

**DEVELOPMENT AND EVALUATION OF SOLID DISPERSION FORMULATED IBUPROFEN TABLETS USING CYCLO
DEXTRINS AS CARRIER****Meka Anand Kumar*^{1,2},**M.Kranthi kumar¹, Dr. P.K.Lakshmi¹, V.S.Giri prasad².¹G.Pulla Reddy College of Pharmacy, Mehdiapatnam, Hyderabad, Andhra Pradesh.²Vikas College of Pharmacy, Jangaon, Warangal, Andhra Pradesh.**ABSTRACT**

In the present investigation, an attempt was made to increase the therapeutic effectiveness of ibuprofen, by increasing the solubility, via solid dispersion using Beta cyclodextrin (β -CD) and 2-hydroxy propyl beta cyclodextrins (2-HP β -CD) as carrier. Eight solid dispersion formulations of ibuprofen were prepared by using different drug: polymer ratios viz. 1:0.5, 1:1, 1:2, and 1:3 for (2-HP β -CD) and β cyclodextrin by co-evaporation method and optimized solid dispersions were evaluated for drug content, In-vitro release studies, FTIR, differential scanning calorimeter (DSC). No interaction between ingredients was confirmed by FTIR, DSC. The formulation with better release was selected and compressed into tablet with weight equivalent to Ibuprofen of 400 mg. The compressed tablets were evaluated for their hardness, disintegration, weight variation, friability and drug content, compared with marketed tablets and finally loaded for stability at 40°C/75%RH and the results found to be satisfactory.

Keywords: Ibuprofen, Solid dispersion, β -CD, HP β -CD, DSC**Correspondence to Author**

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Pradesh.**Email:** anand.mvrs@gmail.com**INTRODUCTION**

The oral route of drug administration is the most common and preferred method of drug delivery due to its convenience and ease of ingestion. It is well established that the active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the G.I.T.¹ The poor dissolution of water-insoluble drugs is a substantial problem confronting the pharmaceutical industry.² The absorption rate of a poorly water-soluble drug, Available online on www.ijprd.com

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 drug absorption.¹ Therefore, the solubility and dissolution behavior of a drug are the key determinants of the oral bioavailability.³ These two aspects form the basis of the Biopharmaceutical classification system (BCS).⁴

Different approaches have been attempted to increase aqueous solubility of poorly soluble drugs, such as conversion of crystalline molecule to its amorphous state⁵⁻¹², a particle size reduction via micronization^{13,14}, solubilization in surfactant systems, cosolvency^{15,16}, hydrotropic solubilization¹⁷, cyclodextrin complexation^{18,19,20}.

Solid dispersion techniques have been used for a wide variety of poorly aqueous soluble drugs such as Nimesulide, Aceclofenac, Nifedipine, Ketoprofen etc., using hydrophilic carriers like polyethylene glycol, polyvinyl pyrrolidone, hydroxypropylmethylcellulose, mannitol, urea etc(a). Solid dispersions improve solubility, wettability, dissolution rate of the drug. However, only few solid dispersion products are commercially available. This is due to poor physical characteristics for dosage form formulation. Similarly use of large quantity of organic solvent in preparation of solid dispersions may pose environmental and safety concerns:

Ibuprofen, a weekly acidic, non-steroidal anti-inflammatory drug having high permeability through stomach but due to its solubility limitation it can't enter in to systemic circulation and gastric emptying time ranging from 30 min to 2 hr, after this time ibuprofen goes in to small intestine where it is solubilise but can't permeate through its membrane. The same problem arises in quantitative analysis; because of poor solubility of ibuprofen it involves organic solvents which are costly and toxic. To improve dissolution of such drug is challenging and rational. The purpose of the present study was to examine the enhancement of solubility of the Ibuprofen using hydrophilic carriers.

The present study focuses on preparation of solid dispersion of ibuprofen using β -CD and 2-HP β -CD as carriers followed by compressing the optimized solid dispersion into tablet dosage and studying the in-vitro release profile comparing with marketed conventional Ibuprofen tablets.

