A study on the solid state characteristics of spray-congealed glyceryl dibehenate solid lipid microparticles containing ibuprofen

Priscilla Chui Hong Wong, Paul Wan Sia Heng, and Lai Wah Chan

GEA-NUS Pharmaceutical Processing Research Laboratory, Department of Pharmacy, National University of Singapore, Singapore

Abstract
Objective: To study the solid state modifications of ibuprofen (IBU)-loaded spray-congealed glyceryl dibehenate (GB) solid lipid microparticles (SLMs) and the influence of polymeric additives using a combination of calorimetric and spectroscopic techniques. Materials and methods: IBU-loaded SLMs were produced by spray congealing with GB as the matrix material. Polyvinyl-2-pyrrolidone-vinyl-acetate (PVP/VA) and ethylcellulose (EC) were employed as additives. Of particular interest in this study were the solid state modifications of the drug and GB matrix induced by spray congealing and the effects of aging, as well as drug–matrix interactions. Fourier transform infrared spectroscopy, nuclear magnetic resonance spectroscopy, differential scanning calorimetry, hot stage microscopy and powder X-ray diffraction provided complementary analyses in understanding drug and lipid matrix polymorphism and interaction. The yield, morphology, drug content and encapsulation efficiencies of SLMs were also investigated. Results and discussion: Drug encapsulation efficiencies and yields of spray congealed SLMs were consistently high for all formulations. GB congealed as an unstable α-polymorph which reverted to the stable β'–polymorph within a few weeks. PVP/VA accelerated the polymorphic conversion in less than a week, while EC took about a year. IBU formed a solid solution with GB regardless of the GB polymorphic form. Conclusions: Spray congealing is efficient for producing drug-loaded SLMs. It induces polymorphic changes in GB. The latter incorporated 20%, w/w IBU as a solid solution and polymeric additives exerted contrasting effects on the GB polymorphic conversion.

Introduction
The biocompatibility, physical diversity, low cost and low toxicity\(^1\) of lipid-based excipients have made them highly valuable in the development of oral dosage forms for various applications, including encapsulation and protection of moisture-sensitive drugs\(^2\), taste masking bitter medicaments\(^3\), reducing gastrointestinal irritation\(^4\), enhancing drug absorption and bioavailability\(^5\), sustaining drug release\(^5,6\) and, more recently, even for cosmetic application such as sunscreens\(^8\). Solid lipid dosage forms are frequently produced as solid lipid microparticles (SLMs) prior to secondary processing. Production of suitable SLMs may be achieved by a wide range of processes ranging from simple methods such as the solvent evaporation\(^9\) and melt dispersion techniques\(^10\), to more equipment-intensive methods including spray drying\(^11,12\), spray congealing\(^13,14\) and melt pelletization\(^15\). Numerous advantages and ease of processing are conferred by lipids, but they are also known to be susceptible to polymorphic transitions\(^16–18\) induced by the production process which may subsequently transform further during storage. This may have undesirable effects on drug product stability, accompanied by variability in the release profiles. In the worst case scenario, polymorphic transition can cause the total expulsion of encapsulated drug from the lipid matrix\(^19–21\).

