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DISSOLUTION OF IBUPROFEN FROM SPRAY DRIED AND SPRAY CHILLED PARTICLES

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ABSTRACT

The formulation of hydrophobic drugs for oral drug delivery is challenging due to poor solubility, poor dissolution and poor wetting of these drugs. Consequently, the aim of this study was to improve the dissolution of a model poorly water soluble drug, ibuprofen. Microparticles containing ibuprofen were produced by spray drying and spray chilling technology in the absence/presence of a hydrophilic surfactant. Poloxamer 127, tri-block copolymer, was chosen as the hydrophilic surfactant to improve drug particle wettability and hence the dissolution rate. The prepared formulations were evaluated for in vitro dissolution and intrinsic solubility. In addition, the produced drug particles were characterised by scanning electron microscopy (SEM), differential scanning calorimeter (DSC) and Fourier transform infrared spectroscopy (FT-IR). SEM revealed changes in the surface morphology of processed ibuprofen, suggesting the effective formation of the drug particles. DSC data showed shifting of the melting peak of the drug towards lower melting temperature in the prepared particles, indicating the possibility of drug /polymer interaction. The results of the dissolution studies of spray dried ibuprofen and spray dried ibuprofen/Poloxamer 127 particles showed significantly ($P < 0.05$) increased percentage drug release compared to control (ibuprofen raw material). For spray chilling, the prepared particles did not improve the dissolution of the drug, the dissolution was even less than that of the control. DSC and FT-IR results demonstrated that spray drying reduced drug crystallinity, but for spray chilled particles there was evidence of polymorphic changes in the drug with and without the surfactant. Consequently, it is believed that spray drying of ibuprofen is a useful tool to improve wettability, solubility and hence the dissolution behaviour of poorly water soluble drugs, in contrast to spray chilling technique.

Keywords: Spray drying, spray chilling, ibuprofen, poloxamer 127, poorly water soluble drugs.

INTRODUCTION

The oral route remains the preferred route of drug administration due to its convenience, good patient compliance and low medicine production costs. In order for a drug to be absorbed into the systemic circulation following oral administration, the drug must be dissolved in the gastric fluids. For hydrophobic drugs, it is the dissolution process which acts as the rate-controlling step and, therefore, determines the rate and degree of absorption. Consequently, many hydrophobic drugs show erratic and incomplete absorption from the gastrointestinal tract of animals and humans, which may lead to therapeutic failure. Thus, one of the major challenges to drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water (Naseem *et al.*, 2004). As a result, much research has been conducted into methods of improving drug solubility and dissolution rates to increase the oral bioavailability of hydrophobic drugs.

Various techniques such as melt adsorption, supercritical fluid processes, and many polymeric carriers such as polyvinyl pyrrolidone (PVP) and polyethylene glycol

(PEG) and silica carrier have been attempted to load poorly water soluble drugs in nano- or micro-crystals and amorphous state to improve their dissolution (Chowdary and Hymavathi, 2001; Kinoshita *et al.*, 2002 and Vasconcelos *et al.*, 2007). Manipulation of the solid state by decreasing crystallinity of drug substances through formation of solid dispersion is one of the methods used for promoting drug dissolution (Kapsi and Ayres, 2001 and Leuner and Dressman, 2000). The solid dispersion technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly water soluble active pharmaceutical ingredients because it is simple, economic, and advantageous technique. The concept of solid dispersion covers a wide range of systems. The enhancement in the dissolution rate is obtained by one or a combination of the following mechanisms: eutectic formation, increased surface area of the drug due to precipitation in the carrier, formation of true solid solution, improved wettability (due to close contact with a hydrophilic carrier), drug precipitation as a metastable crystalline form or a decrease in substance crystallinity (Craig, 2002). The type of solid dispersion formed depends on both the carrier-drug combination and the method of manufacture (Craig, 2002 and – Serajuddin, 1999).

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Microwaves irradiation was used recently (Moneghini *et al.*, 2008) for the preparation of solvent-free solid dispersions and for enhancement of release of the poorly soluble drug, ibuprofen, with polyvinyl pyrrolidone/polyvinyl alcohol and hydroxypropyl- β -cyclodextrin as hydrophilic carriers. However, the resulting products need to be pulverised using for example mills.

