

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

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 (Burgoyne&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 x40.⁸

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 220 nm 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.:

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

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

7.2 (PB) in test tubes, vortexed for 2 min, and shaken at 25 °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 °C 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 220 nm. The percentage of drug

release at various time intervals will be calculated and plotted against time.

Statistical analysis

Quantitative data are presented as mean $\pm$ 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.

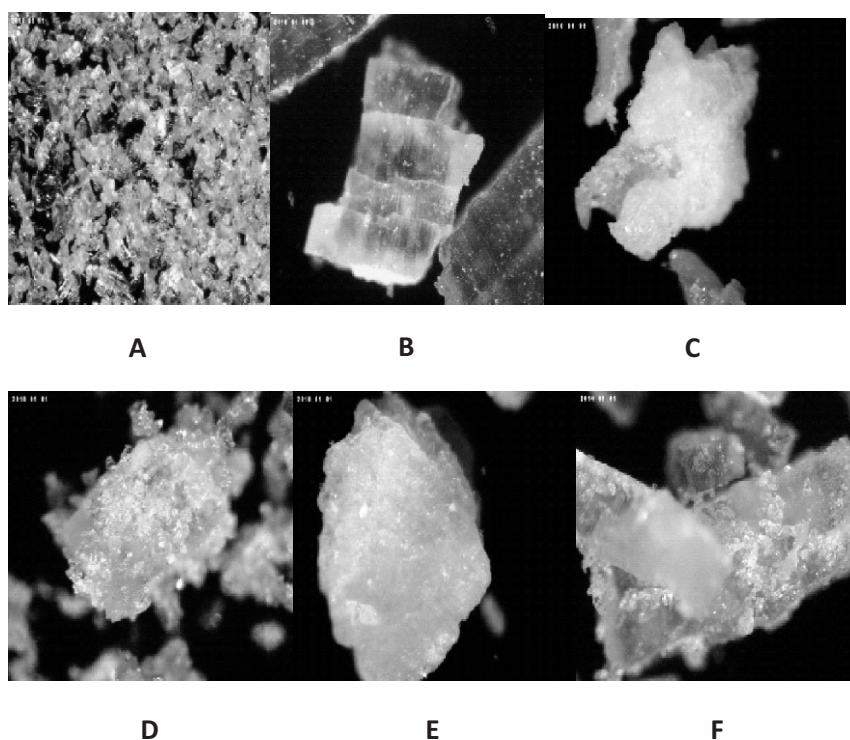
RESULTS

Particle morphology

The particle morphology of the prepared solid dispersions was as shown in figure 4 C and E.

Figure 4: Microscopic images of samples. (A) Ibuprofen (B) PEG 6000 (C) 1:2 w/w solid dispersions (D) 1:2 w/w

Particle morphology



physical mixture (E) 1:10 w/w solid dispersions (F) 1:10 w/w physical mixtures.

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%.