Spray congealing is a rapid, one-step melt process\(^12,22\) capable of preparing microparticles with high-drug encapsulation efficiencies. Briefly, a hot molten mixture is atomized into a chamber where the molten droplets solidify upon contact with cooling air. The congealed microparticles obtained are dense, spherical and free flowing, which make them amenable for secondary blending as feeds for tableting or capsule filling\(^23\). An added advantage of this process is that it does not require water or organic solvents, and this gives spray congealing the potential in formulating water-sensitive drugs\(^24\). In spray congealing, low-melting point materials, which may be hydrophilic or hydrophobic, are usually employed as matrix forming materials. Hydrophilic matrix materials, often used for enhancing drug release, include various grades of polyethylene glycols\(^25\), poloxamers\(^26\) and gelucires\(^27\). On the other hand, hydrophobic matrix materials have been used for taste masking and sustaining drug release, and include waxes\(^28\), glycerides\(^29\), hydrogenated vegetable oils\(^30\) and fatty acids\(^31\). Typically, formulations for spray congealing consist of...
the matrix material, active substance(s) with or without other additives such as those used as release modifiers. The active substances and additives are either dispersed within the lipid matrix as discrete aggregates of various sizes (solid dispersion) or dissolved (molecularly dispersed) as a solid solution. Despite the advantages of spray congealing, drastic temperature changes and high-shear forces encountered in the process are known to induce polymorphic transitions in the lipid matrix or encapsulated drug, sometimes both\(^{28,32}\). Polymorphism of drug as well as a conversion to an amorphous state can have profound effects on drug stability and solubility, the latter being more favorable for improving the solubility of poorly water-soluble drugs. Amorphous states may also be unstable, and any subsequent reversion to the more stable polymorphs can lead to changes in drug release properties over time\(^{14,33}\).

In this drug formulation study, ibuprofen (IBU) was spray-congealed with a melttable lipid matrix material, glyceryl dibehenate (GB). GB occurs as a mixture of glycerol esters of behenic acid, commonly used as a coating agent for pellets\(^{34}\) and as a lubricant for tablets and capsules\(^{35}\). More recently, GB has been used in the preparation of aqueous colloidal dispersions to form SLFs, nanoparticles and nanostructured lipid carriers for the entrapment of lipophilic drugs\(^{20}\). GB had also been employed as a waxy matrix material in melt granulation\(^{36}\). Polymeric additives, such as polyvinylpyrrolidone/vinylacetate (PVP/VA) and ethylcellulose (EC), were added to investigate their effects on the polymorphism of the drug and/or matrix. PVP/VA is a copolymer of vinylpyrrolidone and vinyl acetate. It acts as a water soluble binder for granulation and as a dry binder in direct tablet compression. More recently, it has been employed as a solubilizer for hot melt extrusion\(^{37}\). EC, a hydrophobic ethylated derivative of cellulose, is utilized as a popular coating agent for modified drug release preparations\(^{38}\).

In this study, calorimetric and spectroscopic techniques were used to examine the solid state characteristics of the spray-congealed microparticles produced. Of particular interest was the miscibility of molten blends of IBU and the polymeric additives with the matrix and the subsequent formation of solid solutions or dispersions on congealing. Polymorphic transformation and storage stability of the drug in GB matrix were also investigated, along with the effects of the two polymeric additives on the crystal structure of IBU and GB.

### Materials and methods

#### Materials

GB (Compritol 888 ATO) was purchased from Gattefosse, St-Priest, France. The polymeric additives used in this study, namely PVP/VA (or Plasdone S630) and EC were supplied by Ashland Inc. (Covington, KY) and BDH Chemicals (London, UK), respectively. IBU (Beacon Pharmaceutical, Singapore), a white crystalline powder with a melting range of 75–78°C, was used as the model drug.

#### Methods

##### Preparation of binary drug-lipid casts

GB was supplied as a fine white powder and could be used as it is. Various amounts of IBU and GB to a total of 10.0 g were accurately weighed into beakers and heated in an oven at 86°C. The molten mixtures were periodically removed from the oven and stirred until homogeneous. The melts were then transferred into a refrigerator at 4°C and allowed to solidify over about 5 min. The solidified casts were gently ground using mortar and pestle, and the powders collected were used for thermal analyses.

##### Preparation of molten mixture for spray congealing

The additives, PVP/VA and EC, were added separately to the matrix material, GB, in various concentrations in a 250-mL beaker to form the drug carrier matrix. All formulations contained 80%, w/w drug carrier and 20%, w/w IBU. The mixtures were heated to 80°C and stirred to form clear homogeneous melts.

