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Development and Characterization of Ibuprofen Solid Dispersion for Solubility and Dissolution improvement using a binary carrier system consisting of D- Mannitol - Polyethylene Glycol 6000

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ABSTRACT

Background: Adequate drug bioavailability is a major problem in most solid dosage formulations. Recent works reported enhanced solubility and dissolution using a carrier. This study was carried out to enhance the solubility and dissolution of ibuprofen using a binary carrier system.

Method: Solid dispersions (SD) of ibuprofen were prepared using PEG 6000 and D (-) mannitol in different ratios (1:0:4, 1:1:3, 1:2:2, 1:3:1, and 1:4:0) by the fusion method. **Results:** Percentage yield of SD was between 96% and 99% and content analysis revealed 100 % drug content. All batches of SD showed better solubility characteristics than Ibuprofen alone or its physical mixtures. The SD batch 3, ratio 1:2:2 with equal amount of PEG and mannitol possessed the best solubility characteristic and drug release profile with $T_{50\%}$ at 17 min. FTIR spectral and DSC thermograms of SDs showed no interaction between the carriers and ciprofloxacin.

Conclusion: The SD3 formulated with 20 % ibuprofen, 40 % mannitol and 40 % PEG 6000 possessed better solubility and dissolution is therefore recommended.

1. Introduction

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) derived from propionic acid. It is a phenyl propionic acid derivative considered the first of the propionics and is used as first line non-steroidal anti-inflammatory, analgesic, and antipyretic agent. It is widely used to treat mild to moderate pain and fever. The main mechanism of action involves the inhibition of prostaglandin synthesis by the non-selective reversible inhibition of the cyclooxygenase enzymes (COX-1 and COX-2). It is poorly aqueous soluble and its oral absorption is dissolution rate limited, which leads to a potential bio-ineqivalence problem[1]. The chemical name is (2RS)-1-[4-(2-Methylpropyl) phenyl] propanoic acid. It is slightly soluble (21 mg/L at 25°C) in water, very soluble in alcohol and most organic solvents.

Enhancement of solubility, therefore, can be appreciated as a very important modality of improving bioavailability of drugs and is an important parameter to be considered in the

formulation development of orally administered drugs with poor aqueous solubility.

Various approaches have been used to improve drug solubility as well as drug dissolution of poorly aqueous soluble drugs and they include micronization, formation of inclusion complexes with cyclodextrins, formation of amorphous drugs, and formation of solid dispersions of drugs using various hydrophilic carriers[2]. Among them, the solid dispersion technique has attracted significant interest as an effective method of improving the dissolution rate as well as the bioavailability of a wide range of poorly aqueous soluble drugs[3,4,5]. Rapid drug dissolution from solid dispersions has been observed due to increased wettability and dispersibility of drug particles, existence of the drug in amorphous form with improved solubility, and absence of aggregation of drug particles using various hydrophilic carriers[6,7,8].

Nadia and his team[9] studied the dissolution profile of ibuprofen solid dispersion prepared with HPMC, HPC, icing sugar, dextrose, mannitol and lactose using the fusion method. The result obtained showed that the rate of dissolution of ibuprofen was considerably improved with HPMC and HPC while dispersions with icing sugar, dextrose, mannitol and lactose showed drug dissolution retardation capability.

Hasnain and Nayak[10] studied the saturated solubility and in vitro dissolution of ibuprofen solid dispersion using PEG 600- PVPK 30 combination carrier by solvent evaporation technique. They attributed the improvement in solubility as well as drug dissolution of ibuprofen solid dispersion using PEG 6000-PVPK 30 to improved wettability, and reduction in drug crystallinity which can be modulated by appropriate level of hydrophilic carriers.

Ofokansi research group[11] evaluated trandolapril solid dispersions based on Eudragit RS 100 and PEG 8000. The in vitro release studies revealed that there was marked increase in the dissolution rate of trandolapril from the solid dispersion when compared to pure drug.

Polyethylene glycol 6000 (PEG) is a polyether compound with many applications from industrial manufacturing to medicine. It is a white or almost white, waxy or paraffin-like, highly soluble in water and used as an inactive ingredient in the pharmaceutical industry as a solvent, plasticizer, surfactant, ointments and suppository base, and tablet and capsule lubricant.