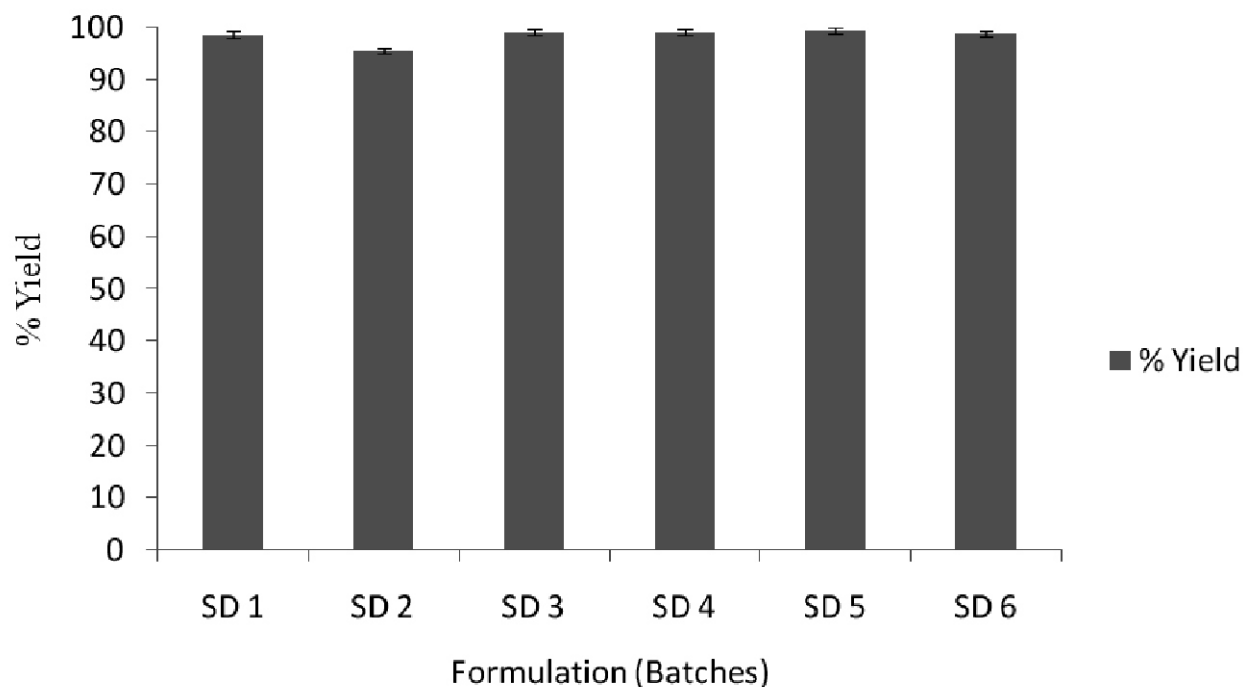


Figure 5: Percentage yield of various batches of solid dispersions

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.

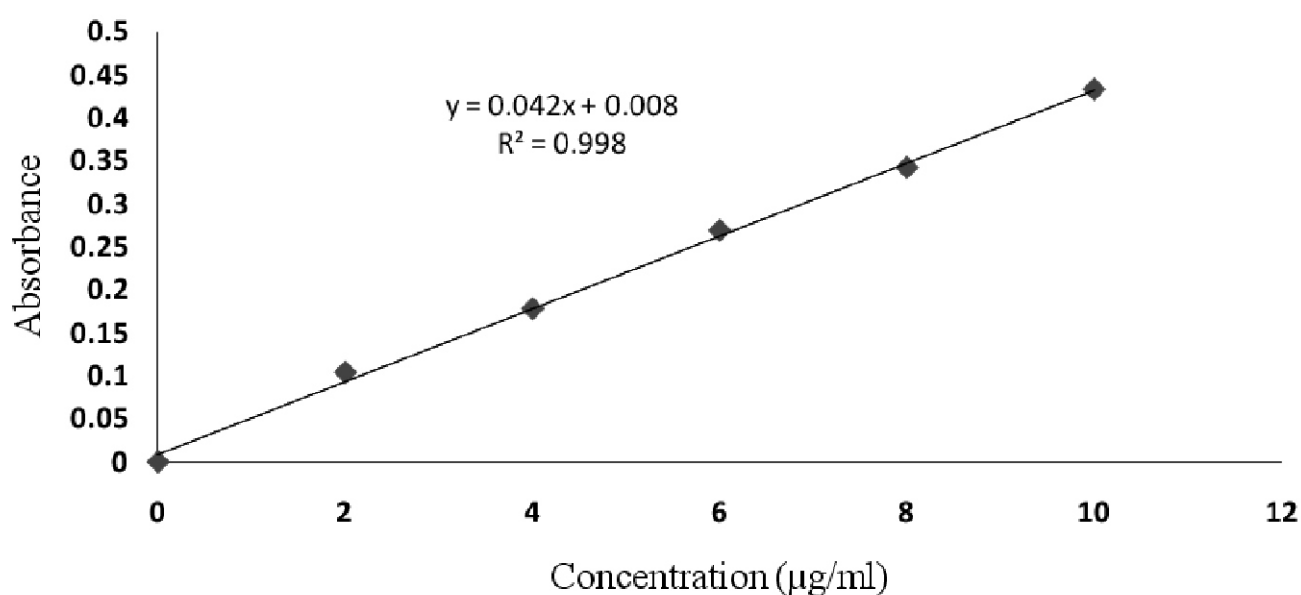


Figure 6: Calibration curve of ibuprofen in ethanol at 220nm

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.