MATERIALS AND METHOD:

Ibuprofen (obtained a gift sample from natco pharma limited), β cyclodextrin (hi media Available online on www.ijprd.com

laboratories pvt ltd, Mumbai), 2-Hydroxy propyl β cyclodextrin (chemika biochemical reagents), Lactose monohydrate (Supertab11SD) DMV, Microcrystalline cellulose pH112, Sodium starch glycolate(S.D.fine chemicals), Colloidal silicon dioxide(Aerosil 200), Magnesium stearate (Synpro)

METHOD OF PREPARATION:

Solid dispersion by co- evaporation method was prepared by dissolving drug in methanol and carrier in aqueous media. Organic solution of drug was added slowly to the aqueous carrier solution followed by the stirring at 300 rpm using magnetic stirrer at 37° C for 24 hrs. The resultant solid dispersion was passed through #120 sieve.

CHARACTERIZATION OF THE PREPARED SOLID DISPERSIONS

The solid dispersions prepared were analyzed for assay and in vitro release of drug by dissolution studies.

Spectral analysis by FTIR

The spectrum analysis of the prepared solid dispersion of IB of HP β CD was studied by FTIR. FTIR spectra were recorded by preparing potassium bromide (KBr) disks using a Shimadzu Corporation (Koyto, Japan) facility (model - 8400S). Potassium bromide (KBr) disks were prepared by mixing few mg of sample with potassium bromide by compacting in a hydrostatic press under vacuum at 6-8 tons pressure. The resultant disc was mounted in a suitable holder in IR spectrophotometer and the IR spectrum was recorded from 4000 cm^{-1} to 500 cm^{-1} in a scan time of 12 minutes. The resultant spectrum was compared for any spectral changes. They were observed for the presence of characteristic peaks for the respective functional group in the compound.

The pure drug and HP β CD were analyzed by FTIR in same manner and were observed for the presence of respective peaks. The IR spectra of solid dispersions matched with those of drug and when HP β CD superimposed.

Differential Scanning Calorimetry:

Differential scanning calorimetry was performed by Differential scanning calorimeter 60 shimadzu to obtain suitable thermo grams. The accurately

weighed sample was placed in an aluminium pan and an empty aluminium pan was used as reference. The experiment was performed under nitrogen flow, at a scanning rate 30°C/min. in range of 50-350 C.

Assay of the Solid dispersions

Assay of the prepared solid dispersions were determined in 7.4 pH phosphate buffer solution. Accurately weighed amounts of solid dispersions equivalent to 10 mg of drug was taken in a 100 ml volumetric flask, 20 ml methanol was added and shaken for 20 min to dissolve the drug. The volume was made to 100 ml with buffer medium separately. Dispersions were filtered and 1 ml aliquot of the above solutions were taken and diluted to 10 ml with buffer medium respectively. The concentration of the resultant solution was 10 µg/ml. The absorbances of these solutions were determined at 222 nm against the blank.

Data treatment of dissolution studies

Dissolution profiles of percentage drug release vs. time were obtained. Amount of drug released at 60 minutes was calculated.

In vitro dissolution study of the solid dispersions

The prepared solid dispersions were accurately weighed equivalent to 100 mg of the drug. These solid dispersions are filled in empty capsules and analyzed for drug release in 900 ml of the dissolution media by powder dispersion technique. The dissolution media in which the tests were performed was 7.4 pH phosphate buffer solutions. The samples were automatically withdrawn at time intervals 5 min, 10 min, 15 min, 30 min, 45 min, and 60 min. Filters were used to avoid the solid particles from being withdrawn which might

Table No 1: Carrier For Solid Dispersions And The Different Ratios Used.

Carrier for Solid dispersion	Drug : polymer
β cyclodextrin	1:0.5
	1:1
	1:2
	1:3
Hydroxy propyl β cyclodextrin	1:0.5
	1:1
	1:2
	1:3

interfere in analysis. The samples were analyzed spectro photometrically at the maximum wavelength (λ_{max}) of the drug which is 222 nm against the empty capsule solution as blank withdrawn at same time intervals. Dissolution of each sample was performed 3 times (n=3) and mean of all determinations was used to calculate the drug release profile. The apparatus used was USP Type II with 100 rpm.