##### Preparation of microparticles by spray congealing

The microparticles were prepared using a laboratory scale spray congealer (Mobile Minor 2000, GEA-Niro, Soborg, Denmark) with a cylindrical chamber (internal diameter: 0.8 m; height: 0.86 m) and conical base. A pneumatic fountain two-fluid nozzle equipped with a 2.0-mm nozzle tip was used for the atomization of the molten feed at an atomizing pressure of 0.2 bar into the cooling chamber maintained at 5–10°C. Atomization air temperature was set and maintained at 86°C for all formulations (10°C higher than the melting point of GB). Air was extracted from the chamber by an exhaust fan. The molten feed was maintained at 5°C above the atomization air temperature by a heat jacket while it was being delivered from the feed reservoir to the spray nozzle using a peristaltic pump (Masterflex, Cole-Parmer, Vernon Hills, IL) at a rate of 50 mL/min. The atomized droplets, upon contact with cold air in the chamber, congealed to form microparticles. The microparticles were collected by a container at the bottom of the chamber, designated as the useful fraction. Fines (<10 μm) were entrained from the chamber with the exhaust air and collected in the cyclone.

##### Preparation of physical mixture

GB was a fine white powder and used as supplied. In the preparation, portions of IBU and GB were accurately weighed and geometrically mixed using a spatula and then further mixed by continuous shaking in a plastic bag for 10 min. It is then hermetically sealed and stored at 25°C in a desiccator until further use.

##### Determination of useful yield and total yield

The product was obtained from two collection points, namely the collection vessel at the bottom of the chamber (useful fraction) and the other at the cyclone (fines).

The useful yield (%) and total yield (%) were calculated as follows:

\[
\text{Useful yield} (\%) = \frac{\text{Weight of useful fraction}}{\text{Weight of starting fraction}} \times 100
\]

\[
\text{Total yield} (\%) = \frac{\text{Weight of useful fraction} + \text{Weight of fines}}{\text{Weight of starting material}} \times 100
\]

The weight of the starting material was determined from the difference in the weight of the container of molten material before and after the spray congealing process.

##### Determination of drug content

The drug-loaded microparticles were accurately weighed and transferred into a 100-mL volumetric flask. Phosphate buffer (pH 6.8) was added to the mark and the flask was placed in a shaker bath (M20S, MT/2, Lauda, Lauda-Königshofen, Germany) at 86°C and agitated at 110 oscillations/min for 30 min. The test mixture was cooled to room temperature before an aliquot sample was removed through a 0.45-μm filter membrane (RC, Sartorius, Goettingen, Germany). Spectrophotometric analysis (UV 1201,
Shimadzu, Kyoto, Japan) was carried out at 221 nm ($\lambda_{\text{max}}$)³⁹. Drug content was expressed as the amount of drug encapsulated per unit weight of microparticles. The drug content of microparticles was determined in triplicates and the results averaged. From the drug content results, the encapsulation efficiencies (%) were calculated as follows:

$$\text{EE} \left(\%\right) = \frac{W_d}{W_t} \times 100$$

where $W_d$ is the assayed drug content and $W_t$ is the theoretical drug content.

Surface examination of spray-congealed microparticles

The morphology of pure IBU and spray-congealed microparticles was examined using a scanning electron microscope (JSM-6010LV, Jeol, Tokyo, Japan). Microparticles were mounted on aluminum stub using conductive carbon tape and observed at 1.0 kV under high vacuum.

Fourier transform infrared (FT-IR) spectroscopy

Interactions between GB and IBU as well as polymeric additives (PVP/VA and EC) were investigated using FT-IR spectroscopy (Spectrum 100, Perkin Elmer, Waltham, MA). The attenuated total reflection method was employed. The prism surface was first cleaned with 90% ethanol and dried using lint-free tissues. A background reading was taken, following which samples of approximately 20 mg were placed on the clean prism surface and compressed. Infrared spectra of the samples were obtained and analyzed. The prism surface was cleaned using 90% ethanol in between samples.

Nuclear magnetic resonance (NMR) spectroscopy

Interactions between GB and polymeric additives (PVP/VA and EC) were further elucidated using NMR spectroscopy. 10 mg each of the individual components and their physical mixtures were accurately weighed and dissolved in 0.5 mL of deuterated chloroform. $^1$H NMR spectra were recorded on a Bruker Avance 400MHz Spectrometer (Billerica, MA) and analyzed.