D (-) Mannitol is also known as mannite or manna sugar and is a white, crystalline solid that looks and tastes like sucrose. Its high solubility in water and safety as an excipient makes it an eligible candidate as a polymer for formulation of solid dispersion with a poorly soluble drug like ibuprofen.

2. Material and Methods

2.1 Material

Ibuprofen powder (Burgoynes and Burbidges, India), Polyethylene glycol 6000 (from Loba Chemie Pvt. Ltd, Mumbai, India), D-Mannitol (Oxford Laboratory, Mumbai, India). Ethanol, potassium dihydrogen phosphate, sodium hydrogen phosphate, sodium chloride, potassium chloride, hydrochloric acid, sodium hydroxide and distilled water utilized were all of analytical grade.

2.2 Method

2.2.1 Preparation of Solid Dispersion by melting or fusion method

The melting or fusion method was employed[12]. Physical measures 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 in an oil bath 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: Preparation of Ibuprofen Solid Dispersion

Batch	Drug (mg)	PEG 6000 (mg)	Mannitol (mg)	Ratio
S.D. 1	200	0	800	1:0:4
S.D. 2	200	200	600	1:1:3
S.D. 3	200	400	400	1:2:2
S.D. 4	200	600	400	1:3:2
S.D. 5	200	800	0	1:4:0

2.2.2 Preparation of Physical Mixtures containing Ibuprofen, PEG 6000 and Mannitol

The physical mixtures were prepared by mixing the required amount of the drug, PEG 6000 and mannitol together in a mortar using a pestle. Physical mixtures of different ratios were prepared as detailed in the table below.

Table 2: Preparation of Ibuprofen-PEG 6000 Physical Mixtures

Batch	Drug (mg)	PEG 6000 (mg)	Mannitol (mg)	Ratio
P.M. 1	200	0	800	1:0:4
P.M. 2	200	400	400	1:2:2
P.M. 3	200	800	0	1:4:0

2.3 Characterization of Solid Dispersion

2.3.1 Particle Morphology

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

2.4 Determination of Percent Yield

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

$$\text{Percent yield} = \frac{Weightofpreparedsoliddispersion}{Weightofderug + carriers} \times 100$$

2.5 Determination of percent drug content

A calibration curve was constructed by preparing different solutions of known concentrations of ibuprofen in ethanol. A quantity of each solid dispersion equivalent to 20mg of pure ibuprofen was then dissolved in 100 mL ethanol, filtered and diluted to a suitable concentration and UV absorbance measured using a UV spectrometer (GS-UV61PC, Double Beam Spectrophotometer) at 220nm [13]. The calibration curve previously constructed was then used to derive the concentration and the percentage drug content derived using the following formula:

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

2.6 Saturation solubility determination

A calibration curve of ibuprofen in Phosphate buffer (0.1 M) of pH 7.2 at 265nm wavelength was constructed. Ibuprofen, physical mixtures, or SDs equivalent to 100mg of ibuprofen were added to 10 mL phosphate buffer pH 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 UV-Visible Spectrophotometer (General Scientific, USA) at 265nm.

2.7 Drug-polymer interaction (FT-IR) study

IR spectroscopy was performed by Fourier Transform Infrared spectrophotometer. The samples (ibuprofen, PEG 6000 and mannitol, as well as physical mixtures and solid dispersions) were analysed with FT-IR to evaluate the drug-polymer interaction.

2.8 Differential thermal analysis

Differential Thermal Analysis was carried out on the samples (Ibuprofen, and solid dispersions**)** to obtain thermograms indicating the effect of heating on the samples.

2.9 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 $p < 0.05$.

3. RESULTS

3.1 Particle Morphology give results on morphology

The inclusion of other molecules to ibuprofen, caused changes in particulate nature of the granules as shown in the morphological studies carried out on individual compounds versus solid dispersions and physical mixtures (Figure 1 A-F).

