$C. After24hr filtered and diluted suitably. The absorbance was checked with UV-VIS spectrophotometer (shimadzu, UV-1700) using distilled water as blank at 226 λ_{max}, 0.1N HCl as blank at 210.5 $\lambda_{max,}$ phosphate buffer pH 6.8 as blank at 222 $\lambda_{max.}$

Differential Scanning Calorimetry (DSC) Studies:

Ibuprofen and its formulations with β–cyclodextrin and sodium lauryl sulphate were subjected to DSC studies. And were scanned at 5^0C/min. Thermal analysis of Ibuprofen and its formulations with β–cyclodextrin and sodium lauryl sulphate will be recorded on a DSC. The temperature axis and cell constant of DSC were previously calibrated with Indium. A heating rate of 5^0/min was employed over a temperature range of 0^0 - 350^0 with nitrogen purging. Powder sample was weighed into an aluminium pan was used as reference.

Preparation of micro crystals of Ibuprofen:

Form 1 and 2 Micro crystals of Ibuprofen prepared, using β–cyclodextrin and sodium lauryl sulphate respectively by following steps

Step 1: The crystals of ibuprofen were prepared by taking the drug and dissolving it in ethanol (1gm ibuprofen in 2 ml of ethanol) and there by adding distilled water (20ml) forming precipitate.

Step 2: During the process of precipitation probably nucleation it is put for agitation under the mechanical agitator for 15-20 min to reduce the size to microns.

Step 3: Different polymers of concentration of 0.5% i.e., β–cyclodextrin and sodium lauryl sulphate are dissolved in distilled water.

Step 4: The crystals of ibuprofen with this polymers were prepared by precipitation method.

Step 5: The mixture of these solutions on agitation are taken for filtration.

Step 6: The crystals formed are collected upon filtration and are dried well by using watt man filter paper till they are free from moisture.

Step 7: The crystals was obtained and it was characterized by DSC, FTIR and particle size analysis.

CHARACTERIZATION OF IBUPROFEN MICRO CRYSTALS:

Ibuprofen micro crystals was characterized by Microscopic studies, FTIR and UV-VIS absorption studies and also by solubility studies and dissolution studies

Assay:

Weighed accurately about 10mg of ibuprofen micro crystals dissolve in 100ml of phosphate buffer pH 6.8 and measure the absorbance of the resulting solution at maximum at about 222nm. Calculate the content Ibuprofen

taking as the value of $A_{1cm}^{1\%}$ at the maximum at about 222nm. Assay can be done from following equation.

$$C = \frac{a}{(A_{1cm}^{1\%} \times 1)}$$

***Invitro* dissolution studies:**

Powder dissolutions were performed using USP apparatus No.2, Thermostatically controlled at 37°C ± 0.5°C and Distilled Water, 0.1 N HCl and phosphate buffer pH 6.8 were used as dissolution media. Ibuprofen crystals were introduced into the 900 ml of dissolution medium, stirred at 50 rpm. Samples were withdrawn at 15, 30, 45, and 60 min through a filter paper. The volume withdrawn at each time interval was replaced with fresh quantity of the dissolution medium. The amount of drug dissolved from Ibuprofen crystals was determined spectrophotometrically.

ANALYTICAL METHOD OPTIMIZATION

Number of analytical methods is available for quantification of Ibuprofen such as ultra-violet spectroscopy, liquid chromatography with UV detection, gas chromatography and mass spectroscopy. The following method was used for further studies.

Standard Curve of Ibuprofen with 0.1N HCl:

10 mg of Ibuprofen was dissolved in 100 ml of 0.1 N HCl, and further dilutions were made by using 0.1 N HCl to obtain concentrations ranging from 5 to 25 µg/ml. The absorbance of solution was measured at 220.5 nm using UV –Visible Spectrophotometer. The readings obtained are tabulated in table no. and figure no 1.

Standard Curve of Ibuprofen with Distilled water:

10 mg of Ibuprofen was dissolved in 100 ml of Distilled water, and further dilutions were made by using Distilled water to obtain concentrations ranging from 5 to 25 µg/ml. The absorbance of solution was measured at 226 nm using UV –Visible Spectrophotometer. The readings obtained are tabulated in table no.4 and figure no. 2.