Differential scanning calorimetry

The thermal characteristics of the drug-lipid casts, physical mixtures and the spray-congealed microparticles of various formulations were determined using a differential scanning calorimeter (DSC-60, Shimadzu, Kyoto, Japan). A hermetically sealed aluminum pan loaded with approximately 5 mg of sample was placed in a DSC furnace and heated from 25 to 150 °C at a rate of 10 °C/min. An empty sealed aluminum pan was used as a reference. The measurements were carried out in triplicates and the results averaged.

Hot stage microscopy (HSM)

The drug-loaded spray-congealed microparticle samples were examined in a hot-stage microscope (BX51, Olympus Optical, Tokyo, Japan) with a heating unit (THMS 600, Linkam Scientific Instruments, Surrey, UK). A small amount of spray-congealed microparticles was spread on a glass slide and heated at 5 °C/min. Changes in the microparticles with temperature were monitored by capturing timed images detailing the entire melting process.

Powder X-ray diffraction analysis

The polymorphic profiles of pure drug, unprocessed materials, physical mixtures and spray-congealed microparticles were obtained using the X-ray powder diffractometer (XRD-6000, Shimadzu, Kyoto, Japan) with Cu Kα radiation ($\lambda = 1.5406$ Å). The voltage and current were 40 kV and 30 mA, respectively. The scanning angle ranged from 10 to 50° (2θ) with a scanning rate of 2° (2θ)/min.

Results

In this study, GB was utilized as a lipid matrix to incorporate the model drug IBU for spray congealing. The additives, PVP/VA and EC, were added separately to the matrix material, GB, in various concentrations. It was found that PVP/VA and EC were only able to be incorporated up to a concentration of 7.5%, w/w, and 2.5%, w/w, respectively; beyond these concentrations, the molten mixtures were too viscous for the purpose of spray congealing.

Thermal analysis of drug-lipid casts

Figure 1 plots the peak melting temperature of GB-IBU casts against the concentration of IBU as obtained from DSC experiments. From 0 to 30%, w/w of IBU, the melting point of GB was increasing depressed in a linear fashion from 75.1 to 59.2 °C. Specifically, for every 1%, w/w increase of IBU solubilized within the solid GB matrix, the melting temperature was depressed by 0.515 °C. Subsequently as the concentration of IBU increased beyond 30%, w/w to 90%, w/w, the melting temperatures of GB in those casts were no longer depressed. The melting peak of IBU was not observed until it accounted for 70%, w/w where it appeared after the melting of GB was completed, resulting in thermograms with two melting peaks for 70, 80 and 90%, w/w of IBU. Representative thermograms of drug-lipid casts at increasing IBU concentration were presented in the supplementary material.

Product yield and characteristics of spray-congealed microparticles

The useful yields of all formulations were greater than 70%, while total yields exceeded 80%. The losses, which were expected of a laboratory scale batch spray congealing process, were mainly due to adherence of the microparticles to the chamber wall and generation of fines (<10 μm) which were collected in the cyclone. These fines were not considered useful as they were outside the desired size range. Drug contents determined for all formulations were comparable to the theoretical drug contents, and the encapsulation efficiencies exceeded 90% (93.8 ± 2.4).

Surface characteristics of spray-congealed microparticles

Spray-congealed microparticles obtained from all formulations were generally spherical, non-aggregated and dense (Figure 2). As shown in Figure 2(A), IBU existed as elongated, prismatic plate-shaped crystals of various sizes as reported elsewhere⁴⁰. However, the surface of the GB microparticle loaded with 20%, w/w IBU was smooth (Figure 2C), suggesting that IBU had formed a solid solution with GB⁴¹,⁴². In comparison, the surface of the microparticles with 2.5%, w/w PVP/VA or EC had small flossy strands (Figure 2D and E). Microparticles containing 5 or 7.5%, w/w PVP/VA exhibited similar morphologies to that of 2.5%, w/w PVP/VA (not shown to avoid repetition). In a separate study (not published), the melts with PVP/VA or EC were found to have higher viscosity, which accounted for the formation of the flossy strands.