Spray drying is one such technique of preparing solid dispersion and is widely used as an alternative to milling to reduce particle size. It has the advantage of being capable of designing the features, such as improved particle wetting by adding small amount of surfactants. Li *et al.* (2008) reported that spray drying of ibuprofen in the presence of gelatin and sodium lauryl sulphate improved the initial dissolution rate of the drug in simulated gastric fluid.

Spray chilling or spray congealing is another form of solid dispersion where the melted mass is atomized into droplets, which quickly solidify in a cool air (Killeen, 1993). The advantage in spray chilling is that no additional manufacturing step is needed to pulverise the solid dispersion. In pharmacy, spray chilling has been used to prepare sustained-release formulations, to improve stability (Schwendeman *et al.*, 1998) and to mask the unpleasant taste (Yajima *et al.*, 1999). The technique also has the advantages of being free from organic solvents compared to spray drying. The method has also been used by the food industry, for example, to encapsulate vitamins and minerals (Gibbs *et al.*, 1999).

Ibuprofen was chosen as a model hydrophobic drug. Ibuprofen (α -methyl-4-(2-methylpropyl)-benzene acetic acid) is one of the safest and most potent non-steroidal anti-inflammatory drugs being widely used in the market for 30 years. The drug used to treat rheumatoid arthritis, osteoarthritis, and mild to moderate pain. It has low aqueous solubility and hence poor dissolution.

The present work was conducted to improve the dissolution of ibuprofen using spray drying and spray chilling techniques. Poloxamer 127 (which is non-ionic amphiphilic surfactant and tri-block copolymer of polyoxyethylene-polyoxypropylene-polyoxyethylene) was used in some formulations in an attempt to increase drug wettability, solubility and hence drug dissolution.

MATERIALS AND METHODS

Materials

Ibuprofen and Poloxamer 127 (PluronicTM F-127) were purchased from Sigma-Aldrich Company Ltd, UK. All other chemicals were of analytical grade and used without further purification.

Preparation of microparticles

Microparticles prepared by spray drying

Spray dried particles consisted of ibuprofen only and ibuprofen/Poloxamer 127 (1:1 (w/w) ratio) were prepared by dissolving the drug or drug/polymer mixture in ethanol/water (40:60 (v/v) ratio) solution. The solution was spray dried using Mini Spray Dryer B-290- (Buchi, Switzerland) at a pump rate of 35%, an air flow rate of 600 L/h, aspirator level at 100%, inlet temperature at 97 \pm 2°C and outlet temperature at 38 \pm 1°C. The formed microparticles were separated using cyclone separator, collected and stored in a desiccator at ambient temperature until ready to be used.

Microparticles prepared by spray chilling

Spray chilled particles were prepared by melting the drug or drug/Poloxamer 127 mixture (1:1 (w/w) ratio) at 90°C. The melt was kept at 90°C and atomised with a specially constructed pneumatic nozzle (Mini Spray Dryer B-290, Buchi, Switzerland) into air kept at 20°C. The inner diameter of the pneumatic nozzle was 0.1mm, the capillary length was 5mm and the pressure was 2 bar. The particles were collected using cyclone separator and stored in a desiccator.

Evaluation of microparticles

Determination of percent yields and drug contents

The percentage yield of each formulation was determined according to the total recoverable final weight of microparticles (prepared by spray drying and spray chilling) and the total original weight of ibuprofen and ibuprofen/Poloxamer 127 mixture.

Drug contents for the prepared microparticles were calculated by dissolving an exact amount of microparticles in 5 mL of ethanol and analysed spectrophotometrically at 272 nm on a UV/Vis spectrophotometer (Campsec- M501 Single Beam Scanning, Savston, Cambridge, UK).

Scanning electron microscopy

Surface morphology of ibuprofen, ibuprofen/Poloxamer 127 spray dried and ibuprofen/Poloxamer 127 spray chilled particles were examined using a scanning electron microscope (Hitachi S3000N Electron Microscope, Hitachi, UK). Ibuprofen particles were fixed on an aluminium stub with a conductive double sided carbon tape and sputter-coated with gold/palladium. The coating was done by exposing the samples to an Argon atmosphere at about 10 Pascals at 20mA for 5 minutes.