Standard Curve of Ibuprofen with 6.8 pH phosphate buffer:

10 mg of Ibuprofen was dissolved in 100 ml of 6.8 pH phosphate buffer, and further dilutions were made by using 6.8 pH phosphate buffers to obtain concentrations ranging from 5 to 25 µg/ml. The absorbance of solution was measured at 222 nm using UV –Visible Spectrophotometer. The readings obtained are tabulated in table no.3 and figure no.3.

RESULTS AND DISCUSSION

FTIR (Fourier Transform Infra-red Spectroscopy) Studies: Ibuprofen

In FT-IR analysis (fig: 4), the spectrum of pure ibuprofen showed an intense and well-defined bands characteristic to ibuprofen at 1717.17 cm-1 (carbonyl stretching of isopropionic acid group) and 2951.01 cm-1 (hydroxyl stretching). This FTIR analysis shows that ibuprofen is pure. Interpretation of IR spectra of ibuprofen has shown in table no.6 and spectrum shown in Figure no.4.

UV-VIS spectrum of Ibuprofen:

UV-VIS spectrum of Ibuprofen in different pH was determined and spectrums are shown in figure 5. λ_{max} (nm) and $A^{(1\%,1cm)}$ of Ibuprofen at different pH (ie., distilled water, 0.1N HCl, phosphate buffer 6.8 pH) is shown in figure 6 & 7.

Microscopic studies:

Morphology of ibuprofen was studied by Microscopy. Ibuprofen shows uniform like crystals. The microscopic photographs shown in figure 8.

FTIR Studies:

Micro crystal form 1: (Drug + β–cyclodextrin)

In FT-IR analysis, the spectrum of pure ibuprofen showed an intense and well-defined bands characteristic to ibuprofen at 1717.17 cm-1 shown at 1720.20 cm-1 (carbonyl stretching of isopropionic acid group) and 2954.01 cm-1shown at 2949.95 cm-1 (hydroxyl stretching) stating that the ibuprofen form 1 had the drug in unchanged from i.e., the excipient had shown variability in the intensity of the peak at 2920.20 cm-1. Interpretation of IR spectra of ibuprofen 33form 1 has shown in table no.6 and spectrum shown in Figure no.9.

Micro crystal form 2:

In FT-IR analysis, the spectrum of pure ibuprofen showed an intense and well-defined bands characteristic to ibuprofen at 1717.17 cm-1 shown at 1720.20 cm-1 (carbonyl stretching of isopropionic acid group) and 2954.01 cm-1shown at 2954.26 cm-1(hydroxyl stretching) stating that the ibuprofen form 1 had the drug in unchanged form i.e., the excipient had shown no variability in the intensity of the peak. Interpretation of IR spectra of ibuprofen form 2 has shown in table no.6 and spectrum shown in Figure no.10.

Microscopic studies:

Morphology of ibuprofen microcrystal form 1 and 2 were studied by Microscopy. The microscopic photographs shown in figure no.11-13.

Solubility Studies:

Solubility of ibuprofen microcrystal form 1 and 2 in 0.1N HCl, distilled water and Phosphate buffer 6.8 pH were studied. The ibuprofen solubility is shown in the tables 5 & 6 given below.

***Invitro* dissolution studies:**

In vitro dissolution studies of Ibuprofen in pure and its crystalline forms were performed in different solvents. From the below mentioned data maximum drug release was observed as 94.59% at 60 min when performed in 0.1 N HCl.[Table No. 10,Figure no. 14] the drug release in distilled water and phosphate buffer pH 6.8 were reported.

The data obtained from *in- vitro* release studies were subjected to Zero order, first order Higuchi's model, Korsmeyer's model and Hixson - Crowell model. Release parameters were given in table no. 11-14.

Correlation Coefficient (R^2) values obtained from PCP Disso V3 software was used to test the applicability of release models. Drug release from Pure drug was observed to follow Krosemeyer model release in all the three dissolution medium, distilled water, 0.1 N HCl and pH 6.8 phosphate buffer.

