Design, formulation and characterization of ibuprofen-polyethylene glycol (6000) solid dispersions

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ABSTRACT

Background: Formulation of solid dispersion has attracted considerable interest where dispersing a poorly water soluble drug in a water soluble polymer matrix improves the dissolution characteristics and bioavailability of the drug.

Aim: The aim of this study was to enhance the dissolution rate and bioavailability of Ibuprofen (BCS class II) using solid dispersion techniques.

Method: Ibuprofen solid dispersion was prepared by fusion method. Drug-carrier physical mixtures were also prepared. Effects of polyethylene glycol 6000 (PEG 6000) was studied for the solid dispersions and physical mixtures. The solid dispersions were investigated for drug content, solubility and dissolution characteristics, surface morphology using optical microscopy and Fourier Transform Infrared Spectroscopy (FTIR). All the solid dispersions showed better solubility characteristics and dissolution rate than physical mixtures. Evaluation of the FTIR results shows that the stretching vibration of ibuprofen carbonyl peak in SDs and physical mixture remained which indicates that the drug crystalline form may not be altered during solid dispersion formation and its attenuated intensities were thought to be due to the lower drug content as the amount of polymer was increased.

Conclusion: The FT-IR and DTA results for SDs and physical mixtures showed no drug-polymer interaction The statistical analysis, solubility and dissolution rate test result of ibuprofen was compared to that of the SD formulations and the values obtained were significantly below 0.05 which indicates that the results are statistically significant. Therefore, solid dispersion may be an effective technique to enhance dissolution rate of Ibuprofen.

Key words: Solid dispersion, Ibuprofen, solubility, bioavailability, PEG-6000, Fusion

Conception, formulation et caractérisation de dispersions solides ibuprofène-polyéthylène glycol (6000)

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RÉSUMÉ

Contexte : La formulation de la dispersion solide a suscité un intérêt considérable lorsque la dispersion d'un médicament mal soluble dans l'eau dans une matrice de polymères solubles dans l'eau améliore les caractéristiques de dissolution et la biodisponibilité du médicament.

Objectif : L'objectif de cette étude était d'accroître la vitesse de dissolution et la biodisponibilité de l'ibuprofène (classe II du SBC) à l'aide de techniques de dispersion solide.

Méthode : La dispersion solide d'ibuprofène a été préparée par la méthode de fusion. Des mélanges physiques porteurs de drogues ont également été préparés. Les effets du polyéthylène glycol 6000 (PEG 6000) ont été étudiés pour les dispersions solides et les mélanges physiques. Les dispersions solides ont été étudiées pour la teneur en médicaments, la solubilité et les caractéristiques de dissolution, la morphologie de surface à l'aide de la microscopie optique et la spectroscopie infrarouge Fourier Transform (FTIR). Toutes les dispersions solides ont montré de meilleures caractéristiques de solubilité et une meilleure vitesse de dissolution que les mélanges physiques. L'évaluation des résultats du FTIR montre que la vibration d'étirement du pic de carbonyle d'ibuprofène dans les SD et le mélange physique subsistent, ce qui indique que la forme cristalline du médicament ne peut pas être modifiée pendant la formation de dispersion solide et ses intensités atténuées étaient considérés comme étant dus à la teneur plus faible en médicaments à mesure que la quantité de polymère augmentait.

Conclusion: Les résultats FT-IR et DTA pour les SD et les mélanges physiques ne montrent aucune interaction médicament-polymère.Le résultat du test d'analyse statistique, de solubilité et de vitesse de dissolution de l'ibuprofène a été comparé à celui des formulations SD et les valeurs obtenues étaient nettement inférieures à 0,05, ce qui indique que les résultats sont statistiquement significatifs. Par conséquent, la dispersion solide peut être une technique efficace pour augmenter la vitesse de dissolution de l'ibuprofène.

Mots clés: Dispersion solide, Ibuprofène, solubilité, biodisponibilité, PEG-6000, Fusion

INTRODUCTION

With recent advances in pre-formulation and formulation studies, pharmaceutical scientists have been applying a wide range of approaches to improve the dissolution rate of poorly soluble drugs. These include formulating in the nano-size range; formulating in a solid solution or dispersion or self-emulsifying drug delivery system; stabilizing the drug in the amorphous form or formulating with cyclodextrins.