In vitro dissolution study of the plain drug

The dose of IB i.e. 100 mg is accurately weighed. These samples were analyzed for the drug release in the same manner of the solid dispersions. The release rates of the pure drug were compared to the release rate of the drug from prepared solid dispersions. The solid dispersions which improved the drug release rate considerably compared to that of the pure drug were selected for the further work.

Tablet preparation and Characterization:

Composition containing equivalent of 500 mg of Ibuprofen were compressed on rotary tableting press using 12.0 mm round flat beveled punch by direct compression technique. Composition of the tablet is given in table no: 2. Prepared tablets were evaluated for hardness (Monsanto hardness tester) friability (Roche friabilator), weight variation and drug content. In vitro dissolution studies were carried out in USP paddle apparatus using 900ml phosphate buffer pH 7.4. The drug release profile of formulated tablet was compared with marketed tablet. Stability studies were also conducted at 40°C / 75% RH for periodic intervals and data of 3 month is evaluated for the parameters as shown in the table.9.

Table No.2: Composition Of Tablet Formulated With Solid Dispersion

S.No	Composition	Mg/tab
1	Solid dispersion equivalent to Ibuprofen	400
2	Lactose monohydrate (Supertab 11sd)	134.5
3	Microcrystalline Cellulose (Avicel 112)	47.0
4	Sodium starch glycolate	10.0
5	Colloidal silicon dioxide	3.0
6	HPMC 5cps	4.0
7	Magnesium stearate	1.5
Tablet weight		600.0

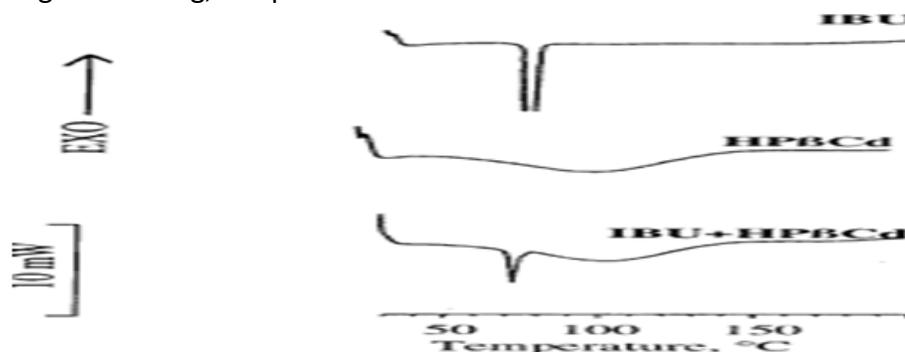
Table No.9: Comparative In-Vitro Release Study Of Marketed Tablets And Solid Dispersion Ibuprofen Tablets Initial And 3rd Month Stability Data

Time	Marketed tablet (%drug release)	Solid dispersion IBU tablet (%Drug release)-Initial	Solid dispersion IBU tablet (%Drug release)-3 rd month
0	0	0	0
5	35.18	51.39	45.30
10	46.67	61.13	60.04
15	60.72	72.44	73.10
30	69.51	82.43	80.37
45	77.27	97.52	94.62
60	91.65	100.48	99.39

RESULTS AND DISCUSSIONS:

Drug content of the solid dispersions was found to be between 98.82 % and 103.43%. All the solid dispersions of co-evaporation technique showed the presence of high drug content and low standard deviations of the results. It indicates that the drug is uniformly dispersed in the powder formulation. Therefore, the method Co-evaporation used in this study appears to be reproducible for preparation of solid dispersion. The occurrence of any interaction between a drug and polymers in the formulation can be predicted by conducting the differential scanning Calorimetry studies. The thermograms of solid dispersions

display the characteristic features of the drug. This indicates no possible interaction between the polymers and Ibuprofen. Thermal study was carried out to ascertain the decomposition of drug The DSC thermogram of pure IB shows a sharp endothermic peak near at 70^o C (Fig 4.) which is attributed to its melting temperature. The DSC of HPβCD showed one sharp endothermic peak at 96^oC which belongs to HPβCD peak. The DSC of optimized formulation shows at 70^o C and at 96^oC, there was no change in the temperature of the optimized formulations when compared to the pure drug; hence it indicates that there was no interaction between drug and excipients.