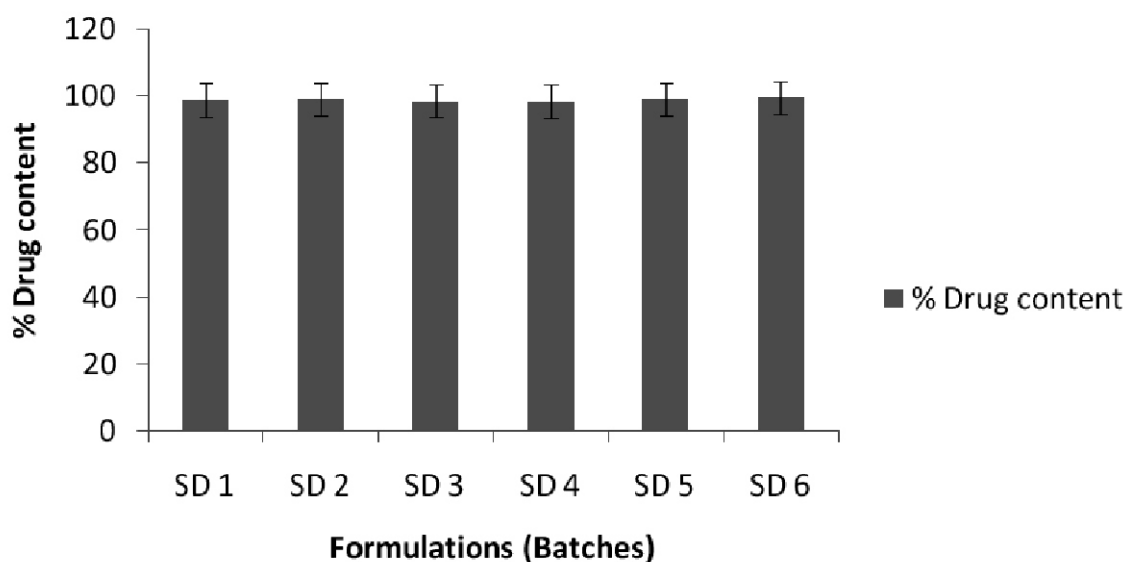


Figure 7: Percentage drug content of the various batches of solid dispersion

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 20-160 μ g/mL.

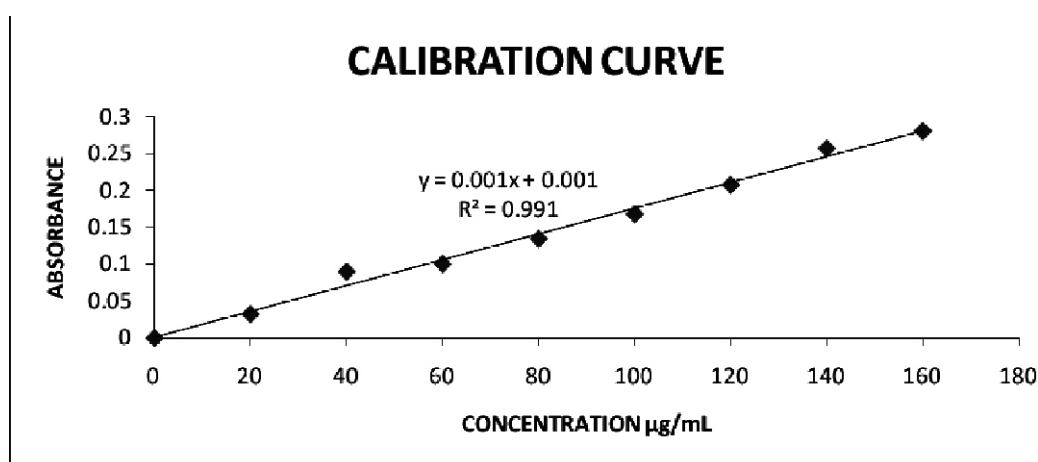


Figure 8: A calibration curve of ibuprofen in phosphate buffer of pH 7.2 at 265nm

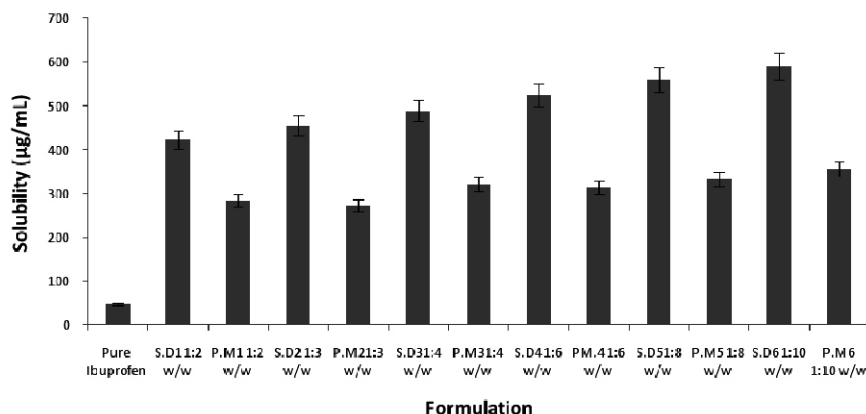


Figure 9: Solubility of solid dispersions in phosphate buffer (pH 7.2).