Among these approaches, solid dispersion technique has been regarded as an efficient means of improving the dissolution rate and the bioavailability of a wide range of poorly aqueous soluble drugs.[1,2,3]

Solid dispersion was introduced to overcome the low bioavailability of lipophilic drugs by forming of eutectic mixtures of drugs with water-soluble carriers. Solid dispersion technique was firstly demonstrated by Sekiguchi and Obi.[5] They proposed the faster absorption of poorly water-soluble drugs such as sulfathiazole by the formation of eutectic mixture with a water-soluble and physiologically inert carriers like urea.[5]

Solid dispersions (SDs) of poorly water soluble drugs in hydrophilic carrier matrix have been reported to improve their solubility and dissolution rate, thereby, improving the rate and extent of absorption (bioavailability) of such drugs.[6,7]

Ibuprofen is a potent non-steroidal anti-inflammatory drug (NSAID) widely used in the treatment of rheumatoid arthritis, osteoarthritis and mild to moderate pains associated with migraine, fever and dysmenorrhea. It is considered the safest of the NSAIDs in the treatment of pain due to inflammatory responses and feverish conditions. It is one of the most frequently prescribed and best tolerated NSAID, especially in children, because of its high benefit-to-risk profile.[10,11] However, ibuprofen has hydrophobic characteristics, practically insoluble in water with saturation solubility of 49 µg/mL at room temperature. Ibuprofen also has a short biological half-life (approximately 2 h) and its solubility and permeability are pH dependent.[12]It is poorly soluble at acidic pH of the stomach but solubilizes at alkaline pH of the small intestine. Its poor solubility (log P value 3.6) in the stomach limits its absorption before gastric emptying (30 min to 2 h) occurs. Although ibuprofen solubilizes in the small intestine, its ionized species cannot permeate through the intestinal membrane.[13] It follows that when administered orally, ibuprofen tends to be eliminated from the gastro-intestinal tract before having the opportunity to dissolve fully and be absorbed into the circulation, resulting in incomplete absorption as well as low and erratic bioavailability with a consequent poor dosing proportionality.[14] This phenomenon translates to low systemic bioavailability requiring the use of high and multiple daily dosing to maintain the required plasma concentration for effective therapeutic activity. The usual consequence includes wasted dosing as well as potentially serious gastro intestinal side effects such as bleeding and ulceration.

Ibuprofen belongs to the Biopharmaceutics Classification System (BCS) class II which exhibits poor water solubility and high membrane permeability.[15] The rate limiting step for BCS class II drugs is dissolution. BCS is a system that classifies orally administered drugs into four classes based on their solubility and intestinal permeability.[16] It has also been reported that rapid absorption rate of oral formulations of ibuprofen enhanced its analgesic properties.[17]

Solid dispersion is a common strategy by which to improve the dissolution rate and absorption of poorly water soluble drugs using hydrophilic polymer carriers as dispersing agent. Solid dispersions using insoluble carriers loaded with hydrophilic drugs lead to a delivery system aimed at optimizing pharmacokinetics and reducing side effects such as gastric irritation due to non-steroidal anti-inflammatory drugs.[18] Solid dispersion has been the most promising method used to enhance the solubility and dissolution rate of poorly soluble drugs. Solid dispersions are of immense importance now-adays in the development of poorly water soluble drugs into oral solid dosage forms with enhanced dissolution rate and thus improved oral bioavailability.[19]

METHOD

Materials

Ibuprofen powder (Burgoynes & Burbidges, India), Polyethylene glycol 6000 (LOBA Chemie, India), sodium dihydrogen phosphate (Sigma-Aldrich), disodium hydrogen phosphate (Sigma-Aldrich). All other reagents used are of analytical grades and were used as received.

Preparation of solid dispersion (melting/fusion method)

The method of Sekiguchi and Obi was employed.[5]Physical mixtures of accurately weighed amount of the drug and a water-soluble carrier were prepared by trituration using a mortar and pestle. These mixtures were then heated on the water bath (HH-420, Lab science, England) at 95°C to a molten state. The melted mixture was then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass was crushed, pulverized and sieved.

Table 1: Formula ratio for preparation of ibuprofen solid dispersion

Batch	Drug (g)	Polymer (g)	Ratio
S.D 1	3	6	1:2
S.D 2	3	9	1:3
S.D 3	3	12	1:4
S.D 4	3	18	1:6
S.D 5	3	24	1:8
S.D 6	3	30	1:10

Preparation of physical mixtures

The physical mixtures (PM) were prepared by mixing the required amount of the drug and PEG 6000 together in a mortar with the aid of a pestle at the same ratio as expressed in table 1.