Fourier transform infrared spectroscopy

The FT-IR spectra of IBU, unprocessed GB, their physical mixture as well as spray-congealed GB-IBU microparticles are shown in Figure 3(A). Spectra of formulations containing 2.5%,...
w/w of either additive were presented for better comparison. For IBU, the large peak at 1708.14 cm$^{-1}$ indicates the prominent C=O stretch of its carboxylic acid moiety. The few small peaks at the 3000–2600 cm$^{-1}$ region indicate C–H stretches. Superimposed on these is a wide absorption band, which is characteristic of hydrogen-bonded dimers of carboxylic acids and suggests that IBU existed as dimers$^{43}$. For the unprocessed GB, the wide peak centered at 3420.85 cm$^{-1}$ indicates the O–H stretch of the hydroxyl groups on the glycerol moiety, while the peak centered at 1736.00 cm$^{-1}$ indicates the strong C=O stretch of its ester groups. Strong absorptions in the 2960–2840 cm$^{-1}$ region indicate C–H stretches of the long carbon chains. Compared to the pure GB microparticles, the C=O absorption band of the IBU-loaded GB microparticles showed a significant shift from 1736.00 to 1719.59 cm$^{-1}$. At the same time, the O–H stretch of GB shifted to 3444.05 cm$^{-1}$. These observations suggest a relatively small degree of hydrogen bonding of GB with IBU.

PVP/VA exhibited two C=O absorption peaks at 1730.31 and 1655.11 cm$^{-1}$, attributed to the acetate and pyrrolidone groups, respectively (Figure 3B). The broad peak at 3444.61 cm$^{-1}$ was due to residual water as PVP/VA is slightly hygroscopic. The spectrum of EC was dominated by a broad complex band between 1200 and 900 cm$^{-1}$, attributed to the overlapping of several C–O bending absorption peaks of its many ether groups (Figure 3C).
Figure 3. FTIR spectra of (A) pure IBU, unprocessed GB, their physical mixture as well as 20%, w/w IBU-loaded spray-congealed GB microparticles; (B) unprocessed GB, pure PVP/VA, their physical mixture and spray-congealed GB-PVP/VA microparticles; (C) unprocessed GB, pure EC, their physical mixture and spray-congealed GB-EC microparticles.
The pyrrolidone C=O stretch of PVP/VA was poorly resolved from the C=O stretch of GB at 1735.92 cm\(^{-1}\) in the physical mixture, appearing as a minor distortion on the right side of the peak (Figure 3B). This is due to the low percentage of PVP/VA. The appearance of a small peak at 1663.36 cm\(^{-1}\) in the spectrum of the corresponding spray-congealed microparticles possibly indicates hydrogen bond formation between GB and PVP/VA. For spray-congealed microparticles composed of GB and either polymeric additive, the broad O–H stretch band of GB showed relatively minor changes. It is not unexpected that the hydrogen bonding between GB and PVP/VA is limited as GB is a very large diglyceride, with a sole hydroxyl group nested between two long and bulky behenate chains. This results in severe steric hindrance, preventing the formation of strong hydrogen bonding with the carbonyl groups of PVP/VA or the ether and hydroxyl moieties of EC (Figure 3C).

Nuclear magnetic resonance spectroscopy

The NMR spectra of GB with/without PVP/VA or EC are shown in Figure 4. The NMR spectrum of unprocessed GB (Figure 4A) consisted of distinct groups of peaks. The set of intense multiplets from δ0.50 to δ2.50 could be attributed to the protons of the long behenate carbon chains. The set of less intense multiplets from δ3.50 to δ4.40 aptly corresponded to the protons of the carbons close to the ester moieties, where the protons were more deshielded due to the electronegativity of the carbonyl groups. The small multiplets in the region of δ4.90 to δ5.30 could be attributed to the protons attached to the glycerol moiety, while the broad singlet at δ6.133 corresponded to the hydroxyl protons. In the presence of PVP/VA, the hydroxyl proton signal disappeared (Figure 4B) and in the presence of EC, it was significantly depressed and shifted upfield to δ6.803 (Figure 4C). These changes were due to the formation of hydrogen bonding between the hydroxyl groups of GB and the two polymeric additives, leading to a deshielding effect on the hydroxyl proton and a concurrent increase in its labile nature. The NMR spectra support observations from FTIR such that GB was capable of hydrogen bonding with PVP/VA and EC.