Fig no 4: DSC thermo gram of drug, excipient and formulation

Infra-red spectral analysis showed that there were no interactions between pure drug and solid

dispersion. The results are shown in table no: 3. and fig no.1, 2, 3.

Table No 3: Interpretation Of Ir Graph Of Ibuprofen Pure Drug

S. No	Region in cm^{-1}	Type of vibration	Functional group present
1	1720	C=O stretching	Ketone
2	2921	C-H stretch	Aliphatic methylene group

INTERFERENCE STUDY ON CARRIERS BY FTIR METHOD

Fig no 1: FTIR graph of IB pure drug

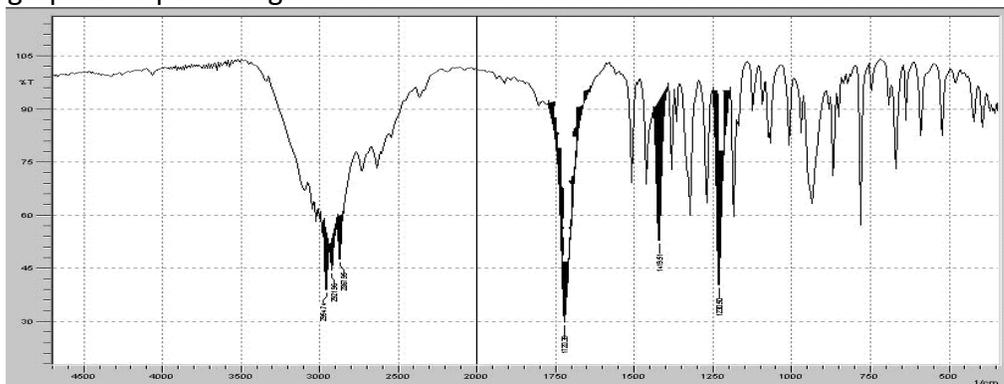


Fig no 2: FTIR graph of HP β CD

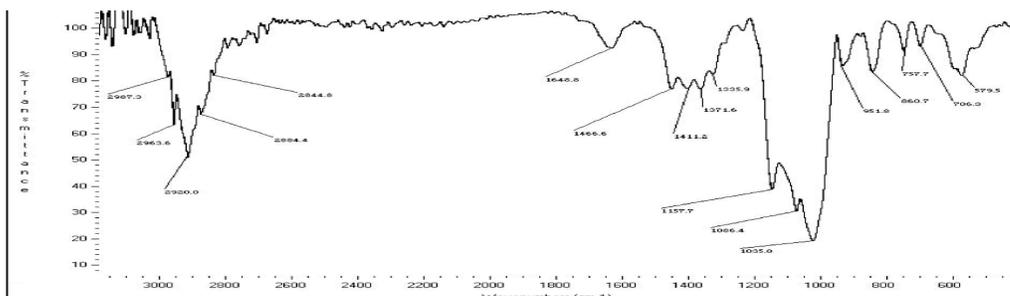
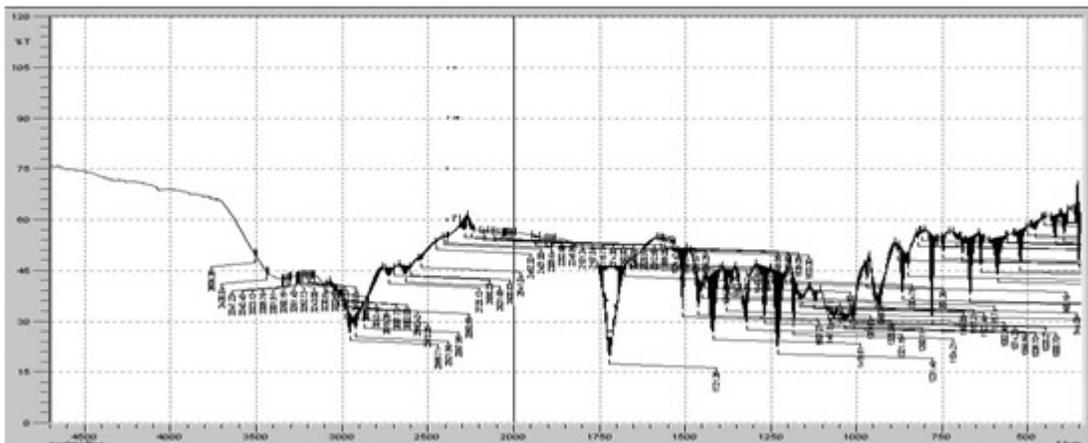


Fig no 3: Interference study of IB with excipients by FTIR method



From the invitro dissolution studies of the solid dispersions it was observed that the release of drug from solid dispersion was increasing with increase in the carrier concentrations and when compared to that of the pure drug, when comparing with

carriers the release of the drug is found to be good in HP β -CD than β -CD and at less concentrations .