Characterization of solid dispersion

Particle morphology

The surface morphology of Ibuprofen, PEG 6000, physical mixtures; and solid dispersions were examined using an optical microscope at magnification of x 40.[8]

Determination of percent yield

The percent yield of ibuprofen solid dispersions was determined by using the following expression:

$$\text{Percent yield} = \frac{\text{weight of prepared solid dispersion}}{\text{weight of drug + carriers}} \times 100$$

Determination of percent drug content

The various batches of the solid dispersions were subjected to drug content analysis. Preparations of solid dispersion equivalent to 25mg of ibuprofen was weighed accurately and dissolved in 50ml of (95 %) ethanol in a 100 ml volumetric flask then filtered and the volume was made up with the solvent to the mark. After suitable dilution, the absorbance of the solution was measured using a UV spectrophotometer (GS-UV61PC, Double Beam Spectrophotometer) at 220nm using appropriate blank solution,.[9]

A standard solution of ibuprofen was also prepared by weighing 100 mg of ibuprofen and dispersed in 100 ml of ethanol with vigorous shaken in a conical flask given a standard solution (1 mg/ml). One milliliter (1 ml) of this solution was further transferred to a 100 ml conical flask, and volume adjusted to the mark with the buffer solution to yield a solution with concentration of 0.01 mg/ml. The absorbance of this standard solution was record spectrophotometrically. Knowing the absorbance of the standard solution and absorbance of the unknown concentration, then the unknown concentration of the microspheres were determined.:

$$\text{Percent drug content} = \frac{\text{practical drug content in solid dispersions}}{\text{theoretical drug content in solid dispersion}} \times 100$$

Calibration curve by spectrophotometry

Preparation of standard curve of ibuprofen

A stock solution of ibuprofen was prepared at 0.01 mg/ml in phosphate buffer saline (pH 7.4). The linearity of the calibration curve (coefficient of Determination $R^2 = 0.99$) was in a concentration range from 20 µg/ml to 180 µg/ml using a GS-UV61PC, Double Beam Spectrophotometer (General Scientific, India) at 220 nm using appropriate blank solution.

Saturation solubility determination

Ibuprofen, physical mixtures, or SDs equivalent to 100 mg of ibuprofen were added to 10 ml phosphate buffer pH 7.2 (PB) in test tubes, vortexed for 2 min, and shaken at 25 $^{\circ}$C and 120 agitations per minute in a Water Bath Shaker (Fisher Scientific, USA)for 24 hours. Resultant samples containing undissolved SDs suspended in the test medium were centrifuged at 10000 rpm for 5 min and the clear supernatants obtained were filtered and quantified using a GS-UV61PC, Double Beam Spectrophotometer (General Scientific, India), at 220 nm.

In-vitro drug dissolution test

The USP dissolution method was used to study the dissolution profile of the samples (ibuprofen, physical mixtures and solid dispersions) using DBK India USP Apparatus II Dissolution Test Instrument –basket apparatus rotating at 50rpm. A 100mg equivalent of the pure Ibuprofen and the various formulations were used. A solution of phosphate buffer of pH 7.2 at 37 ± 0.5 ºC was employed as a dissolution medium. At pre-determined time intervals; 5, 10, 20 30, 45 and 60 min, a 5 mL aliquots was withdrawn and replaced with the same volume of phosphate buffer solution. The withdrawn samples were filtered and drug concentrations were quantified using

UV spectrophotometer (GS-UV61PC, Double Beam Spectrophotometer) at 220nm. The percentage of drug release at various time intervals will be calculated and plotted against time.

Statistical analysis

Quantitative data are presented as mean ± standard deviation. The significance of the differences between means was assessed using Analysis of Variance (ANOVA) Test with a statistical significance level set at $p < 0.05$.

Drug-polymer interaction (FT-IR) study

IR spectroscopy was performed by Fourier transformed infrared spectrophotometer (FTIR). The samples (pure ibuprofen, PEG 6000 as well as physical mixtures and solid dispersions) were analyzed Fourier Transfer Infra-Red spectrophotometer (Nicolet iS5 FT-IR Spectrometer, Thermo Scientific)to evaluate the drug-polymer interaction.

RESULTS

Particle morphology

The particle morphology of the prepared solid dispersions was as shown in figure4 C and E.

Percentage yield

The percentage yield of all batches was determined and the results are shown in the figure 5 below ranging from 95% to 99 %.