In vitro dissolution studies

The dissolution studies were performed using United State Pharmacopoeia type II dissolution test apparatus (Erweka DT 6, Heusenstamm, Germany). Ibuprofen particles equivalent to 100 mg of drug were placed in the dissolution vessel containing 900 mL of water maintained

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at 37°C ±0.5°C and stirred at 100 rpm. Ibuprofen raw material was used as control. Filtered samples, using 0.45µm membrane filter, were collected periodically and replaced with a fresh dissolution medium. The concentration of ibuprofen released was determined spectrophotometrically at 272 nm on a UV/Vis spectrophotometer (Campsec-M501 Single Beam Scanning, Savston, Cambridge, UK).

The dissolution studies were conducted in triplicates for each formulation (spray dried or chilled ibuprofen particles with and without Poloxamer 127 and control). Student's t-test was used as a test for significance.

Fourier-transform Infrared spectroscopy (FT-IR)

Fourier-transform infrared (FT-IR) spectra of ibuprofen and ibuprofen/Poloxamer 127 particles (spray dried and spray chilled) were obtained using IR spectrophotometer (PerkinElmer FT-IR System, Spectrum BX, Perkin-Elmer, UK). The samples were scanned over the wave number range from 4000 to 550 cm⁻¹.

Differential scanning calorimetry (DSC)

The changes, if any, in the thermal characteristics of ibuprofen in the prepared formulations were studied by differential scanning calorimeter (DSC Q1000, TA instrument, England). Approximately 3-6 mg samples of ibuprofen, Poloxamer 127, and ibuprofen/Poloxamer 127 particles (prepared by spray drying and spray chilling technology) were hermetically sealed in aluminum pans and heated between 20 and 90°C with a heating rate of 5°C/min. The DSC instrument was calibrated with sapphire and indium before running the samples.

RESULTS AND DISCUSSION

Percentage yields and drug contents

For spray dried drug formulations, the collected powders were white and fairly free-flowing. The percentage yields from ibuprofen and ibuprofen/Poloxamer 127 were 35±0.25% and 50±1.3%, respectively. Such small yield for the drug alone consider to be acceptable for small scale, bench top spray drier as a result of inability of the cyclone separator to trap particles smaller than 2 µm and adherence of these particles to the inner wall of the spray drier (Maa *et al.*, 1998) and Maury *et al.*, 2005). The increased yield in the case of ibuprofen/Poloxamer 127 preparations may be attributed to the increase of the concentration of solids in the feed solution as Poloxamer 127 was included (2% of each ibuprofen and the surfactant). Drug content for the surfactant containing formulation was found to be 94.5±0.001%.

The percentage yields for spray chilled ibuprofen and ibuprofen/Poloxamer 127 particles were 70±2.1 and 82±2.83%, respectively. Such yields are higher compared to spray dried products. For spray chilled ibuprofen/Poloxamer 127 product, drug content was 92±0.01%.

Scanning electron microscopy

Scanning electron microscopy (SEM) was conducted to ibuprofen raw material and the prepared drug particles. SEM of pure ibuprofen appears as crystalline structure, almost rectangular shape (fig. 1a). For spray dried ibuprofen (fig. 1b) with and without the surfactant, SEM showed particles that are quite different from the starting material; these particles have irregular porous surface of uniform and homogeneous mass with some surface crusts. The porous surface may result from the rapid evaporation of the solvent during processing. The surface crust may be formed as a result of the superior movement of the surfactant to the liquid/gas interface during the drop formation due to surfactant amphiphilic properties. This explanation is in agreement with that by Wong *et al.* (2006) for spray dried griseofulvin.