The drug release from ethanol treated, crystals with Beta-Cyclodextrin and crystals with SLS in all the media follows Krosmeyer release model with n value < 0.5.

Table 1. Standard curve of Ibuprofen in 0.1N HCl

Concentration(µg/ml)	Absorbance
0	0
5	0.051
10	0.109
15	0.176
20	0.222
25	0.268

Table 2. Standard Curve of Ibuprofen with Distilled water

Concentration(µg/ml)	Absorbance
0	0
2	0.095
4	0.155
6	0.235
8	0.338
10	0.401

Table 3. Standard Curve of Ibuprofen with 6.8 pH phosphate buffer

Concentration(µg/ml)	Absorbance
0	0
5	0.261
10	0.527
15	0.8
20	1.098
25	1.361

Table 4. FTIR spectrum interpretations

Characteristic Peaks	pure Drug	Drug+B-CD	Drug+SLS
carbonyl stretching of isopropionic acid group	1717.17 cm^{-1}	Present	Present
hydroxyl stretching	2951.01 cm^{-1}	Present	Present but % transmittance increased

Table 5. Solubility studies of ibuprofen crystals in 0.1N HCl

Type	Solubility in mg/ml
Pure Ibuprofen	0.187
treated crystals	0.234
Micro Crystal form 1	0.198
Micro Crystal form 2	0.218

Table 6. Solubility studies of ibuprofen crystals in Distilled water

Type	Solubility in mg/ml
Pure Ibuprofen	0.116

treated crystals	0.153
Micro Crystal form 1	0.271
Micro Crystal form 2	0.314

Table 7. Solubility studies of ibuprofen crystals in Phosphate buffer 6.8

Type	Solubility in mg/ml
Pure Ibuprofen	2.914
treated crystals	3.005
Micro Crystal form 1	3.612
Micro Crystal form 2	3.463

Table 8. Percentage drug release of ibuprofen its formulations in 0.1 N HCl

Time (min)	% Drug release in 0.1N HCl			
	Pure IBU	Treated crystal IBU	IBU+B-CD	IBU+ SLS
0	0.00	0.000	0.00	0.00
15	32.34	43.995	78.71	62.89
30	47.28	68.240	89.47	79.37
45	89.05	93.314	99.86	91.64
60	81.98	96.899	96.11	95.91

Table 9. Percentage drug release of ibuprofen its formulations in Distilled water

Time In min	% Drug release in Distilled water			
	Pure IBU	Treated crystal IBU	IBU+B-CD	IBU+SLS
0	0.000	0.00	0.00	0.00
15	52.297	34.65	42.14	27.48
30	89.364	38.63	49.90	30.48
45	94.489	42.92	59.19	33.85
60	82.127	44.31	63.53	37.96

Table 10. Percentage drug release of ibuprofen its formulations in 6.8 pH phosphate buffer

Time In min	% Drug release in 6.8 pH phosphate buffer			
	Pure IBU	Treated crystal IBU	IBU+B-CD	IBU+ SLS
0	0.000	0.00	0.000	0.00
15	70.386	85.25	38.386	28.81
30	87.032	92.69	44.363	36.16
45	94.737	98.81	50.120	40.23
60	79.004	99.87	55.658	48.19

Table 11. Release Kinetics of Ibuprofen(pure)

Ibuprofen(pure)		Zero order model	First order model	Higuchi model	Krosemeyer model	Hixson-Crowell model
0.1 N HCl	**R^2**	0.914	0.825	0.898	**0.914**	0.746
	m	1.471	-0.015	11.52	0.739	0.066
	c	5.996	2.029	-4.75	0.638	1.133
Distilled water	**R^2**	0.705	**0.635**	0.684	**0.898**	0.601
	m	1.376	0.016	12.16	0.353	0.063
	c	22.36	1.835	5.729	1.354	1.522
pH 6.8 Phosphate buffer	**R^2**	0.572	0.5	**0.353**	**0.828**	0.601
	m	1.215	-0.014	11.45	0.126	0.063
	c	29.76	1.716	11.68	1.722	1.522