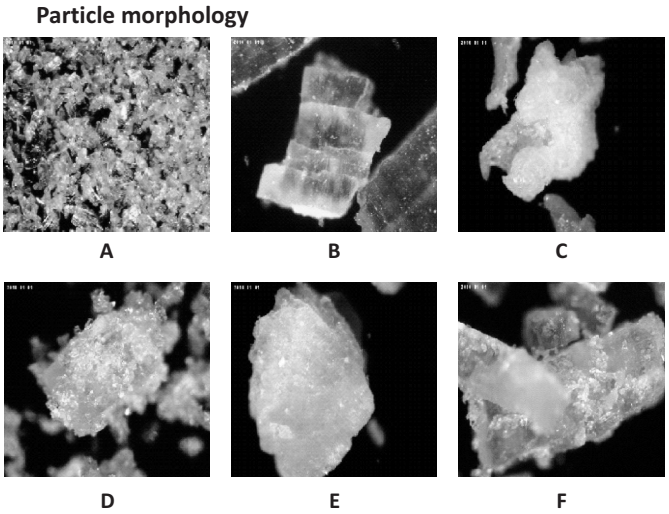


Figure 4: Microscopic images of samples. (A) Ibuprofen (B)PEG 6000 (C) 1:2 w/w solid dispersions (D) 1:2 w/w physical mixture (E) 1:10 w/w solid dispersions (F) 1:10 w/w physical mixtures.

Percentage drug content

A calibration curve of ibuprofen in ethanol at 220nm wavelength was obtained and is shown in figure 6. The curve was found to be linear within the range of 2-10µg/mL.

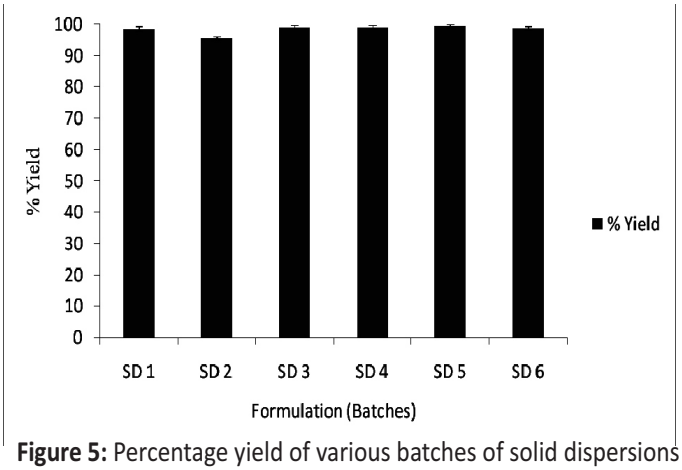


Figure 5: Percentage yield of various batches of solid dispersions

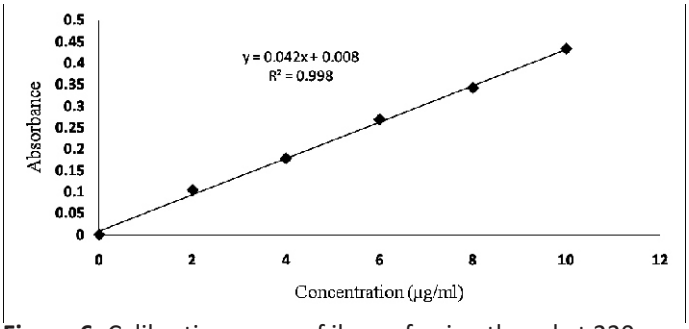


Figure 6: Calibration curve of ibuprofen in ethanol at 220nm

The equation obtained was used to calculate the drug content in the amount of each preparation that is equivalent to 25mg of ibuprofen powder. The percentage drug content was calculated for each preparation. The percentage drug content ranged between 98% and 100%. The results are presented in the chart in figure 7.

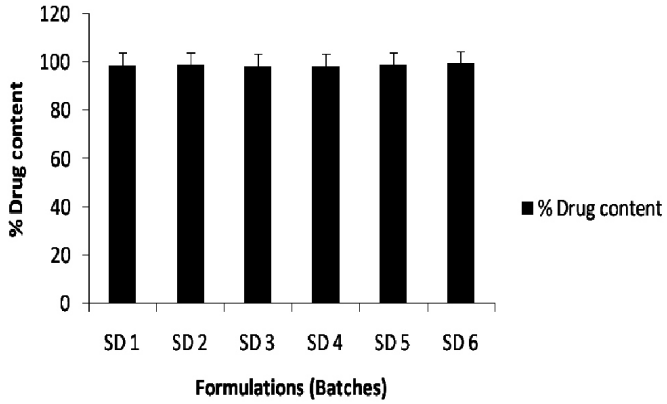


Figure 7: Percentage drug content of the various batches of solid dispersion

Saturation solubility determination

A calibration curve of ibuprofen in Phosphate buffer of pH 7.2 at 265nm wavelength was obtained and is shown in figure 9. The curve was found to be linear within the range of 20-160µg/mL..