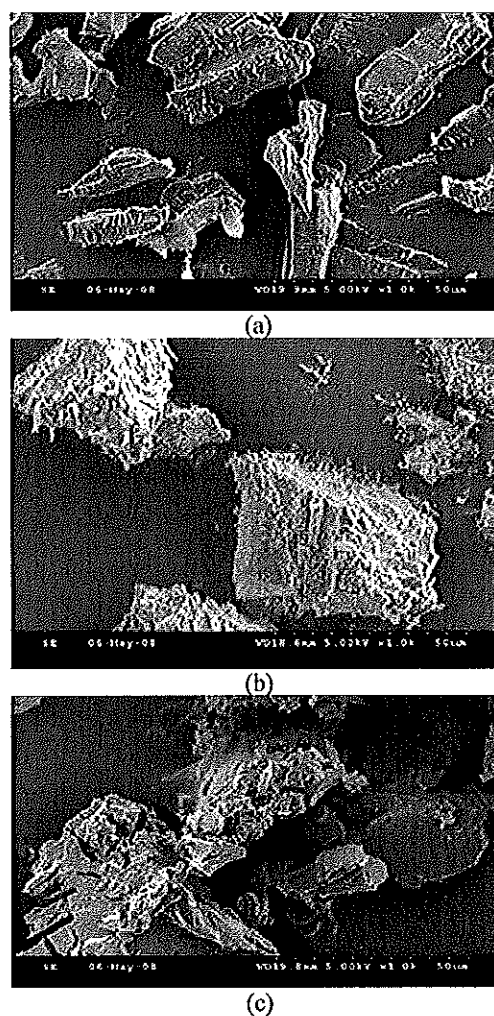


Fig. 1: Scanning electron microscopy of: (A) ibuprofen raw material, (B) spray dried ibuprofen/Poloxamer 127 (1:1) and (C) spray chilled ibuprofen/Poloxamer 127 (1:1).

For spray chilling, the produced particles were highly irregular small masses with rough edges and lack of sphericity (fig. 1c). The surface of the particles was nonporous and wrinkled.

In vitro dissolution

The dissolution profiles represented as percentage drug released versus time of spray dried particles, spray chilled particles and the control (raw drug material) are illustrated in fig. 2. The data revealed that spray dried ibuprofen and ibuprofen/Poloxamer 127 (1:1) particles improved the dissolution of the drug. Interestingly, for the two spray chilled formulations; the rate was lower than that for the control. For further clarifying of the dissolution profiles, the percentage drug dissolved from each formulation will be considered individually and compared to the control, as illustrated below.

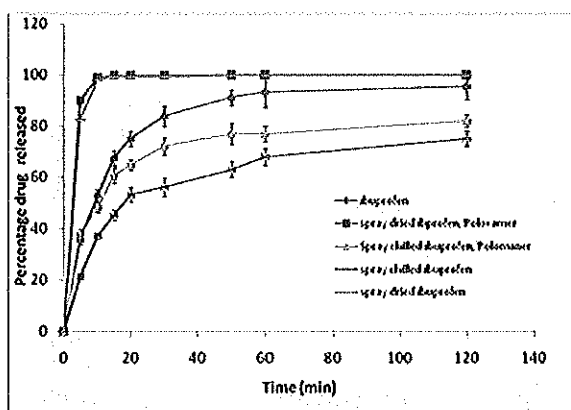


Fig. 2: Dissolution profile of ibuprofen formulations ($n = 3$). The error bars were omitted from spray dried particles with and without Poloxamer 127 for clarity.

Both spray dried formulations (ibuprofen with and without the surfactant) showed burst release, spray dried drug/ Poloxamer 127 particles was the fastest with about $90 \pm 0.26\%$ of the drug being dissolved within 5 minutes compared to $82 \pm 1.13\%$ for the spray dried drug particles. For the control, the percentage drug released was only $36 \pm 0.64\%$ after 5 minutes. The drug released using spray drying technology (fig. 2) was significantly higher ($P < 0.05$) compared to drug release from the raw material. In the meantime, the percentages of drug dissolved at 120 min for the two spray dried preparations were not significantly different ($P > 0.05$) from one another. This result may indicate that spray drying of ibuprofen only could be an effective tool to enhance dissolution of ibuprofen, and hence drug bioavailability. A study by Li *et al.* (2008) indicated that spray drying of ibuprofen with sodium lauryl sulphate, a surfactant, was a successful technique to enhance ibuprofen dissolution and bioavailability. However, the amount of ethanol used as a solvent was 70% i.e. this amount was higher than the

amount of ethanol (40%) employed in our study; accordingly, the effect of residual solvent will be minimised. Also, in the same study (Li *et al.*, 2008) the most effective ratio of the drug:sodium lauryl sulphate was 1:1.2 but in our study the ratio of the drug: Poloxamer 127 was 1:1w/w, meaning that Poloxamer 127 in a low concentration is more effective with ibuprofen compared to sodium lauryl sulphate.

