Original Article

Enhancement Of Dissolution Profile By Solid Dispersion Using Kneading Technique

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Abstract

This article investigates enhancement of the dissolution profile of ibuprofen using solid dispersion with β-cyclodextrin. The article also describes the preparation of oridispersible tablets of ibuprofen by using a high amount of superdisintegrants. A phase solubility method was used to evaluate the effect of various water-soluble polymers on aqueous solubility of ibuprofen. β-cyclodextrin was selected and solid dispersions were prepared by the method of kneading. Dissolution studies using the USP paddle method were performed for solid dispersions of ibuprofen. Infrared (IR) spectroscopy, differential scanning calorimetry (DSC), and x-ray diffractometry (XRD) were performed to identify the physicochemical interaction between drug and carrier, hence its effect on dissolution. IR spectroscopy, XRD, and DSC showed no change in the crystal structure of ibuprofen. Dissolution of ibuprofen improved significantly in solid dispersion products (F3 99% in 15 minutes). Tablets containing solid dispersion exhibited better dissolution profile, wetting time, water absorption ratio and disintegration time than other batches. Thus, the solid dispersion technique can be successfully used for improvement of dissolution of ibuprofen.

KEYWORDS: Solid dispersion, ibuprofen, dissolution enhancement, orodispersible tablet**.**

1 INTRODUCTION

Out of many categories, NSAID's are the most widely prescribed medications in the world. As a therapeutic class, NSAID's exhibit analgesic, anti-inflammatory, antipyretic, and platelet inhibitory properties. Ibuprofen, a COX-2 inhibitor , is a potent non-steroidal anti-inflammatory drug. It is a weakly acidic drug having high permeability through stomach because it remains 99.9% unionized in stomach (pKa of Ibuprofen -4.43)(1). Inspite of having excellent oral bioavailability (96%) ,its problem of poor aqueous solubility makes its absorption and dissolution rate limited and which eventually delays its onset of action(2-3). To overcome this problem of solubility there are number of techniques available and reported in literature to enhance the solubility of poorly water soluble drug, such as solid dispersions, complexation, micronization supercritical fluid process, polymorphs and eutectic mixtures etc. we can use the technique of solid dispersion in which the hydrophilic carriers are used to help increase the low aqueous solubility(4-5).This technique has been implied to many such poorly aqueous soluble drug entities such as Nimesulide, Nifedipine, Nimodipine and so on. The hydrophilic carriers which are usually used during solid dispersion are Polyethylene glycols, Polyvinylpyrrolidone, Gums & Sugars,etc (6-7).

Solid dispersion, which was introduced in the early 1970s, is essentially a multicomponent system, having drug dispersed in and around hydrophilic carrier(s)(8). Solid dispersion technique has been used for a wide variety of poorly aqueous soluble drugs for improvement of dissolution characteristics and bioavailability of poorly aqueous-soluble drugs. β—cyclodextrin, PEG 6000 and Polyvinylpyrrolidone (PVP) has been used for the preparation of solid dispersion as a component of the binary system for various drugs(9-10).

The present work aims to evaluate the potential of the solid dispersion technique for development of orodispersible tablets of ibuprofen using β—cyclodextrin, PVP K-30and PEG 6000 as the hydrophilic carrier. Furthermore, the study undertakes to investigate kneading as a method for preparation of such binary systems, their solid state characterization, interaction in the liquid state, and attempts to see the possible mechanism of improved dissolution rate(11-12).The main advantage of orodispersible tablets is that the bioavailability of drugs may increase due to oral and pre-gastric absorption, resulting in reduction of first-pass metabolism in the gastrointestinal tract(4,13).

MATERIALS AND METHOD

MATERIALS:

Materials ibuprofen (IB) was a gift sample from Sampras Healthcare Ltd (Nashik, India). Polyvinyl pyrrolidone (PVP-K30), *β*—cyclodextrin, PEG 6000 was kindly provided by research lab Fine Chem Industries (Mumbai). All reagents and solvents used were of analytical grade.

METHODS:

Pre-Formulation Study

Melting point :

Melting point is used for determination of purity and identification of the drug. The melting point of ibuprofen was determined by using melting point apparatus(14).