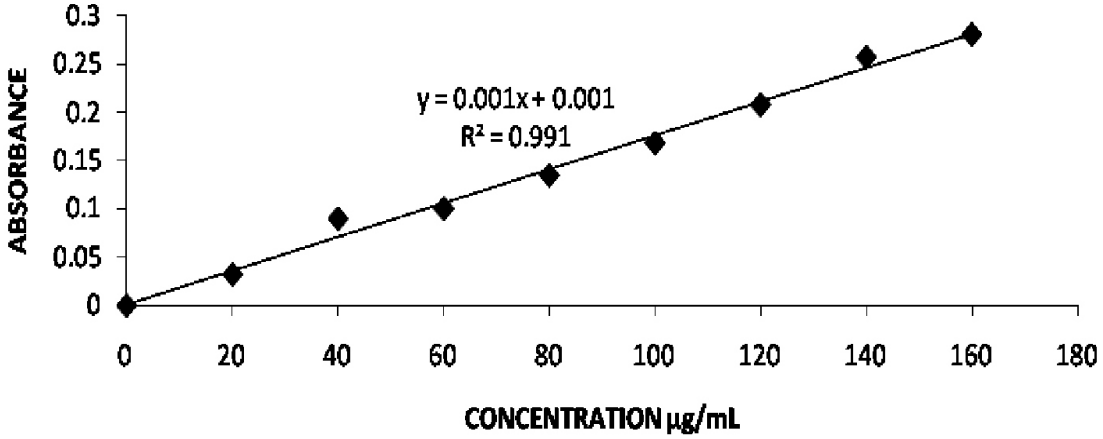


Figure 8: A calibration curve of ibuprofen in phosphate buffer of pH 7.2 at 265nm

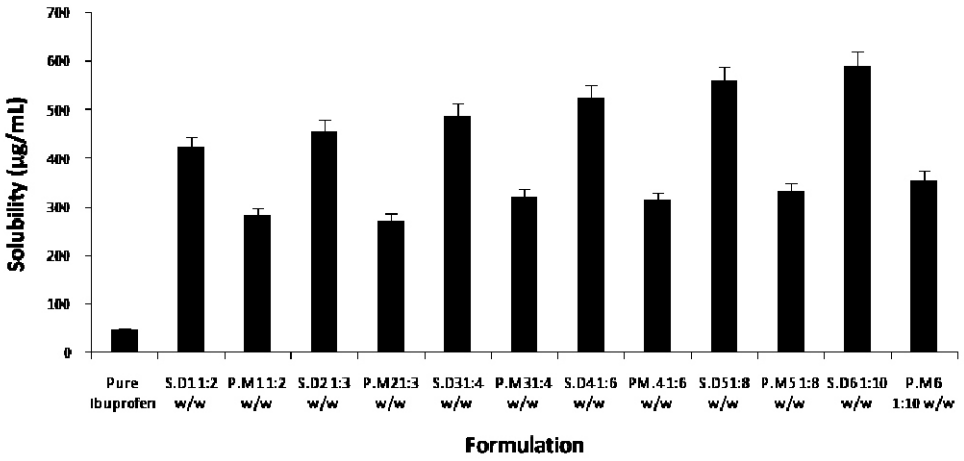


Figure 9: Solubility of solid dispersions in phosphate buffer (pH 7.2).

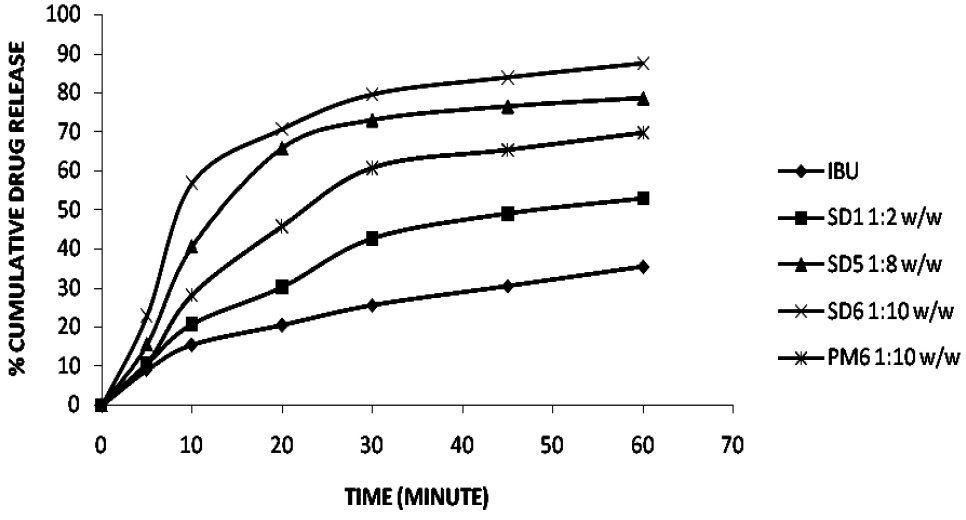


Figure 10: Dissolution profiles of solid dispersions in phosphate buffer (pH7.2).