Table 12. Release Kinetics of Treated Crystals

Treated Crystals		Zero order model	First order model	Higuchi model	Krosemeyer model	Hixson-Crowell model
0.1 N HCl	R^2	0.929	0.954	0.982	**0.989**	0.703
	m	1.62	-0.028	13.09	0.588	0.067
	c	11.86	2.134	-1.856	0.964	1.314
Distilled water	R^2	0.635	**0.673**	0.876	**0.998**	0.546
	m	0.612	-0.003	50638	0.121	0.047
	c	13092	1.926	5.458	1.420	1.307
pH 6.8 Phosphate buffer	R^2	0.629	0.976	0.873	**0.981**	0.544
	m	1.422	-0.045	13.12	0.12	0.063
	c	32.36	2.017	12.84	1.790	1.737

Table 13. Release Kinetics of Micro Crystal Form 1

Micro Crystal Form 1		Zero order model	First order model	Higuchi model	Krosemeyer model	Hixson-Crowell model
0.1 N HCl	R^2	0.365	0.265	0.551	0.665	0.362
	m	0.964	-0.015	10.35	0.067	-0.032
	c	50.41	1.384	30.40	1.864	3.232
Distilled water	R^2	0.747	0.826	0.935	0.995	0.801
	m	0.63	-0.003	5.727	0.294	-0.012
	c	14.567	1.929	5.99	1.151	4.398
pH 6.8 Phosphate buffer	R^2	0.669	0.799	0.875	0.963	0.751
	m	0.771	-0.0056	1.687	0.241	-0.016
	c	21.938	1.8886	10.763	1.355	4.253

Table 14. Release Kinetics of Micro Crystal Form 2

Micro Crystal Form 2		Zero order model	First order model	Higuchi model	Krosemeyer model	Hixson-Crowell model
0.1 N HCl	R^2	0.608	0.951	0.846	**0.991**	0.917
	m	1.243	-0.036	11.91	0.182	-0.056
	c	39.64	1.913	20.03	1.681	3.966
Distilled water	R^2	0.658	0.731	0.866	**0.972**	0.704
	m	0.516	-0.003	4.815	0.241	-0.009
	c	15.084	1.925	7.53	1.185	4.384
pH 6.8 Phosphate buffer	R^2	0.74	0.83	0.922	0.9489	0.806
	m	0.708	-0.047	6.428	0.2808	-0.014
	c	16.906	1.917	7.312	1.22	4.354