Quantification of Ibuprofen by UV Spectroscopy:

Stock solution (100_g/mL) of ibuprofen was prepared in phosphate buffer (pH 6.8), which was then analyzed in the range 200–400 nm, using a UV double-beam spectrophotometer (shimadzu 1800) for the determination of λ max. From this stock solution, standard solutions in the range 3–24 μg/ml were prepared, and the absorbance of each standard solution was determined spectrophotometrically at the λ max obtained. Using absorbance–concentration data, a calibration curve was constructed [15].

FTIR Studies of Ibuprofen:

The FTIR spectra of Ibuprofen were recorded using a Fourier Transform Infrared spectrophotometer (BRUKER

10074425) with diffuse reflectance principle. The spectrum was scanned over a frequency range 4000–400 cm-1. The peaks obtained in the spectra were compared with corresponding functional groups in the structures of ibuprofen [16].

Drug-excipients Compatibility Studies:

Interaction of drug i.e. Ibuprofen with the excipients, which was present in the formulations is monitored with the help of FTIR (BRUKER 10074425). The FTIR spectrums of the Ibuprofen and physical mixture of Ibuprofen: *β*—cyclodextrin: PVP-K30: PEG 6000 : SSG : cross povidone: Mannitol: Mg sterate, in 1:1 proportion, respectively were compared for any possible drug–excipients interaction [13].

Preparation of orodispersible Tablets:

The formulation and development was done by following three steps that is selection of carriers, preparation of solid dispersion by kneading method and formulation of Orodispersible tablet by direct compression method.

Selection of carriers:

Physical mixtures:

Ibuprofen and PEG 6000, PVP K30 & β-cyclodextrin in 1:1, 1:2, 1:3 w/w ratios were prepared by blending the two components in geometric proportion in a glass mortar for 20 minutes in order to obtain a homogeneous mixture. The paste formed was dried under vacuum for 24 hours. The resulting mixtures were sieved through 60 mesh sieve and stored in desiccators until further evaluation(17).

Kneading Method:

Each SD preparation containing different ratio of Ibuprofen and PEG 6000, PVP K30 & β-cyclodextrin was prepared by the kneading method. Carrier was taken in a mortar, and 50% ethanol (V/V) was added and triturated to get slurry. Then, slowly drug was incorporated into the slurry, and trituration was further continued for one hour. Slurry was then air-dried at 25°C for 24 hours, pulverized, and passed through sieve no. 60. The resulting sample was stored in a desiccator until further evaluation(18).

Manufacturing process:

Preparation of solid dispersion by kneading method of Ibuprofen and selected carrier:

SD preparation containing of Ibuprofen and β-cyclodextrin in 1:3 ratio was prepared by the kneading method. *β*-CD was taken in a mortar, and 50% ethanol (V/V) was added and triturated to get slurry. Then, slowly drug was incorporated into the slurry, and trituration was further

continued for one hour. Slurry was then air-dried at 25°C for 24 hours, pulverized, and passed through sieve no. 60. The resulting sample was stored in a desiccator until further use (19-21) .

Solubility study:

An excess quantity of Ibuprofen was placed in 25 ml capacity glass vials containing 10 ml of different solutions (distilled water and phosphate buffer at pH 6.8). The samples were sonicated for 1 hours at room temperature and capped glass vials were shaken for 24 hours at room temperature using mechanical shaker .The sealed glass vials where equilibrated for 24 hours at room temperature. The supernatant solution was then passed through a Whatmann Filter Paper and the amount of the drug dissolved was analyzed UV-Visible spectrophotometry (Shimadzu, 1800) at 222 nm after suitable dilution. This study was also carried out to select a suitable dissolution medium for the in vitro drug release studies(20).

Fourier Transform infrared (FTIR) Spectroscopy

Physicochemical characterization was performed using FTIR spectroscopy. The infrared spectrum sample was recorded and the spectral analysis was done. The dry sample of drug was taken & directly placed and analyzed by IR (Brucker alpha) instrument. The drug polymer interaction was studied by FTIR spectroscopy.The spectra were recorded for pure drug using FTIR. The scanning range was 400-4000 cm^{-1} (16).