In-Vitro drug dissolution rate test

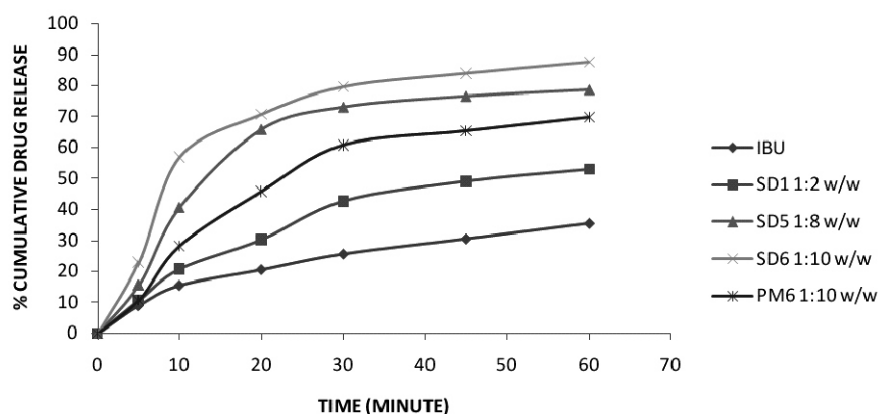


Figure 10: Dissolution profiles of solid dispersions in phosphate buffer (pH7.2).

Statistical analysis

The data obtained from the saturation solubility and in-vitro dissolution rate test were subjected to ANOVA test with $p < 0.05$ 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) s tudy