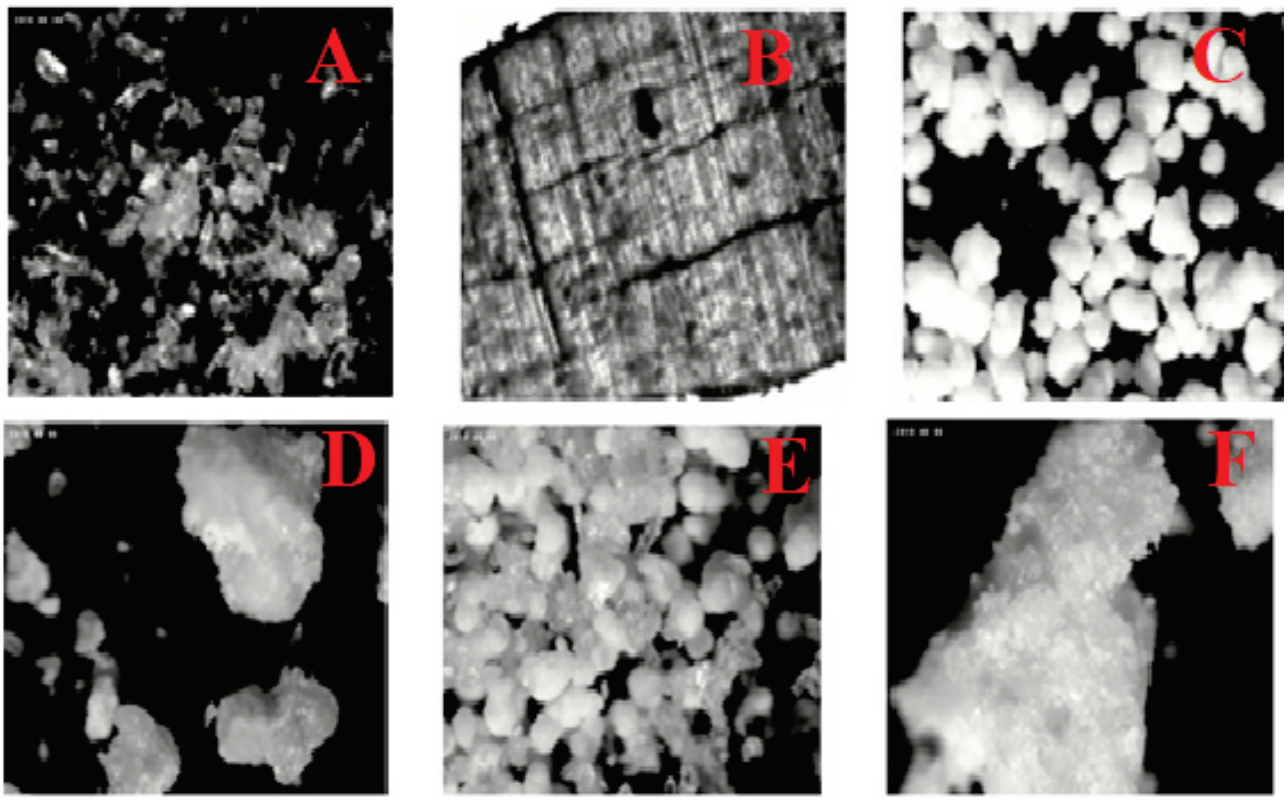

Figure 1: Microscopic Images of Samples.

(A) Pure Ibuprofen, (B) PEG 6000, (C) Mannitol, (D) 1:2:2 w/w solid dispersion, (E) 1:2:2 w/w physical mixture, (F) 1:4:0 w/w solid dispersion.

3.2 Percentage Yield

Figure 2: Percentage yield of different batches of Solid Dispersion

3.3 Percentage Drug Content

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

The equation obtained was used to calculate the drug content in the amount of each preparation that is equivalent to 20mg of ibuprofen powder. The percentage drug content was calculated and was found to be almost 100% for each preparation, ranging between 98% and 99%.

3.4 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 5. The curve was found to be linear within the range of 20-160µg/mL.