Differential scanning calorimetr (DSC):

Differential Scanning Calorimetry (DSC) DSC analysis was performed using Shimadzu-Thermal Analyzer DT 40 (Kyoto, Japan) on 2- to 8-mg samples (Sartorius BP 210 S electronic microbalance, Goettingen, Germany). Samples were heated in an open aluminum pans at a rate of 20°C/min in a 50 to 200°C temperature range under a nitrogen flow of 40 mL/m(20)

X-Ray diffraction (XRD):

X-ray powder diffraction patterns were recorded on a X Pert PRO (PAN analytical NL) diffractometer using Cu K radiation was employed. at a voltage of 45 kV and 40 mA. The sample was scanned from 0-90° diffraction angle (2Ɵ) range(22).

Tablet Preparation and Characterization:

Orodispersible tablet of Ibuprofen were prepared by direct compression technique using rotary tablet compression machine. The solid dispersion of Ibuprofen β-Cyclodextrin Complex (1:3) was blended with the excipients. All the ingredients of the formulations (except lubricant) were passed through sieve number 60. Firstly solid dispersion and Sodium starch glycolate or crosspovidone, mannitol & aspartame were mixed properly in mortar and pestle to make uniformity in powder blend. Finally, Mg. stearate was added and mixed 1-2 min (Table 1). The final blend was evaluated and compressed into tablets using 8 station rotary tablet compression machine (Jaguar JMD-4-8) using 12mm flat die and punches by direct compression technique(20).

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Ibuprofen β-Cyclodextrin Complexes	372.96	372.96	372.96	372.96	372.96	372.96
SSG	12.5	25	37.5	-	-	-
Cross povidone	-	-	-	12.5	17.5	22.5
Mannitol	92.04	79.54	67.04	92.04	87.04	82.04
Magnesium Stearate	7.5	7.5	7.5	7.5	7.5	7.5
Aspartame	15	15	15	15	15	15
Total Weight (mg)	500	500	500	500	500	500

Table 1 : Formulation table for ODT's using complexes prepared by kneading method

Characterization of Precompressed powder blend:

Bulk Density:

Accurately weighed quantities of powder (M) were transferred into measuring cylinder and initial volume (V) were measured. The bulk density was calculated by the following equation(3),
Bulk density = Mass of powder/ Bulk volume

Tapped Density:

Accurately weighed quantities of powder (M) were transferred into measuring cylinder . The cylinder was then subjected to a fixed number of taps (～ 100 times) until the powder bed volume had reached the minimum level. The final volume was recorded and the tap density was calculated by the following equation(3),
Tapped density = Mass of powder/ Tapped volume

Carr's Index and Hausner's Ratio:

The Carr's Index and Hausner's ratio were measured by using bulk density and tapped density of the powder. Carr's Index of the powder was found out by using following formula(3),
% Carr's Index **=** [(Tapped density – bulk density)/Tapped density]×100
Hausner's Ratio = Tapped density/ Bulk density

Angle of Repose:

The dry mixture powders were permitted to flow through the funnel immovable to a stand at certain height (h). The angle of repose was then considered by measure the height and radius (r) of the heap of powders formed(3).

$\text{Tan } \theta = h/r$

Characterization of Compressed Tablet:

Crushing Strength:

The crushing strength of the tablet was determined by using Monsanto hardness tester. The tablet was placed diagonally between the two plungers of tester and pressure was measured on a scale in Kg/cm^2, showing that the tablet broke down completely into two parts(4).

Weight variation:

Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation(23).

Thickness

The thickness of tablets was determined by using digital Varnier caliper (Zoom Classic) for that three tablets from every formulation were used and the results were averaged[24].

Water Absorption Ratio:

Three Orodispersible tablet were weighed separately and placed on the double-folded tissue paper wetted by 6ml water. Wetted Orodispersible tablet were reweighed (25).
$R= [(W_a- W_b)/W_a]\times100$

Where, W_a– Weight of tablet after water absorption.
W_b – Weight of tablet before water absorption.

Wetting time:

A piece of tissue paper folded twice was placed in a small petri dish containing 10ml of dye solution (methylene blue aqueous solution). A tablet was carefully placed on the surface of the paper and the time required for the dye solution to reach the upper surface of the tablet was noted as the wetting time(26). The wetting time for each formulation was carried out in triplicate and the results were expressed as mean ±SD(n=3).