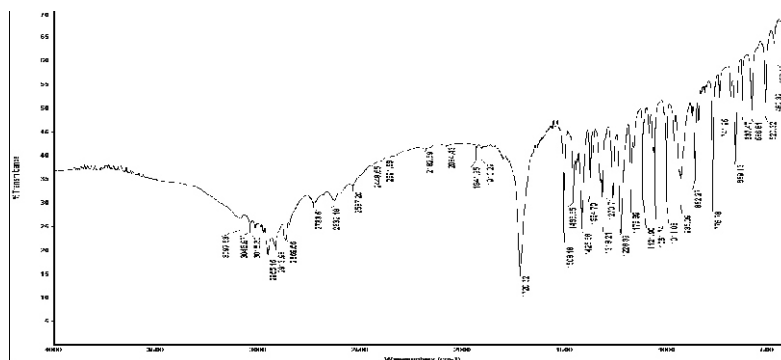


Figure 11: FT -IR s pectra of pure ibuprofen powder

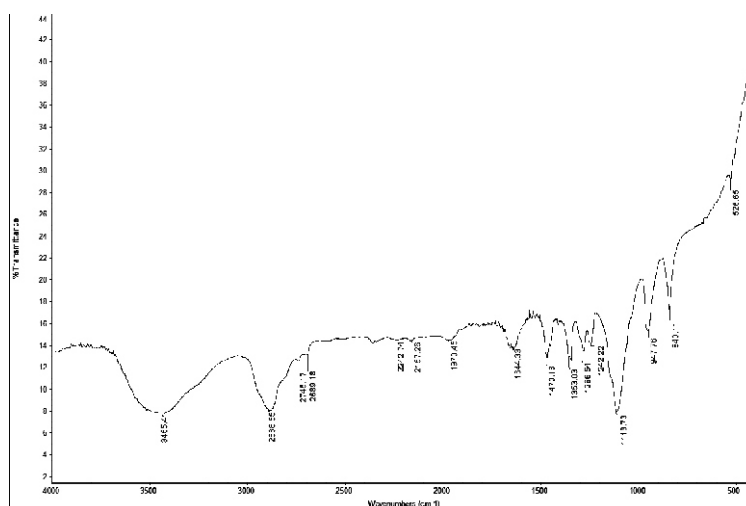


Figure 12: FT-IR spectra of polyethylene glycol 6000

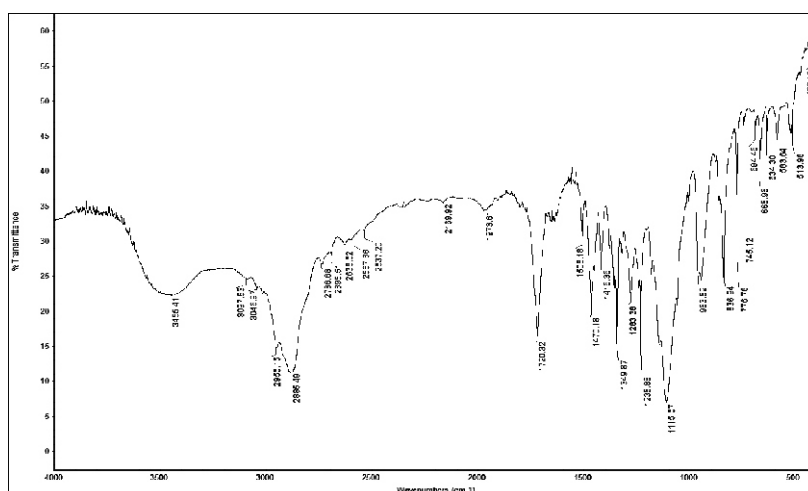


Figure 13: FT-IR spectra of S.D1 (1:2 w/w solid dispersion)

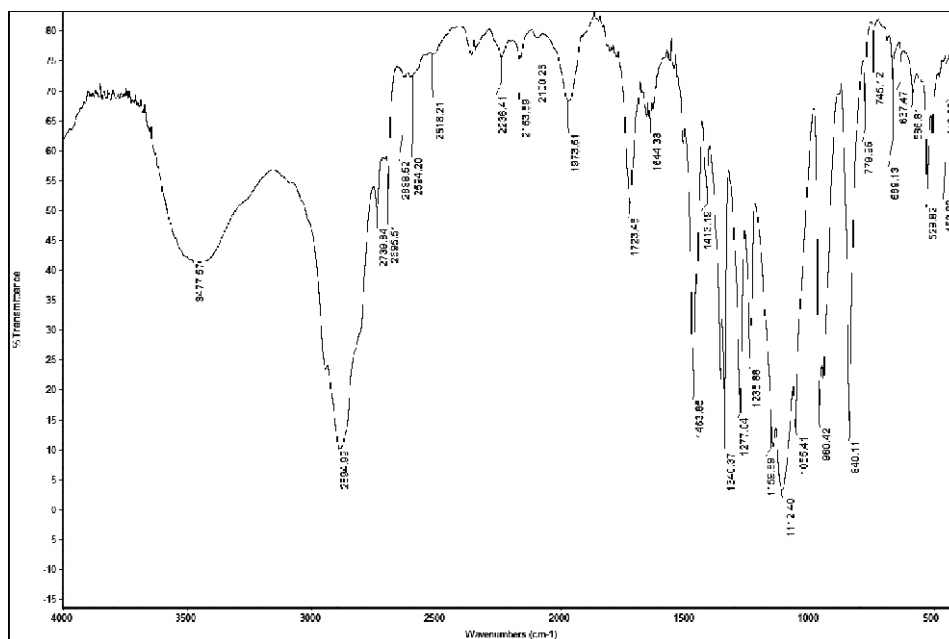


Figure 14: FT-IR spectra of S.D6 (1:10 w/w solid dispersion)