Statistical analysis

The data obtained from the saturation solubility and in-vitro dissolution rate test were subjected to ANOVA test with pfi0.05 and n=2. All values obtained were significantly below 0.05. The values were between 0.000026 and 0.000447 for the saturation solubility test, and between 0.000101 and 0.028621 for the dissolution rate test.

Drug - polymer interaction (FT - IR) study

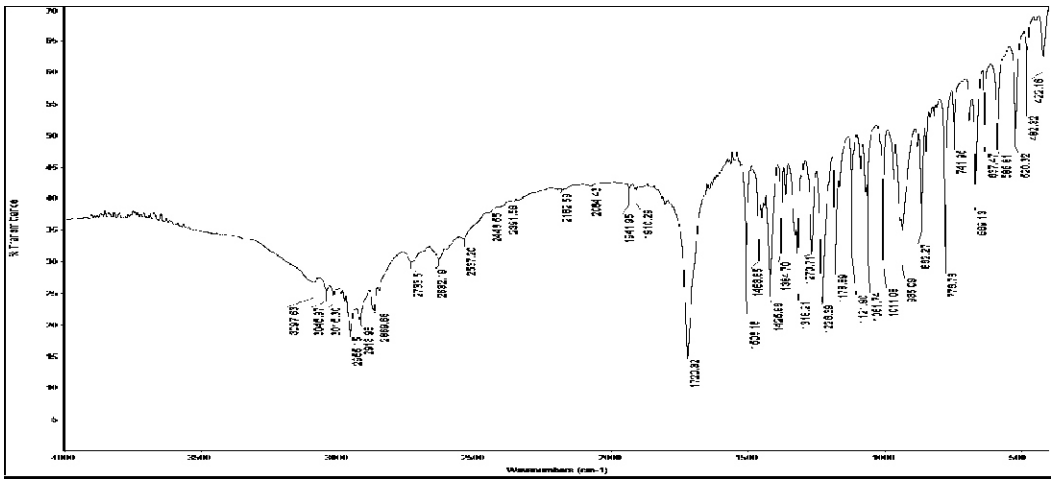


Figure 11: FT - IR spectra of pure ibuprofen powder

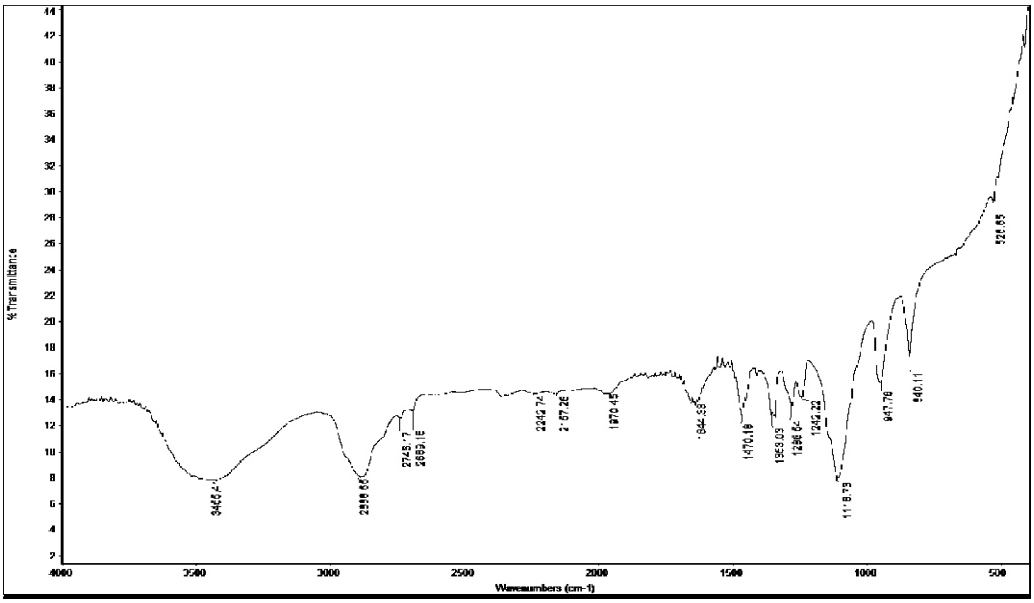


Figure 12: FT-IR spectra of polyethylene glycol 6000

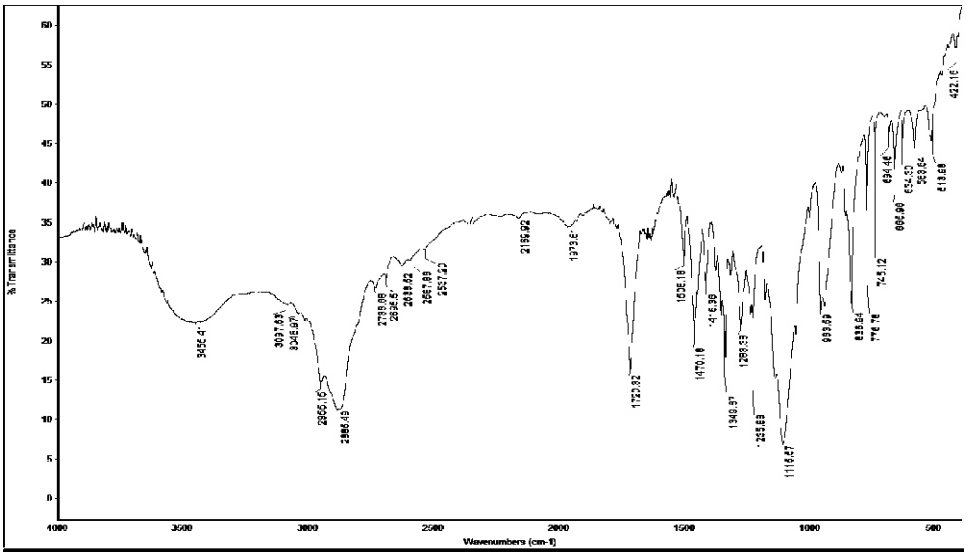
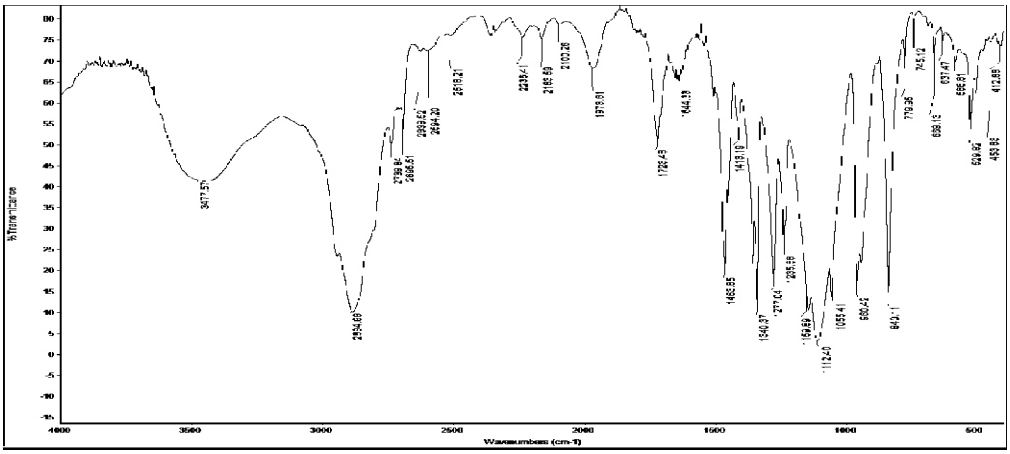


Figure 13: FT-IR spectra of S.D1 (1:2 w/w solid dispersion)