Figure 1. Standard curve of Ibuprofen in 0.1N HCl

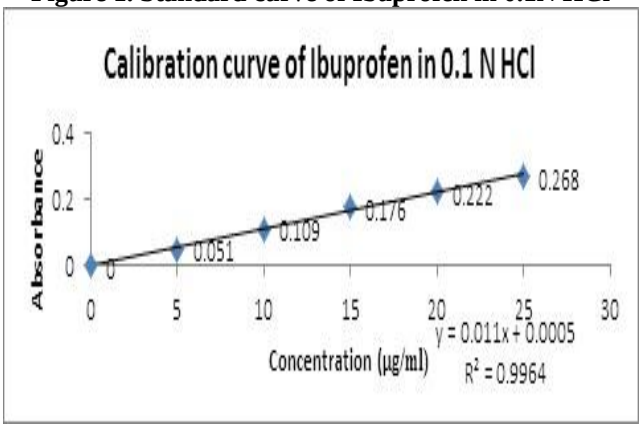


Figure 2. Standard Curve of Ibuprofen with Distilled water

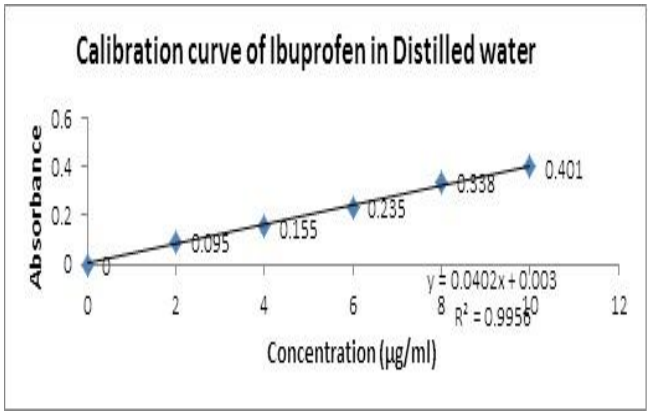


Figure 3. Standard Curve of Ibuprofen with 6.8 pH phosphate buffer

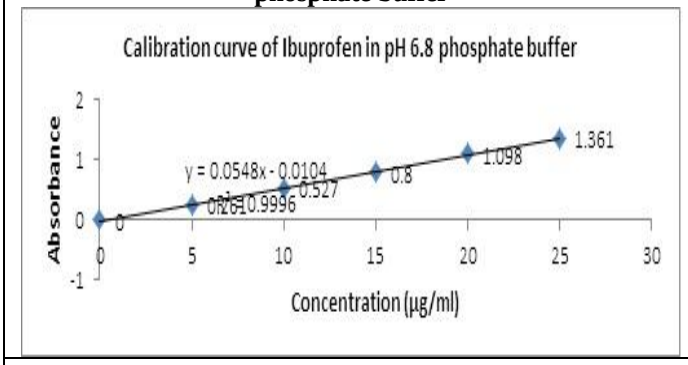


Figure 4. FTIR spectrum of pure drug ibuprofen

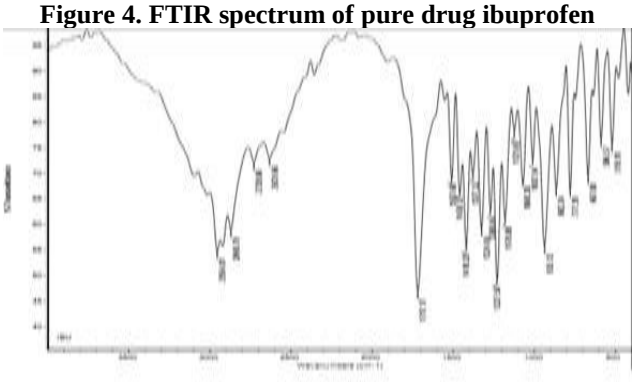


Figure 5. UV Spectrum in 0.1N HCl: (λ_{max} 220.5 nm)

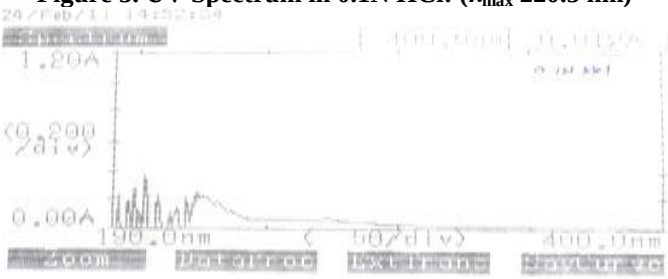


Figure 6. UV Spectrum in distilled water: (λ_{max} 226 nm)

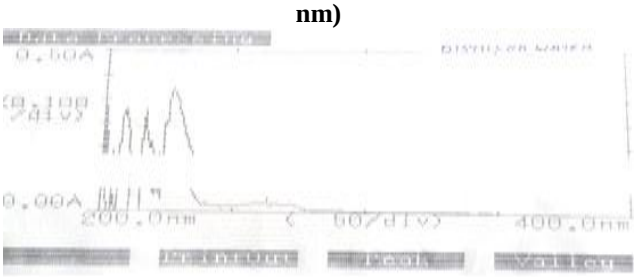


Figure 7. UV Spectrum in phosphate buffer 6.8 pH: (λ_{max} 222nm)