3.5 In-Vitro Drug Dissolution Rate Test

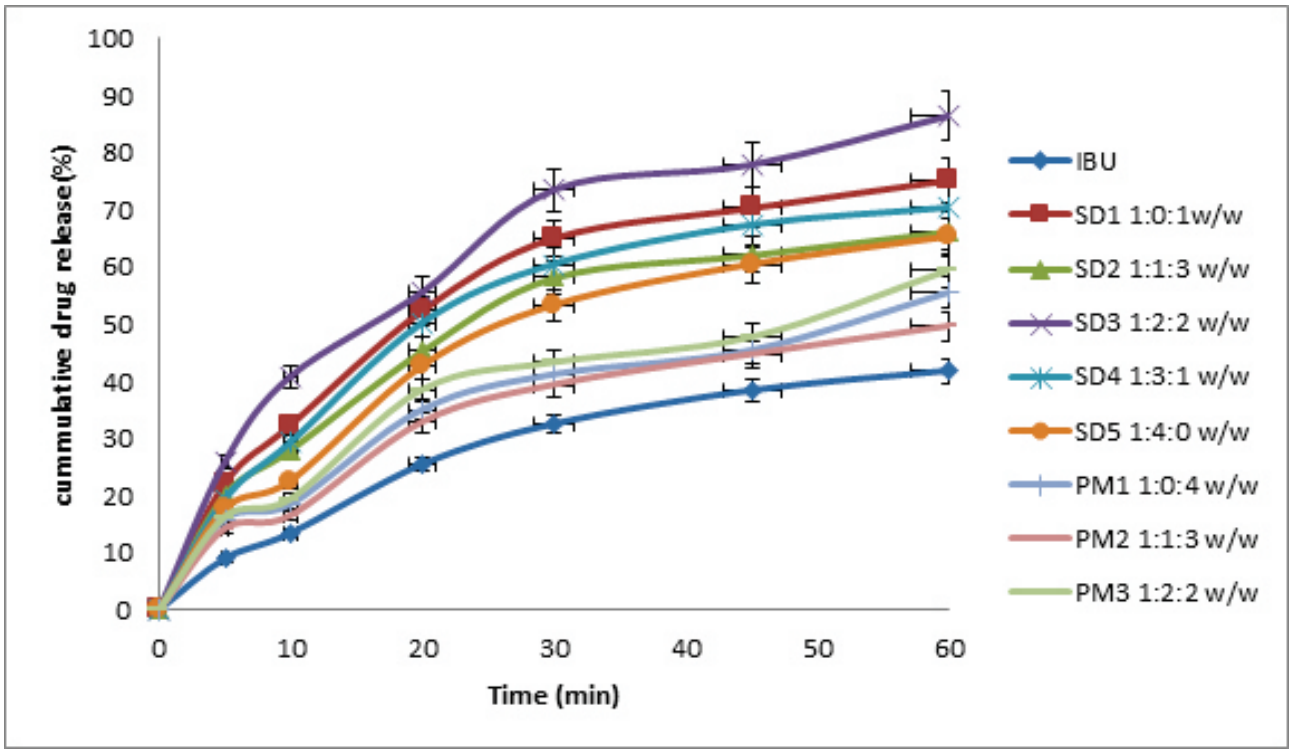

Figure 2: Dissolution profiles of solid dispersions of Ibuprofen in phosphate buffer (pH7.2± 0.5) (PM Physical Mixture, SM Solvent Evaporation, FM Fusion Method)

The $T_{50\%}$ is the time taken for 50 % of the drug to be released. The values obtained from figure 4 for SD1-5 and PM1-3 are in the following order: SD3 (1:2:2 w/w) 17 min.; SD1 (1:0:1 w/w) 20 min.; SD4 (1:3:1 w/w) 22 min.; SD2 (1:1:3 w/w) 24 min.; SD5 (1:4:0 w/w) 28 min.; PM3 (1:2:2 w/w) 52 min.; PM1 (1:0:4 w/w) 56 min.; and PM2 (1:1:3 w/w) >60 min.; IBU >> 60 min

3.6 Dug-Polymer Interaction Study using FTIR

The FT-IR spectra of ibuprofen solid dispersions showed no significant shift and no disappearance of characteristic peaks, suggesting that there is no interaction between the drug and polymers hence, there is no degradation in the drug molecule (Figure 3).