Spray drying usually produces amorphous materials (Corrigan *et al.*, 2004). The amorphous solid state has the advantage of increased solubility and therefore faster dissolution rate compared to crystalline material, and this may explain such improvement in ibuprofen dissolution; this will be confirmed later by DSC data. Poloxamer, as a surfactant, usually improve the wetting ability of the particles. Wetting prevents aggregation of particles when exposed to the aqueous medium. Subsequently, this allows the particles to present a larger surface area available for dissolution. This could clarify the higher initial percentage drug release of spray dried product in the presence of Poloxamer 127, after which there was no difference between ibuprofen spray dried formulations (with and without the surfactant).

Poloxamer 188 and polyethylene glycol 20000 were used as hydrophilic carriers in solid dispersion systems to improve the dissolution of ibuprofen (Newa *et al.*, 2007; Newa *et al.*, 2008). The authors prepared ibuprofen solid dispersion systems using low-temperature melting method in which hot water (at about 95°C) was circulating around mixtures of the drug and the carrier to produce molten products and then the hot water was replaced by cold water to solidify the produced solid dispersion systems which were subsequently grounded using pestles and mortars. Newa and co-authors claimed that the low-temperature melting technique is an appropriate technique to improve ibuprofen dissolution by reducing drug crystallinity and eutectic formations as shown in their results. However, from our point of view this technique may be valid for low melting point carriers such as poloxamers and low melting point drugs such as ibuprofen (its melting point, M.P., is about 75°C); but this technique is difficult to be applied for poorly water soluble drugs with high melting points as in the case of furosemide (its M.P. is around 205°C) and glibenclamide (its M.P. is around 173°C). Accordingly, spray drying technique that used in the current study (in absence and presence of Poloxamer 127) is more applicable for a wide range of hydrophobic drugs with the aim of enhancement dissolution of these drugs.

For spray chilled preparations, the percentage drug dissolved in the first 5 minutes from spray chilled ibuprofen particles was only about $21 \pm 2.6\%$, compared to $36 \pm 0.64\%$ for control. Incorporation of Poloxamer 127 in the spray chilled preparations improved the intrinsic

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solubility of the drug up to $38 \pm 1.7\%$ after 5 minutes, which was non-significantly different from that of control ($P > 0.05$). By the end of the dissolution time, the percentages of drug dissolved were 75 ± 3.2 and $82 \pm 1.4\%$ for preparations in the absence and presence of the surfactant, respectively compared to 95% drug dissolution from the control. Such unexpected results may be explained on the basis of the formation of melt-solidified bonds. Spray chilled particles were prepared by melting of the drug or drug/surfactant mixture at a high temperature followed by rapid solidification via atomising of the content into a cool air and it was stated that bonds (which formed during the crystallisation) were formed by the solidified melt of ibuprofen. These bonds were reported to be very strong bonds resulting in high compactness of the particles (Paradkar *et al.*, 2003 and Kamble *et al.*, 2004). The presence of Poloxamer 127 in spray chilled ibuprofen improved the wettability of the particle to some extent compared to spray chilled drug alone (fig. 2), but still insufficient to overcome the strong intermolecular bonds of the coalesced molecules of the drug. Other assumption could be the formation of another polymorph during the processing due to melting of the drug. Consequently, these results could be further explained by the adopted characterisation methods.

Characterisation of particles by FT-IR and DSC

To understand the possible interaction between the drug and the carrier (i.e., Poloxamer 127, in this study) and to explain the dissolution results, the prepared particles (ibuprofen and ibuprofen/Poloxamer 127) as well as ibuprofen alone were characterised using FT-IR and DSC. Absence or shifting of characteristic peaks, in either infra red spectrum or DSC thermogram, of the drug after processing would indicate changes in the drug characteristics or possibilities of drug-carrier interactions.