Disintegration Test:

Disintegration times of the prepared ODTs were determined with six tablets in distilled water kept at 37 ± 0.5ºC using a Electrolab disintegration tester. The disintegration time was defined as the time necessary for the ODT to completely disintegrate until no solid residue remains or only a trace amount of soft residue remains on the screen. A digital stopwatch was used to measure the disintegration time to the

nearest second. Only one ODT was analyzed at a time in order to ensure utmost accuracy. All results are presented as mean value ± SD (n = 6)(27).

Uniformity of Drug content:

Five tablets were powdered, and powder equivalent to 100 mg of Ibuprofen was accurately weighed & transferred into a 100 ml volumetric flask. Initially, 5 ml methanol was added & shaken for 10 min. Then, the volume was made up to 100 ml with pH 6.8 phosphate buffer. The solution was filtered, diluted suitably and analysed UV-Visible spectrophotometrically at 222nm(28).

Invitro Drug release/ Dissolution studiesof Ibuprofen Formulation:

The dissolution study of the prepared ODTs was carried out using a USP Apparatus II rotating paddle at 37 ± 0.5 °C and at 50 rpm using 900 mL of pH 6.8 phosphate buffer as a dissolution medium. At predetermined time intervals (3, 6, 9, 12, 20 and 15 min), 5-mL aliquots of the release medium were withdrawn for drug analysis.The absorbance of the collected and filtered samples were measured UV-Visible spectrophotometrically at 222 nm.

RESULTS AND DISCUSSION:

Characterization of the Pure Drug:

The melting point of Ibuprofen, β-cyclodextrin, SSG, PEG 6000, PVP K30, MCC, mannitol and Mg stearate were found to be 76-78°C [17] 290-301 °C, 200-201 °C, 59-63 °C, 170-175°C,, 263-265 °C, 165-167 °C and 198-200 °C, respectively. From these melting points we know the purity of above mentioned compounds. The calibration curve was found to be linear in the concentration range of 3–24 µg/mL having coefficient of regression value R^2=0.9995 and Slope y = 0.388x - 0.0231.Calibration curve refers to UV Visible measurements. By using the above mentioned slope equation we can easily find out the value of x (concentration of drug) in the content uniformity and in the percentage of drug release study. The FTIR spectra of pure Ibuprofen (Fig.1) showed the peaks at wave numbers (cm^{-1}), corresponding to the functional groups present in the structure of the Ibuprofen (Table **2**). The FTIR spectrum of TM exhibited characteristic signals. The presence of absorption bands corresponding to the functional groups present in the structure of TM, and the absence of any well defined unaccountable peak showed a confirmation of the purity of the drug sample.

Figure 1: FTIR Spectra of Ibuprofen

Functional Groups	**Wave Length (cm^{-1})**
O-HStretching	3506.96
C-HBending	2945.73
C=OStretching	1709.71
C=CStretching	1518.22

Table 2: Interpretation of FTIR spectrum of Ibuprofen

Selection of carriers

solid dispersion and physical mixtures with different polymers with different ratio was evaluated for its solubility, FTIR, DSC analysis.

Solubility Study of Different Carriers

Solid Dispersion	Ratio	Solubility (mg/ml)	
		Physical Mixture	Kneading Method
Ibuprofen + PEG 6000	1:1	0.260	0.411
	1:2	0.289	0.459
	1:3	0.327	0.496
Ibuprofen + PVP K30	1:1	0.415	0.710
	1:2	0.358	0.654
	1:3	0.349	0.620
Ibuprofen + β-cyclodextrin	1:1	0.418	0.756
	1:2	0.452	0.769
	1:3	0.498	0.894

Table 3: Ibuprofen Solubility study with different carriers

From this solubility study we concluded that ibuprofen solubility were more in β-cyclodextrin 1:3 ratio is 0.894mg/ml (Table 3).

Drug-excipients Compatibility Studies

The stability of Ibuprofen in the presence of excipients used in the formulations was observed. The FTIR spectrum of the ibuprofen (IB) was compared with FTIR spectrum of the physical mixture of ibuprofen and excipients (PM) and solid dispersion of ibuprofen (SD) which did not show any shifting of the functional group of ibuprofen (Fig.2), therefore, there was no possible drug-excipients interaction.