The thermal analysis was studied by Differential Thermal Analysis (DTA), thermograms of pure ibuprofen, SD1, to SD5 were obtained. The melting point of Ibuprofen corresponded with that described in literature. Formulations containing mannitol had a melting point lowering effect on the product (Figure 4).

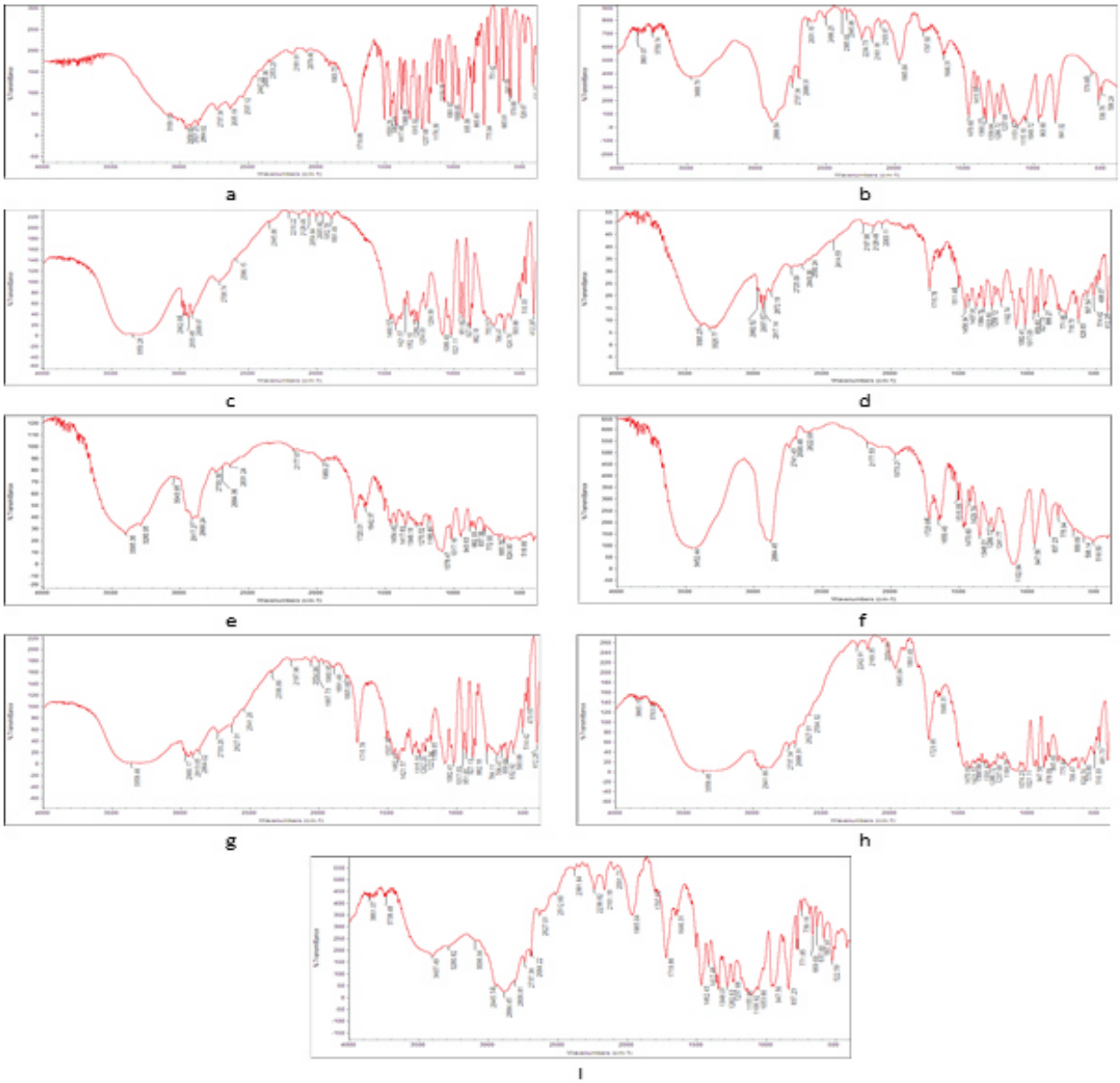

Figure 3: FT-IR spectra of pure Ibuprofen powder (a), polyethylene glycol 6000 (PEG 600) (b), D(-) Mannitol (c), SD1 (1:0:4) (d), SD3 (1:2:2) (e), SD5 (1:4:0) (f), PM1 (1:0:4) (g), PM2 (1:2:2) (h), PM3 (1:4:0) (i).