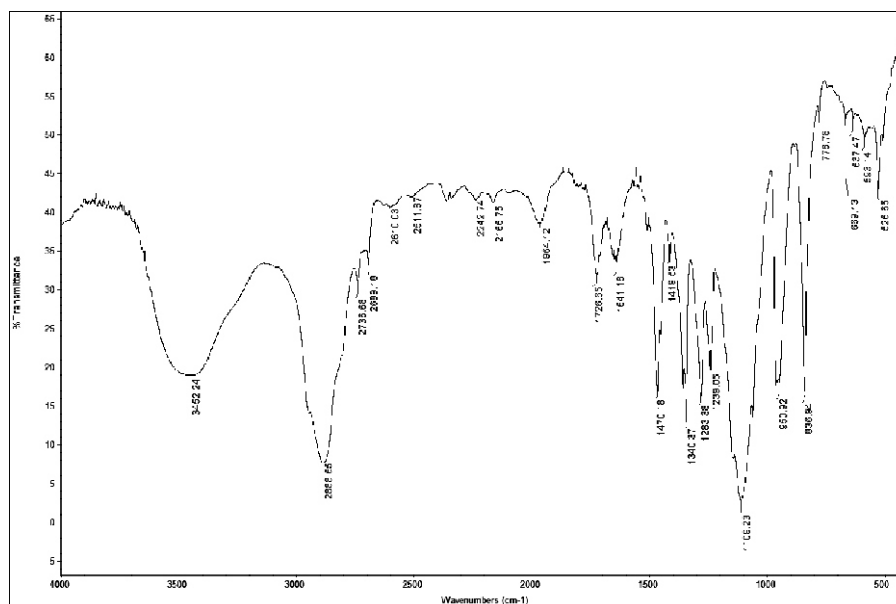


Figure 15: FT-IR spectra of P.M6 (1:10 physical mixture)

DISCUSSION

The drug, ibuprofen was selected for this study based on its poor solubility and dissolution rate which gives rise to bioavailability problems.

From studies of the surface morphology of pure ibuprofen powder, polyethylene glycol 6000, the 1:2 w/w and 1:10 w/w solid dispersions and their corresponding physical mixtures, many differences were observed. From the images of ibuprofen (A) obtained, it was seen that the ibuprofen is crystalline in nature. PEG 6000 was found to be smooth-surfaced irregular waxy particles (B). The 1:2 w/w (C) and 1:10 w/w (E) solid dispersions were seen to appear as though the drug particles were embedded in the waxy polyethylene glycol 6000 matrix. The surface morphology of SDs almost resembled that of pure PEG 6000, indicating that ibuprofen was adsorbed into the PEG 6000 and homogeneously dispersed into the polymer. 1:2 w/w (D) and 1:10 w/w (F) physical mixtures appeared to contain individual ibuprofen and PEG6000 particles. The microscopic pictures suggested that the individual surface properties of PEG 6000 and ibuprofen were lost during melting and solidification indicating the formation of effective SD systems.

From the preliminary studies on the solid dispersions, the percentage yield and percentage drug contents of the solid dispersions were found to be almost 100%. The percentage yields of the solid dispersions (SD1, SD2, SD3, SD4, SD5 and SD6) were 98.66%, 95.58%, 99.00%, 99.19%, 99.40% and 98.73% respectively while the percentage drug contents were 98.91%, 99.10%, 98.60%, 98.50%, 99.20% and 99.60% respectively. These high yields and drug contents indicate that the fusion method is an efficient method for the preparation of solid dispersions.

From the solubility analysis, the saturation solubility of ibuprofen was found to be 47.77µg/mL. Solubility and dissolution of ibuprofen increased with the increment in the ratio of PEG6000 in the solid dispersions, this trend was also seen with the physical mixtures. However, the physical mixtures showed lower solubility and dissolution rate compared to the solid dispersions. Solubility was increased between 5 to 7 folds in the physical mixtures and up to 8 to 12 folds in the solid dispersion. From the dissolution analysis of ibuprofen, 1:2 w/w; 1:8 w/w; 1:10 w/w solid dispersions and 1:10 w/w physical mixture, it was found that the amount of ibuprofen released increased with increasing ratio of the polymer in the solid dispersions and also in the physical mixture but not as much as the solid dispersion. The test was carried out for

60 minutes and the cumulative percentage of drug released after 60 minutes were 35.321 %, 52.926 %, 78.527 %, 87.388 % and 69.662 % in ibuprofen, 1:2 w/w solid dispersion, 1:8 w/w solid dispersion 1:10 w/w solid dispersion and 1:10 w/w physical mixture respectively. Enhanced solubility and dissolution of ibuprofen from physical mixtures could be related to the surface activity, wetting effect and solubilizing effect of PEG6000 that may lead to reduced agglomeration and hence increased surface area.^{20,21,22,23,24,25,26,27}

Ibuprofen and PEG 6000 are completely miscible in the liquid phase, this indicates polymer–drug interaction at elevated temperatures and the ibuprofen can act as a hydrogen bond acceptor or donor. For the fact that ibuprofen-PEG 6000 SD systems were completely miscible in the liquid state and immiscible in the solid state indicates that they might have crystallized out simultaneously as microfine crystals from the molten mixture. This effect leads to increased ibuprofen surface area that possibly played an important role for enhanced dissolution rate^{28,29}.