From the Table No 4 and Fig No.5, it was observed that percentage drug released by solid dispersion of IB with β -CD (1:3) showed increased

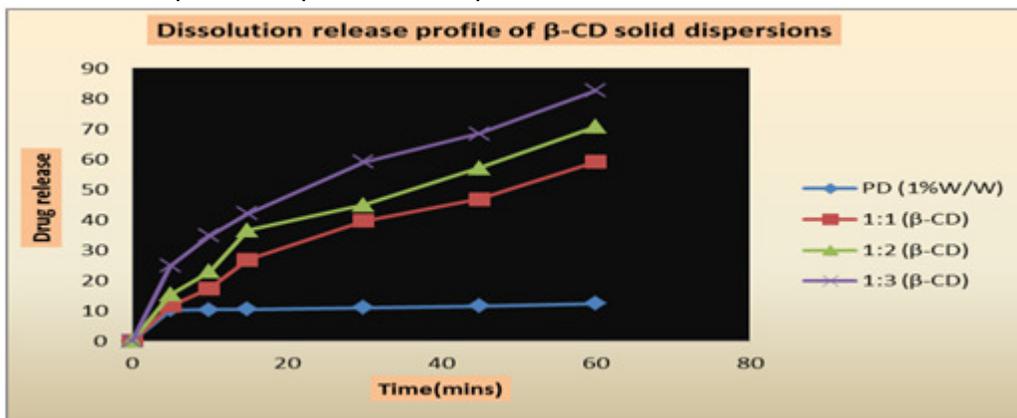
release when compared to pure drug. Concentration of β -CD was increased the percentage drug release increased 1:1 D: β -CD ratio

(59.1%), 1:2 D: β -CD ratio (70.8%), 1:3 D: β -CD ratio (82.6%), and pure drug (12.45%) in 60 minutes.

Table No 4: Percentage Release Profiles Of Ib With B -Cd As Carrier In 7.4 Ph Phosphate Buffer.

Time (mins)	PD (1%W/W)	1:1 (β -CD)	1:2 (β -CD)	1:3 (β -CD)
0	0	0	0	0
5	10.21	11.6	15.4	24.8
10	10.35	17.4	23	34.8
15	10.61	26.9	36.6	42.1
30	11.03	39.7	44.9	59.1
45	11.64	46.9	57.1	68.4
60	12.45	59.1	70.8	82.6

Fig no.5: Dissolution release profile of β -CD solid dispersions



From the Table No.5 and Fig No.6, it was observed that percentage drug released by solid dispersion of IB with HP β -CD (1:3) showed increased release when compared to pure drug and solid dispersion of IB with β -CD which may be due to increased wettability of the drug by using such hydrophilic carriers and more drug getting available for dissolution because HP β -CD is more hydrophilic in nature, inclusion capacity²⁸ The 1:0.5 ratio of D:

HP β -CD (72.58%) showed greater release than 1:1 D: HP β -CD ratio (59.30%), 1:2 D: HP β -CD ratio (94.89%), 1:3 D: HP β -CD ratio (99.98%), and pure drug (12.45%) in 60 minutes. Physical mixture of both polymers were prepared using the concentration of 1:0.5 and comparatively studied which in turn showed the same kind of release where HP β -CD showed better release.