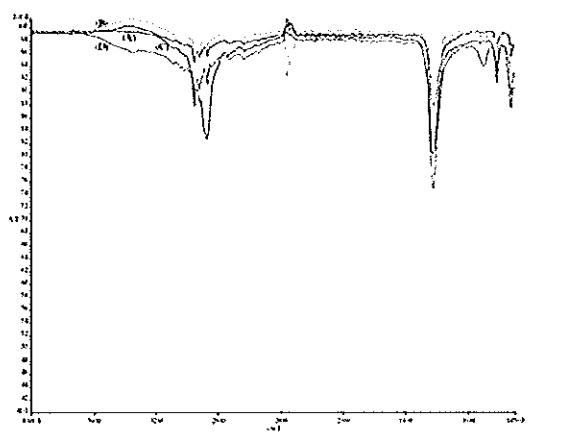


Fig. 3: FT-IR spectra of ibuprofen formulations: (A) pure ibuprofen (control), (B) spray dried ibuprofen, (C) spray dried ibuprofen/Poloxamer 127 (1:1), (D) spray chilled ibuprofen.

In FT-IR analysis (fig. 3), the spectrum of pure ibuprofen (fig.3a) showed an intense and well-defined bands characteristic to ibuprofen at 1720 cm^{-1} (carbonyl stretching of isopropionic acid group) and 3000 cm^{-1} (hydroxyl stretching). Spectra of spray dried ibuprofen and spray dried ibuprofen/Poloxamer 127 products (fig.3b and c) showed the same peaks.

For spray chilled particles, the characteristic peaks of the drug can be still recognised at the same wavenumber for spray chilled preparations (fig.3d). However, there is an appearance of a new peak at 1548 cm^{-1} which is not present in the control, suggesting a possible formation of a new polymorphic structure or a new bond formation, a situation which might explain the obtained dissolution results.

The FT-IR data could be further supported by the results of the DSC studies. In DSC thermograms (fig. 4), ibuprofen raw material showed an apparent endothermic peak at 76.33°C with enthalpy of fusion (ΔH) of 127.7 J/g (fig. 4a). A similar endothermic peak was observed for spray dried ibuprofen (fig. 4b) but with decrease degree of crystallinity as indicated by low enthalpy (46.12 J/g) i.e. the drug crystallinity was decreased to about 36.1%. This value was obtained by using equation (1) taking into account the thermal data were normalised. The decreased crystallinity of the spray dried ibuprofen may be the cause of enhanced dissolution of this formulation as indicated by dissolution study (fig. 2).

$$\left(\frac{\text{Melting enthalpy of the drug after processing}}{\text{Melting enthalpy of the drug before processing}} \right) \times 100 \text{ Eq. 1}$$

The melting peak of Poloxamer 127 alone was observed at 52.70°C. For DSC profile of spray dried ibuprofen containing Poloxamer 127 (fig. 4c), the drug endothermic peak was shifted to a lower melting temperature of 45.52°C with enthalpy of 84.56 J/g, indicating interaction between ibuprofen and Poloxamer 127. The reduction of the enthalpy of fusion indicates the decrease in crystallinity of the drug and suggest some amorphous formation, which may explain the elevated drug dissolution rate for these particles.

The DSC thermograms of spray chilled ibuprofen (fig. 4d) showed the characteristic endothermic peak for the drug at 72.68°C with enthalpy of 87.31 J/g, with the appearance of small endothermic peak at 50.59°C with enthalpy of 5.610 J/g. Such additional peak may support the previous assumption (see above) of the formation of another polymorphic structure of ibuprofen during the process of spray chilling. The DSC scans and FT-IR studies for spray chilled ibuprofen formulations support the idea of formation of new polymorph with less solubility characteristics compared to the parent drug. Therefore, based on these results together with the