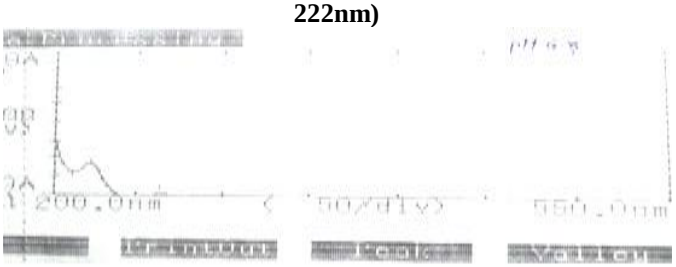


Fig 8. [A] Pure Ibuprofen

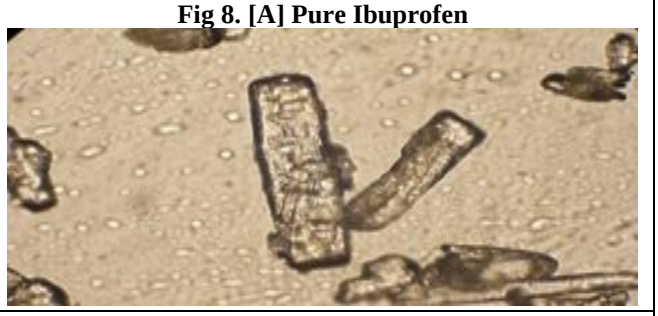


Figure 8. [B] Pure Ibuprofen

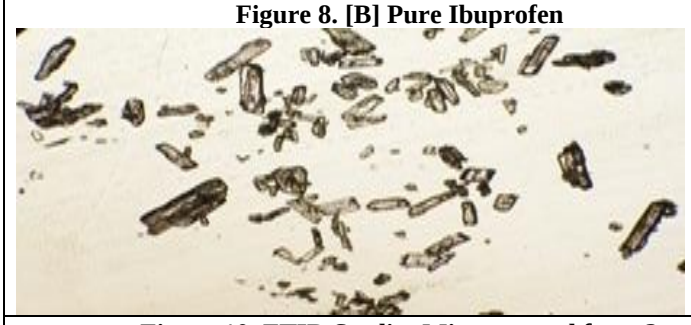


Figure 9. FTIR Studies Micro crystal form 1(Drug + β–cyclodextrin)

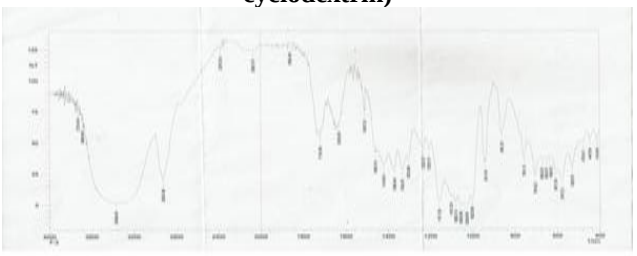


Figure 10. FTIR Studies Micro crystal form 2 (Drug + sodium lauryl sulphate)