3.7 Differential Thermal Analysis

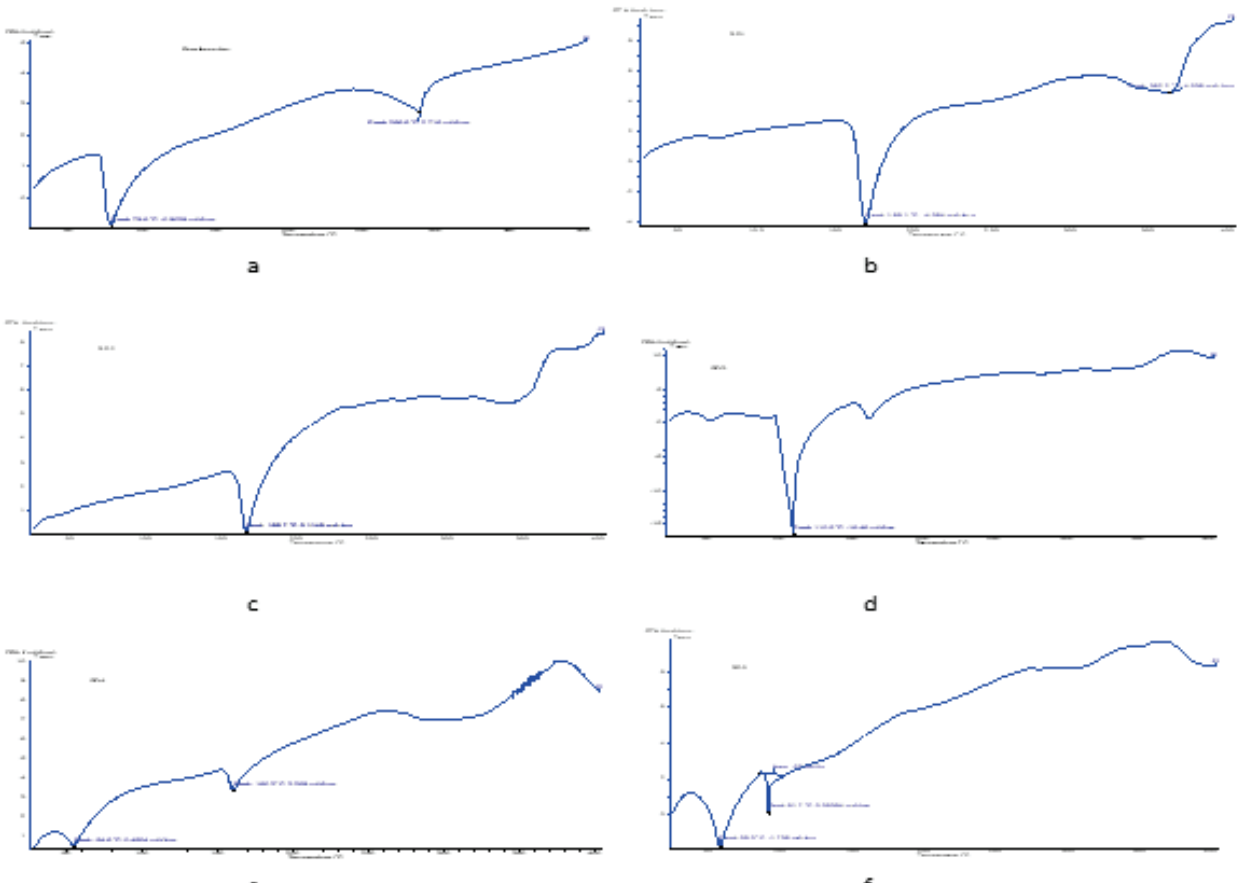

Figure 4: Thermogram of pure ibuprofen (a), SD1(b), SD2 (c), SD3(d), SD4(e), SD5(f)

3.8 Statistical Analysis

The data obtained from the saturation solubility was subjected to ANOVA test with $p<0.05$ and $n = 2$. All values obtained were significantly below 0.05. The value was between 0.000016 and 0.00047 for the saturation solubility test.