Table No 5: Percentage Release Profiles Of Ib With Hp B Cd As Carrier In 7.4 Ph Phosphate Buffer

Time (mins)	Pure Drug(1%W/W)	1:0.5 (HP β CD)	1:1 (HP β -CD)	1:2 (HP β -CD)	1:3 (HP β -CD)
0	0	0	0	0	0
5	10.21	17.51	37.26	40.63	48.63
10	10.35	22.57	49.87	54.93	60.41
15	10.61	34.28	58.92	68.04	72.6
30	11.03	46.49	66.43	78.00	80.39
45	11.64	53.20	79.41	82.83	96.21
60	12.45	72.58	89.30	94.89	99.98

Fig no.6: Dissolution release profile of HPβ-CD solid dispersions

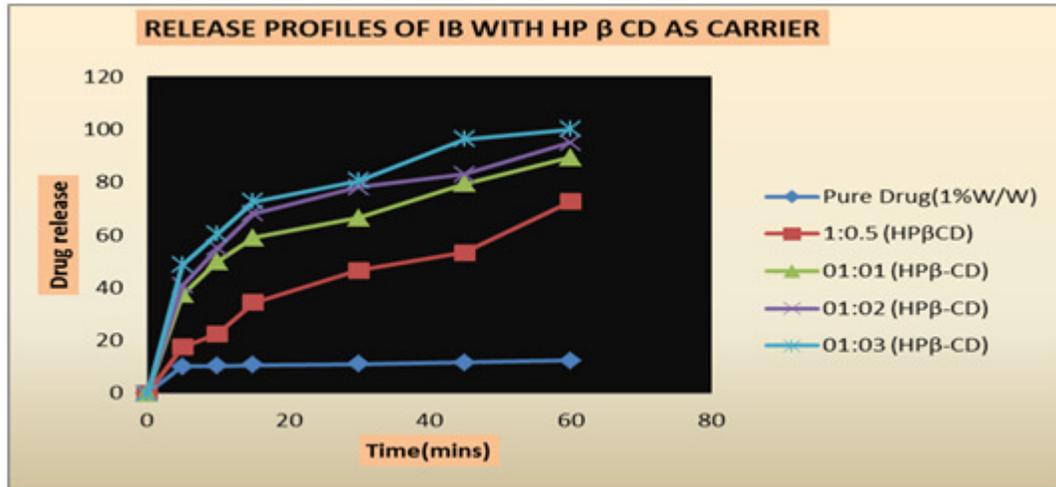


Fig no.7: Comparative dissolution profile of marketed tablet and solid dispersion Formulated ibuprofen tablets

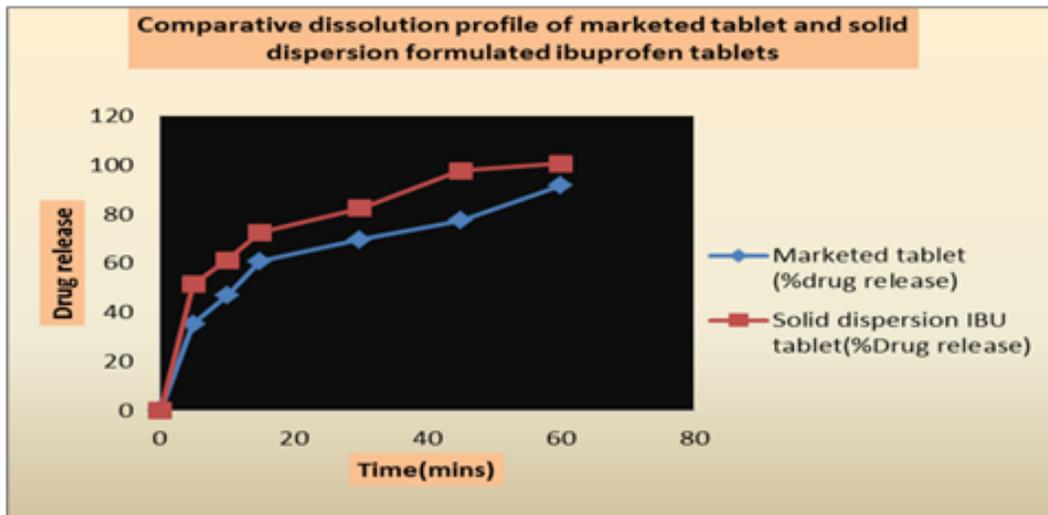
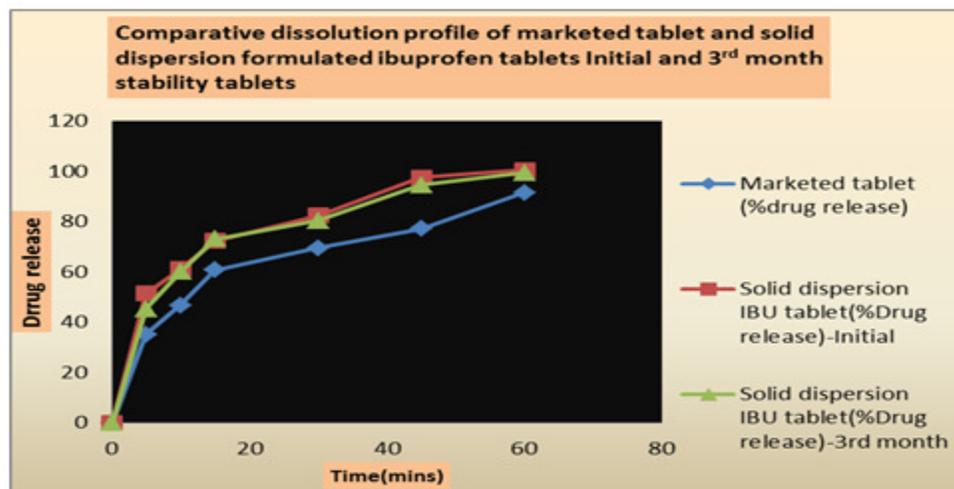