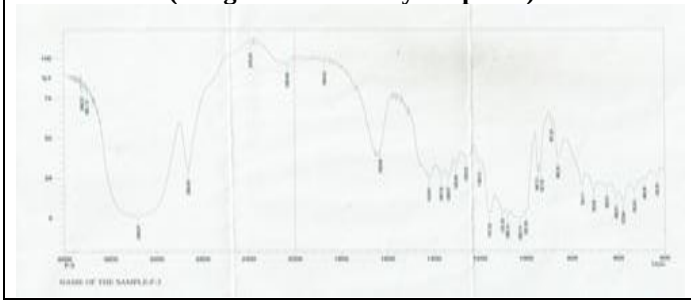


Figure 11. Treated Ibuprofen Crystal

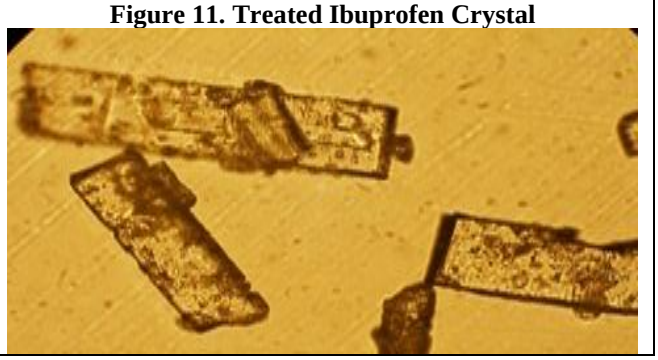


Figure 12. Drug + Beta CD Crystal

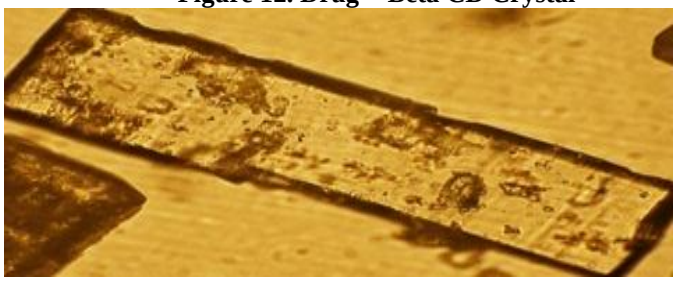


Figure 13. Drug + SLS

Figure 14. Percentage drug release of ibuprofen its formulations in Distilled water

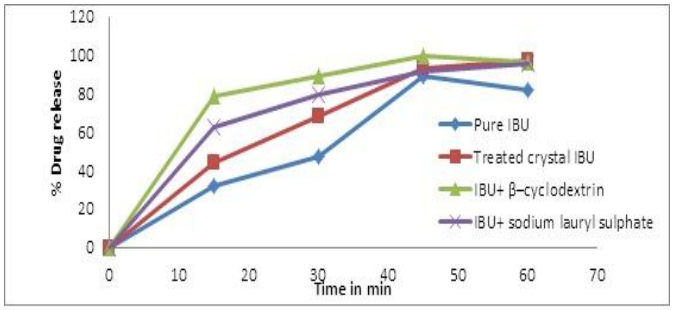


Figure 15. Drug release profiles for ibuprofen its formulations in Distilled water

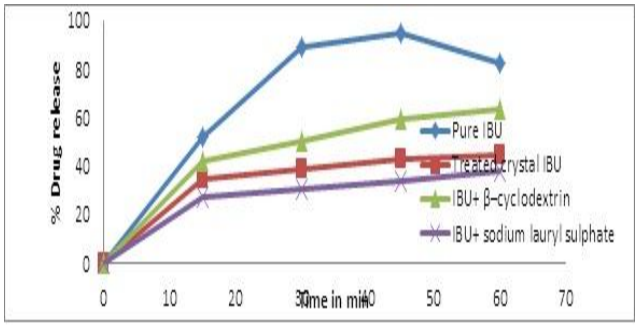
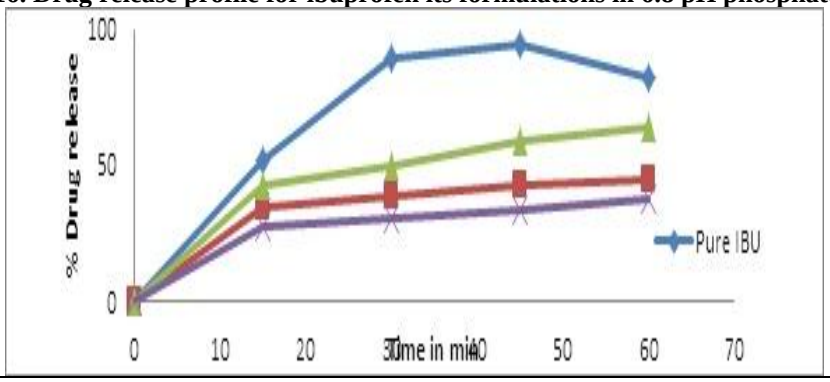


Figure 16. Drug release profile for ibuprofen its formulations in 6.8 pH phosphate buffer



CONCLUSION

The present studies were carried out to study the solubility of ibuprofen with different excipients i.e. Beta-Cyclodextrin and SLS by reducing size of the crystal to micron level by the process of micronisation. This process increases surface area there by increasing the solubility ultimately bioavailability. The overall results indicate that prepared crystals had enhanced solubility compared to ibuprofen pure drug. Crystals prepared with Beta-Cyclodextrin had shown appreciable enhancement of solubility.

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