4. Discussion

In this study, solid dispersions of ibuprofen were formulated by the fusion method. The method was found to be efficient and produced a high yield in terms of product yield as well as content. The percentage yield obtained was 96.6±1.2 %, 97.4± 2.1%, 98.7± 1.1 %, 98.1± 2.0 % and 99.3±0.5 % for SD1 to SD5 respectively while the percentage content obtained was 99.4±0.5 %, 99.0± 0.4 %, 98.5± 1.2 %, 98.9±1.0 % and 99.6±0.2% for SD1 to SD5 respectively.

Surface morphology studies showed pure ibuprofen to be crystalline, PEG 6000 to be smooth-surfaced with fibre-like features indicating a flaky or waxy texture, and mannitol to be a somewhat crystalline powder with a smooth surface. In the image of SD3 (1:2:2) obtained, the crystalline Ibuprofen appeared smooth and seemed to be embedded in the matrix of mannitol and polyethylene glycol. This matrix was also observed in SD5 (1:4:0) where crystals of Ibuprofen could be faintly seen through what appeared to be a wax-like covering. The image of the physical mixture, PM2 (1:2:2), obtained showed some degree of dispersion of the crystalline drug in the polymers, although some crystals could still be seen separated from the polymers. These findings indicate that the method used (fusion method) led to the formation of linkages between the drug and the carrier, allowing the drug to be embedded in an effective matrix system of the soluble carrier. This implies that the dispersion will enable the poorly soluble drug to be "delivered" by the hydrophilic carriers effectively, such that the solubility of the drug will be improved.

Upon saturation solubility analysis, the saturation solubility of ibuprofen in 0.1M phosphate buffer (pH 7.2) was found to be 59.13µg/mL. The solubility was found to

be increased in the physical mixtures as well as the solid dispersions, but the solid dispersions showed a far higher increase than the physical mixtures. The solid dispersions had increased solubility up to 9 times more than pure ibuprofen while the physical mixtures had about a 4-fold increase. The solid dispersion containing equal proportions of PEG 6000 and mannitol (SD3) had the greatest saturation solubility at 540.6µg/mL indicating synergistic increase in solubility. This result shows that drug bioavailability could be achieved with SD3 than SD1 (mannitol alone as carrier), and SD5 (PEG 6000 alone as carrier). This result shows improvement over the earlier research conducted by Shittus *et al* in which PEG 6000 alone was employed as hydrophilic carrier in SD of ibuprofen.

Statistical analysis of saturation solubility values (n=2) was carried out using ANOVA with $p<0.05$ being the pass grade. The value obtained was significantly below 0.05 which indicates that the results are statistically significant.