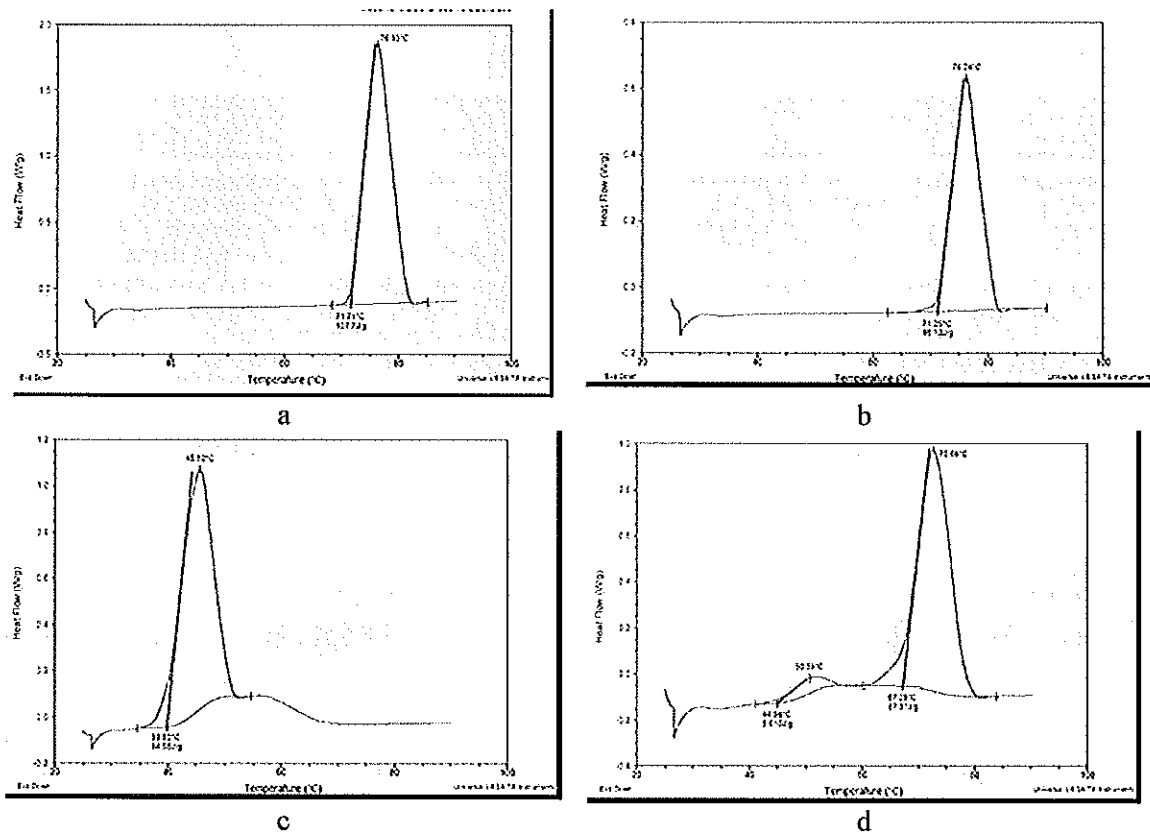


Fig. 4: DSC thermograms of ibuprofen formulations: (A) pure ibuprofen (control), (B) spray dried ibuprofen, (C) spray dried ibuprofen /Poloxamer 127 (1:1) and (D) spray chilled ibuprofen.

assumption of formation of melt-solidified bonds could explain the low dissolution from particles prepared by spray chilling technique. Hence spray chilling is not a suitable technique to improve dissolution of ibuprofen.

CONCLUSIONS

Spray drying and spray chilling were used to produce microparticles for the model hydrophobic drug, ibuprofen in an attempt to improve the drug dissolution rate. Poloxamer 127 was incorporated into the particles to enhance particle wettability, solubility and dissolution. Spray drying of ibuprofen with and without Poloxamer 127 enhanced drug dissolution rate compared to the control.

Dissolution studies showed that spray dried particles containing surfactant have the highest initial drug dissolution followed by particles without surfactant and then the control. As the experiment continued, there was no difference in drug release from both spray dried formulations, a result that may indicate that spray drying of ibuprofen alone is a useful tool to improve the drug dissolution due to decreased crystallinity. Interestingly,

spray chilled ibuprofen particles reduced the drug release compared to the control due to, as suggested, either the formation of a new polymorph as indicated from the FT-IR and DSC data or the formation of melt-solidified bonds.

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