Moreover, the enhancement of dissolution from the solid dispersions may be attributed partly to the reduction in particle size in ibuprofen crystalline due to the formation of eutectic system with PEG6000. The similarity in the dissolution profiles of 1:1 to 1: 10 w/w SDs could indicate that along with eutectic formation, a combination of other factors such as surface activity, wetting, and solubilization effect of PEG 6000 might have affected ibuprofen solubilization and dissolution.

From the statistical analysis, solubility and dissolution rate test result of ibuprofen was compared to that of the formulations with $p < 0.05$ and $n=2$ using ANOVA. The values obtained were significantly below 0.05 which indicates that the results are statistically significant.

In FTIR analysis, the spectrum of pure ibuprofen showed an intense, well-defined infrared band at around 1720.32 cm^{-1} (carbonyl-stretching of isopropionic acid group), another peak at 2955.15 cm^{-1} which indicates the presence of O-H group of the carboxylic acid overlapping the sp^3 C-H stretch, and another peak at 1508.18 cm^{-1} which indicates the arene group of the aromatic ring. The PEG6000 showed a characteristic spectrum of C-H stretching of OC_2H_5 groups from 2888.65 cm^{-1} , a peak at 3455.51 cm^{-1} which indicates OH groups and C-O stretching from 1000 to 1200 cm^{-1} .

A decrease in intensities of the peaks with increasing amount of PEG6000 was observed in the FTIR spectra of the solid dispersions and the physical mixture, and also the spectra appears as though there was overlap between the spectra of ibuprofen and PEG 6000.

In the spectra of SD1, there was disappearance of some minor peaks while some broadened and the major peaks remained intact but with lower intensities. Also, there was appearance of two new peaks at 2885.49 cm⁻¹ and 3455.41 cm⁻¹ which corresponds to the C–H stretching of OC₂H₅ groups and O–H groups of PEG 6000 respectively.

In the spectra of SD6, there was disappearance of some minor peaks while some broadened and the major peaks remained intact but with lower intensities. SD6 showed IR spectra almost similar to that of its corresponding physical mixtures. Presence of the stretching vibration of ibuprofen carbonyl peak in SDs and physical mixture 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. This observation fits well with the previous studies in which ibuprofen was found to be primarily crystalline.^{7,20} However, we could not carried out in-vivo bioavailability study in order to correlate the formulated ibuprofen SD with the in vitro drug release.

CONCLUSION

The rate limiting step for BC class II drugs absorption is govern by solubility and dissolution. The utilization of PEG 6000 as a solubility enhancing agent in the formulation of Ibuprofen SD proved to be more efficient in improving the solubility and the dissolution profile of Ibuprofen by several folds. The solubility of the SD and physical mixture of Ibuprofen and PEG 6000 increased by 12 and 7 folds respectively. Finally, the absence of major shift in the peak positions, retention of drug peak, and the almost equivalent addition spectra (of ibuprofen and PEG 6000) for SDs and physical mixtures suggested the absence of interactions in the solid state between PEG 6000 and the ibuprofen.

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APPENDICES

Table for percentage yield of the various batches of solid dispersion

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

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

Concentration ($\mu\text{g/mL}$)	Absorbance $\pm$ SD
2	0.433 $\pm$ 0.12
4	0.342 $\pm$ 0.10
6	0.269 $\pm$ 0.11
8	0.178 $\pm$ 0.05
10	0.104 $\pm$ 0.01

Table for percentage drug content

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

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

Concentration ($\mu\text{g/mL}$)	Mean Absorbance $\pm$ SD
20	0.0325 $\pm$ 0.0007
40	0.0900 $\pm$ 0.0070
60	0.1005 $\pm$ 0.0035
80	0.1345 $\pm$ 0.0049
100	0.1680 $\pm$ 0.0028
120	0.2075 $\pm$ 0.0035
140	0.2570 $\pm$ 0.0028
160	0.2805 $\pm$ 0.0049

Formulation and Characterization of Ibuprofen Solid Dispersion

Table for the solubility of ibuprofen and the various formulations

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

Table for dissolution profile of ibuprofen and the formulations

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