Vibrating bonds in functional groups absorb energy at a frequency that corresponds to the vibrational frequency of the bond. As a result, the vibrational spectrum of a molecule is a unique physical property of that molecule. Pure ibuprofen showed characteristic peaks at 3109.19 cm^{-1} indicating C-H stretching in aromatic ring, 2864.02 cm^{-1} to 2958.00 cm^{-1} indicating C-H stretching in alkanes and a sharp stretch at 1719.86 cm^{-1} indicating C=O band in carboxylic acid (COOH) group present in ibuprofen. The carbonyl group in ibuprofen confers a degree of hydrophilicity on ibuprofen, but the non-polar alkyl and benzene groups decrease its polarity significantly. However, the preparation of ibuprofen solid dispersions with hydrophilic carriers confers more polar groups to the ibuprofen molecule making it more soluble. Mannitol showed characteristic broad band at 3350.28 cm^{-1} with strong intensity indicating the presence of O-H stretch and peaks at 2908.97 cm^{-1} to 2962.09 cm^{-1} indicating a saturated C-H stretch. PEG 6000 showed characteristic peaks at 3468.79 cm^{-1} indicating the presence of O-H with a narrower band than seen in mannitol and 2888.54 cm^{-1} indicating C-H symmetrical stretching[15]. FT-IR spectrum of SD1 (1:0:4) showed slight reduction in intensity of the carbonyl peak (1715.78 cm^{-1}) compared to pure ibuprofen (1719.86 cm^{-1}) and the O-H band of mannitol was observed at 3395.23 to 3325.77 cm^{-1}. In SD3 (1:2:2), the carbonyl peak was also observed to have a lower intensity at a wavelength of 1720.01 cm^{-1}, but the characteristic O-H stretch of mannitol is still seen at 3395.36 to 3280.95 cm^{-1} with a narrower dip (higher intensity) than in either PEG 6000 or mannitol alone. SD5 (1:4:0) was observed to have a smooth O-H dip resembling that observed in PEG 6000 with a wave number also close to that of PEG 6000 (3452.44 cm^{-1} for SD5 and 3468.79 cm^{-1} for PEG 6000). The characteristic carbonyl peak was also observed at 1723.95 cm^{-1} also with a lower intensity than that observed in pure ibuprofen. In all solid dispersions, other characteristic peaks such as peaks for the saturated C-H stretch in mannitol and ibuprofen as well as the aromatic C-H stretch in ibuprofen and symmetrical stretching in PEG 6000 were also observed indicating the presence of all constituent compounds as expected. The FT-IR spectra obtained for physical mixtures were similar to that of the solid dispersions. PM1 (1:0:4) had almost a completely identical spectrum as SD1, save for the increased intensity in O-H peak in SD1. PM2 (1:2:2) also had a very similar spectrum to SD3, the major difference also being the slightly more intense O-H peak of SD3. PM3 (1:4:0) was also like SD5 but had the lowest wave number for the O-H stretch (3407.49 cm^{-1}). The presence of the carbonyl group in all solid dispersions and physical mixtures indicates the presence of ibuprofen in all samples. In the samples (solid dispersions as well as physical mixtures), the inclusion of other molecules to ibuprofen lead to changes in particulate nature of the granules as confirmed by the morphological studies carried out on individual compounds versus solid dispersions and physical mixtures. In summary, the FT-IR spectra of ibuprofen solid dispersions showed no significant shift and no disappearance of characteristic peaks found in pure ibuprofen, suggesting that there is no interaction between the drug and polymers which may lead to degradation in the drug molecule. The absence of generation of new peak in any of the solid dispersions confirms absence of strong chemical interaction[16].

On thermal analysis by Differential Thermal Analysis (DTA), thermograms of pure ibuprofen, SD1, SD2, SD3, SD4, and SD5 were obtained. The melting point of Ibuprofen corresponded with that described in literature. Taking cue from melting point described for PEG 6000 (55-62°C) and mannitol (166-168°C), it was observed that formulations containing mannitol and either or both of the two other compounds (with lower melting point) had a melting point lowering effect on the product.

The analysis of drug release profile (figure 10), shows that SD3 (1:2:2 w/w) with equal ratio of mannitol and PEG 6000

released 50 % of ibuprofen in 17 min ($T_{50\ \%}$). Specifically, ideal ratio for SD3 (1:2:2 w/w) used is ibuprofen: mannitol: PEG 6000 (20 %: 40 %: 40 %). This batch is recommended for application in the formulation of solid dispersion of ibuprofen using composite carriers to improve its bioavailability.

5. Conclusion

In this investigation, the hot melt approach was used for the preparation of Ibuprofen solid dispersions. The solubility and the dissolution rate of the drug were significantly increased in all of the solid dispersion prepared with PEG and mannitol. The corresponding physical mixture samples had lower dissolution rates than the solid dispersion systems. The best result was obtained from solid dispersions SD3, (ratio 1:2:2) containing equal amount of PEG and mannitol. It also possessed the best solubility characteristic and drug release profile with T50% at 17 min. This result must be as due to a greater wettability of the drug by the hydrophilic carrier, as well as an increase in surface area [17]. Hence, the solid dispersion method, using SD3 containing 20 % ibuprofen, 40 % mannitol and 40 % PEG 6000 could be considered as an appropriate technique for dissolution enhancement of Ibuprofen.

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