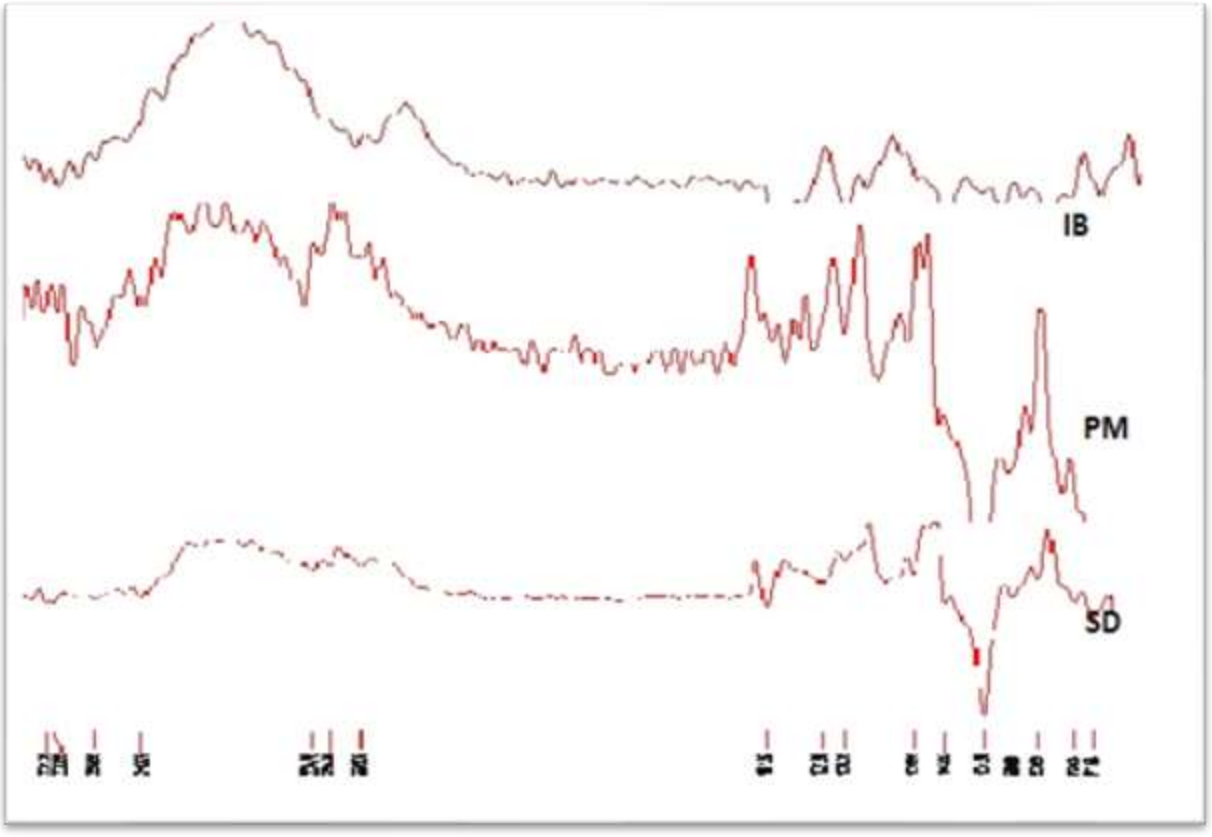

Figure 2 . FTIR Spectra of ibuprofen and various binary systems with β- -cyclodextrin.

Differential Scanning Calorimetry (DSC) :

Thermal behavior of pure drug and corresponding drug carrier system are depicted in Fig. 3. The DSC curve of ibuprofen profiles a sharp endothermic peak (Tpeak = 77.55°C) corresponding to its melting, indicating its crystalline nature. The DSC thermogram of physical mixture of ibuprofen showed an endothermic peak at 76.29°C and β-cyclodextrin showed endothermic peak at 119.88°C due to the liberation

of water of crystallization. The DSC thermogram of solid dispersion of ibuprofen showed an endothermic peak at 75.95°C &β-cyclodextrin showed endothermic peak at 92.74ºC. However, the characteristic endothermic peak, corresponding to drug melting was broadened and shifted toward lower temperature, with reduced intensity, in both physical mixtures as well as solid dispersions. This could be attributed to higher polymer concentration and uniform distribution of drug in the crust of polymer, resulting in complete miscibility of molten drug in polymer.