Fig no.8: Comparative dissolution profile of marketed tablet and solid dispersion formulated ibuprofen tablets Initial and 3rd month stability tablets



Solid dispersion showing better release with Drug: HP β -CD in the ratio of 1:3 was formulated into tablet dosage form and evaluated for its parameters. All parameters were within the specified I.P. limits (Table No.7). The thickness and diameter of the tablets were found to be 3.98 ± 0.2 mm and 12.0 mm. Weight variation was within the I.P. limits ($\pm 5\%$). The hardness of the different formulations ranged from 7 to 9 kg/cm². All the formulations exhibited less than 1% friability. The drug content analysis of Ibuprofen in all the formulations was found to be (98.6 % w/w) within the I.P. limits ($\pm 5\%$). The time taken for the

tablets to disintegrate was evaluated in all the formulations and found to be 5min 21 sec. (I.P. limits uncoated tablet is < 15min).and the in-vitro release profile of solid dispersed ibuprofen tablet was showing better release than the marketed sample. Finally the Solid dispersion formulated Ibuprofen tablet was loaded for stability to check its integrity and release characteristics after exposing to exaggerated conditions after three month of the study the Physical appearance and release characteristics was not affected (Table No: 8)

Table No.7: Physical Parameters Of The Solid Dispersed Formulated Tablets.

S.No	Parameters	Observed values	Limits
1	Assay	98.6%	95%-105%
2	Weight variation(mg)	601.55 ± 1.55	570-630
3	Disintegration time	5min. 21sec	NMT 15 min
4	Content uniformity	98.82 % -103.43%	95%-105%

Table No.8: Physical Parameters Of The Solid Dispersed Formulated Tablets After Three Months $40^{\circ}\text{C}/75\% \text{RH}$

S.No	Parameters	After 3 month ($40^{\circ}\text{C}/75\% \text{RH}$)	Initial values	Limits
1	Assay	96.34%	98.6%	95%-105%
2	Weight variation(mg)	600.55 ± 1.60	601.55 ± 1.55	570-630
3	Disintegration time	5min. 53sec	5min. 21sec	NMT 15 min
4	Content uniformity	96.9 % -101.27%	98.82%-103.43%	95%-105%

CONCLUSIONS:

Ibuprofen belongs to NSAID used in the treatment of Pain management, but in cases of immediate relief of the pain drug has to reach the systemic circulation rapidly which is the barrier in case of Ibuprofen to provide a better therapy if drug is released effectively and this is achieved by formulating drug in term of Solid dispersion as tablet in the present work which showed far better release than the Marketed product. Hence Ibuprofen-Solid dispersion tablet could be considered as better choice of treatment of immediate pain relief with faster release, achieving good patient compliance

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