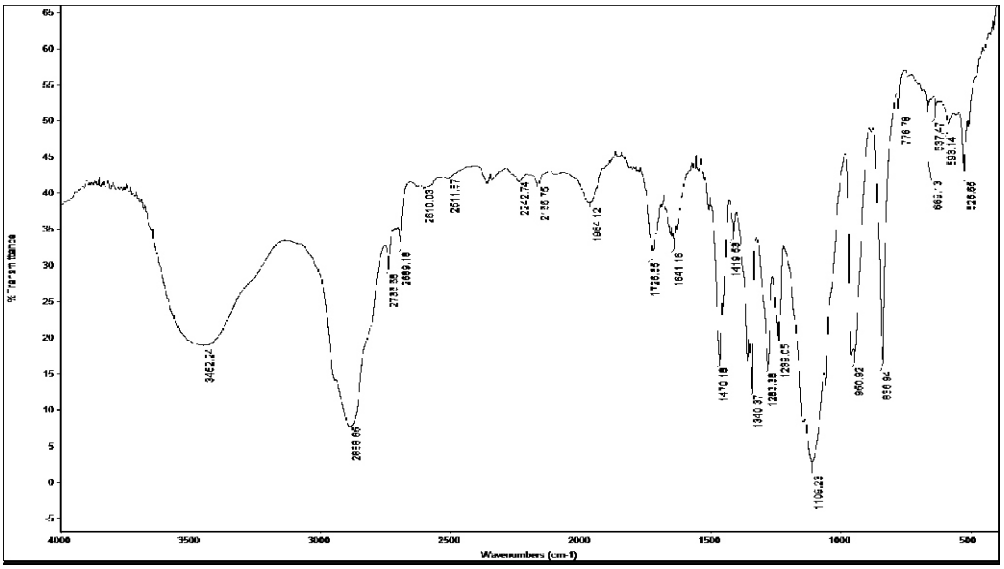


Figure 15: FT-IR spectra of P.M6 (1:10 physical mixture)

DISCUSSION

The drug, ibuprofen was selected for this study based on

dissolution and in vivo bioavailability. Pharmaceutcal Research 12(3): 413-420.

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Table for percentage yield of the various batches of solid dispersion

Batches	Percentage yield (%)
SD1	98.66 ± 0.5
SD2	95.58 ± 1.2
SD3	99.00 ± 0.05
SD4	99.19 ± 0.2
SD5	99.40 ± 0.4
SD6	98.73 ± 0.8

Formulation and Characterization of Ibuprofen Solid Dispersion

Table for concentration and absorbance of ibuprofen in ethanol at 220nm

Concentration (µg/mL)	Absorbance ± SD
2	0.433 ± 0.12
4	0.342 ± 0.10
6	0.269 ± 0.11
8	0.178 ± 0.05
10	0.104 ± 0.01

Table for percentage drug content

Batches	Percentage drug content (%) ± SD
SD1	98.96 ± 1.24
SD2	99.10 ± 1.50
SD3	98.60 ± 0.82
SD4	98.50 ± 0.87
SD5	99.20 ± 1.10
SD6	99.60 ± 1.30

Table for concentration and absorbance of ibuprofen in Phosphate buffer of pH 7.2 at 265nm

Concentration (µg/mL)	Mean Absorbance ± SD
20	0.0325 ±0.0007
40	0.0900 ±0.0070
60	0.1005 ±0.0035
80	0.1345 ±0.0049
100	0.1680 ±0.0028
120	0.2075 ±0.0035
140	0.2570 ±0.0028
160	0.2805 ± 0.0049

Table for the solubility of ibuprofen and the various formulations

FORMULATION	SOLUBILITY ±SD (µg/mL) (n= 2)
Pure Ibuprofen	47.77±0.42
S.D1 1:2 w/w	423.65±11.23
S.D2 1:3 w/w	456.29±1.66
S.D31:4 w/w	489.53±2.08
S.D4 1:6 w/w	526.29±4.16
S.D51:8 w/w	561.00±0.83
S.D6 1:10 w/w	590.41±2.49
P.M1 1:2 w/w	285.12±1.66
P.M21:3 w/w	273.94±1.66
P.M31:4 w/w	322.47± 0.42
PM.4 1:6 w/w	315.41± 0.42
P.M5 1:8 w/w	333.94± 0.83
P.M6 1:10 w/w	358.06± 8.32

Table for dissolution profile of ibuprofen and the formulations

Time (mins)	% cummulative amount of drug released ± SD (n=2)				
	Ibuprofen	**SD1**	**SD5**	**SD6**	**PM6**
5	8.97 ± 0.1872	10.69 ± 0.3444	10.69 ± 0.3744	18.9 ± 0.7487	12.55 ± 0.7487
10	9.42± 0.0010	11.26 ± 0.4133	17.90 ± 1.4953	33.83 ± 2.2503	17.65 ± 1.1272
20	11.46 ± 0.1861	14.79 ± 0.7445	32.82 ± 0.7549	48.57 ± 0.3577	26.74 ± 0.3639
30	12.51 ± 0.0936	30.75 ± 2.2461	42.53 ± 0.0104	64.46 ± 0.7341	36.95 ± 0.3660
45	11.39± 0.0931	33.30 ± 1.1355	56.27 ± 1.1335	82.82 ± 0.7591	62.43 ± 1.3039
60	11.32± 0.2808	36.66± 0.3556	62.93 ± 1.1064	85.39 ± 1.5119	69.53 ± 0.7477