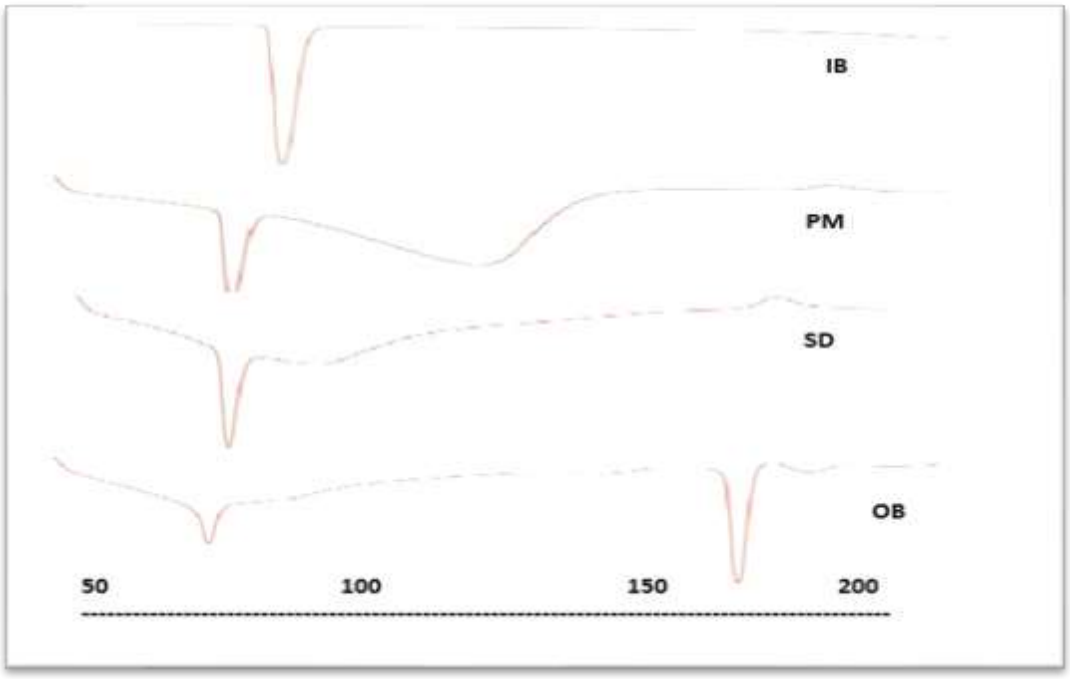

Figure 3 . DSC curves of ibuprofen and various binary systems.

X-ray Diffractometry:

The XRD pattern of pure drug showed intense peaks indicating the crystalline nature of Ibuprofen. The diffractograms were recorded to examine the IBU crystallinity. The diffractograms of the Ibuprofen showed sharp peaks at angle of 5.87, 11.94, 12.51, 13.72, 16.32, 16.61, 19.89, 22.10, 24.33. The diffractograms of kneading method (SD) & optimized formulation(F3) showed decreased intensity of the drug peaks indicating a decrease in the crystallinity of the drug. The peaks are broadened in the kneading method (SD) & optimized formulation(F3) indicating the amorphous nature of Ibuprofen, which might be also the reason for enhanced solubility & dissolution (Fig. 4).

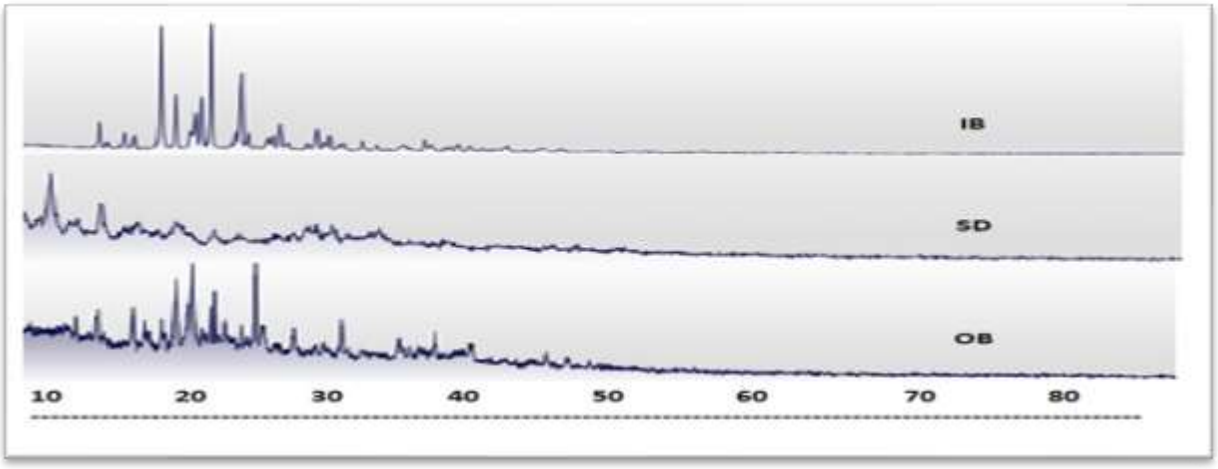

Fig 4. XRD spectra of ibuprofen and various binary systems.

Evaluation of Precompressed Blend:

The blend of all the batches was evaluated for parameter like angle of repose was found to be between 27.67 to 34.96. Bulk density was found to be between 0.38 to 0.45 (gm/cc) and tapped density between 0.45 to 0.57 (gm/cc). Carr's Index was found to be between 11.11 to 13.46, Hausner's ratio ranged between 1.12 to 1.15. All the formulations showed good blend properties for direct compression technology as shown in table 4.

Batches	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's ratio	Angle of Repose (Ɵ)
F1	0.45	0.52	13.46	1.15	34.96
F2	0.41	0.47	12.76	1.14	29.89
F3	0.40	0.45	11.11	1.12	27.67
F4	0.41	0.47	12.76	1.14	34.77
F5	0.38	0.43	11.62	1.13	34.18
F6	0.41	0.47	12.76	1.14	32.19

Table 4 : Precompression Characterization of Tablets

Evaluation of orodispersible tablet of IB:

Results for hardness, friability , content uniformity and disintegration time are indicated in table and were found to be well within limits. The hardness of the tablets was found to be between 2.5 and 2.73 kg/cm^2 , and friability was found to be below 1% which indicated good mechanical strength. The uniformity of drug content was found to be in the range 91.18 to 98.90 shown in table 5. The tablets produced were of uniform weight with acceptable weight variation in the range from 0.102 mg to 0.084 mg. Maximum % weight deviation was found to be 5.12%. Hence, all the formulations passed the test for weight variation as per USP.

The swelling properties of disintegrating agent depend on wetting time showing the existence of small amount of water and were found to be in the range of 91-706 seconds. It has been observed that disintegration time is an important parameter in the development of orodispersible tablet. In the present study, tablets of all developed formulations were disintegrated in the range from 49 ± 8.794 s to 112± 11.335 s (Table 5).

As per the USP, the acceptable time limit specified for the tablet disintegration is 3 minutes. Here, all our developed formulations passed this disintegration test limit [4, 11]. By using SSG we get the fast disintegration time of tablet, and we get the synergistic effect of disintegration of tablets. Out of six formulations F3 showed disintegration time (49 ± 8.794 s) at concentration (8%) of SSG. When we compared disintegration time F1, F2 and F3 the concentrations of SSG were found to be 3%, 6% and 8%, respectively. We observed the disintegration time 110s, 76s and 49s, respectively. Similarly, we compared disintegration time F4, F5 and F6 and the concentration of crosspovidone were found to be 3%, 4% and 5% respectively. We observed the disintegration time 112s, 101s and 83s, respectively Therefore, it can be concluded that we achieved the desired or fast disintegration time by using SSG in (8 %). Drug content used in terms of explaining the degree of uniformity in the amount of drug substances among dosage unit is expressed in percentage, for all formulations found between 92.18% and 98.18% **(**Table 5), thus meeting the standards reported in the official compendia[28-29].

Batch Code	Hardness (Kg/cm^2) (n=3)	Thickness (mm) (n=3)	Friability (%)	Water Absorption Ratio (%)	Wetting Time (Sec.) (n=3)	Disintegration Time (Sec.) (n=6)	Drug Content (%) (n=5)
F1	2.6±0.081	5.1±0.081	0.61	64.58	348.66±6.600	110±10.328	92.23
F2	2.73±0.169	5.13±0.094	0.69	70	156.66±6.236	76.5±6.021	92.18
F3	2.5±0.0816	5.2±0.081	0.61	79.59	91.66±2.357	49±8.794	98.90
F4	2.67±0.124	5.3±0.081	0.53	56	491.66±10.274	112.167±11.335	91.23
F5	2.7±0.0816	5.5±0.081	0.46	53.06	618.33±19.293	101±10.149	93.54

F6	2.70±0.081	5.3±0.081	0.53	51.02	706.33±8.219	83.167±14.679	92.76

Table 5 : Results Of Quality Control Tests Of Designed Orodispersible Tablets Of Ibuprofen

In vitro Drug Release/dissolution Studies of Ibuprofen Formulations

Dissolution studies of all formulations showed the maximum percentage drug release for F3-99.95%, F2- 93.87%, F1-88.64%, F4-84.26%, F5-77.2%, and F6-67.5% in 15 minutes time period (Fig.5). All formulations showed the extended drug release and F3 showed the highest drug release when compared to other formulations.

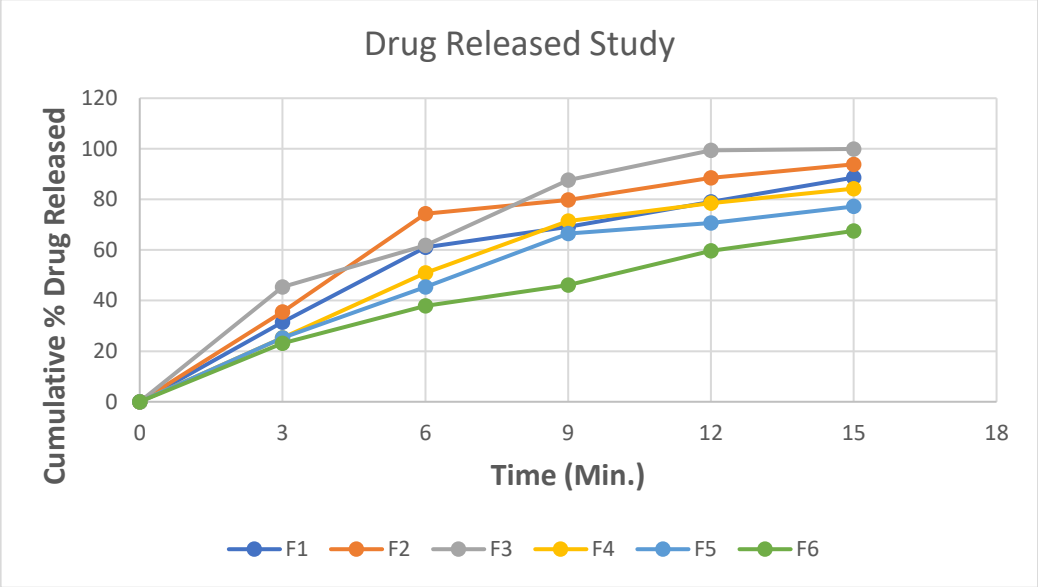

Fig 5. Dissolution profile for F1 to F6.

CONCLUSION

The present research was undertaken with an aim to design and characterize fast orodispersible tablets of Ibuprofen using direct compression method with the addition of solid dispersion and super disintegrating agents. Ibuprofen has the NSAID's so, it was used in emergency treatment for the management of relieve pain, reduce inflammation, and bring down a high temperature. Main objective of super-disintegrant was to break the tablet in less time period and improve the solubility of ibuprofen by using solid dispersion kneading method. FTIR study revealed no drug excipients interaction. Solubility of Ibuprofen is increased by using Kneading Method and it is increased from 0.237 mg/ml to 0.894 mg/ml. In Polymer like β-cyclodextrin, PVP K30, PEG 6000 were used to increase the solubility of Ibuprofen. In β-cyclodextrin solubility of Ibuprofen is found to be 0.894mg/ml is more as compared to other polymer. Kneading solid dispersion and physical mixture was evaluated and it shows excellent flowability properties when formulation of F3 was compared with the rest of the formulations for disintegration time, water absorption ratio, wetting time, % drug release, and content uniformity, it was found to be superior to others because it was disintegrated within 49 seconds and percentage drug release was found to be 99.95 % within 15 minutes. Therefore, during the development of orodispersible tablet by using SSG and β-cyclodextrin , the concentration of disintegrants was animportant parameter in optimizing the disintegration time of tablet.

CONFLICTS OF INTEREST:

The authors declare that they have no competing interests.

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