Differential scanning calorimetry

The melting endotherm of IBU (m.p. ca. 76 °C) is shown in Figure 5(A). This melting endotherm was absent from the DSC thermograms of all spray-congealed formulations with 20%, w/w IBU (Figure 5B and C). It is possible that this is due to amorphization of IBU in the GB matrix. However, the sharp melting peak of IBU was not observed in the DSC curve of the corresponding physical mixtures either. This suggests that IBU had dissolved in the molten GB, similar to what has been reported in other studies.13,27,42,44.

The melting peak of GB was broad and aligned with the composition of the Compritol 888 ATO brand of GB, which consisted of mono-, di- and tri-glycerides in a mixture dominated by the diglyceride45 (Figure 5B). The melting point centered at 75.8 °C, which corresponded to the stable β'-polymorph of GB as
Figure 4. 1H NMR spectra of (A) unprocessed GB; (B) GB with 10%, w/w PVP/VA and (C) GB with 10%, w/w EC.
Figure 5. DSC thermograms of (A) pure IBU; (B) unprocessed GB, spray-congealed pure GB microparticles, physical mixture of GB with 20%, w/w IBU and 20%, w/w IBU-loaded GB microparticles; (C) 20%, w/w IBU-loaded GB microparticles showing the effect of PVP/VA and EC. Peak melting temperatures of all thermograms were reflected in Table 1. All experiments were performed in triplicates.
indicated by XRD studies. The physical mixture of GB and IBU showed a broad melting peak with some degree of melting point depression that could be attributed to the partial dissolution of IBU in GB during the heating process. In contrast, the melting endotherm of the drug-loaded spray-congealed GB microparticles showed two poorly resolved peaks centered at 60.4 and 66.9°C (Table 1). The presence of two melting points for the microparticles suggests the possibility of two coexisting polymorphs of GB46, which is highly possible when a lipid of large molecular weight is spray-congealed17,20. Notably, both melting points were significantly depressed compared to that of unprocessed GB (75.8°C) owing to the presence of 20%, w/w of IBU. The higher melting point also corresponded to that which was obtained with the GB-IBU casts in the presence of 20%, w/w IBU.

Only thermograms of formulations containing the highest possible concentrations of either polymer were presented as these would represent the greatest possible influence on the melting point of GB. No distinct melting peaks were observed for PVP/VA and EC. Comparison of the thermograms of spray-congealed GB with and without these polymers revealed that the two melting peaks centered at 60.4 and 66.9°C had not shifted despite significant changes in their relative intensities (Figure 5C). The higher melting peak was more pronounced in the intensity for the GB-IBU-PVP/VA formulation, whereas the relative intensities of the two melting peaks were similar for the GB-IBU-EC and the GB-IBU formulations.

**Hot stage light microscopy**

Hot stage light microscopy was carried out to optically examine the melting process of the GB matrix. From the series of light microscope images captured from the video recording of the heating of spray-congealed GB microparticles containing 20%, w/w IBU, two distinct melting events were observed (Figure 6). The microparticles showed the first sign of melting at 60°C (circled). This was complete by around 62°C. Subsequently, the next melting event occurred at 70°C, eventually forming a clear liquid with no suspended particulates by 71°C. These two melting events coincided with the two melting temperatures observed in the analysis of GB microparticles with 20%, w/w.

**Powder X-ray diffraction studies**

Unprocessed GB exhibited broad Bragg peaks at 21.3° and 23.5°, with d-spacings of 4.17 and 3.78 Å, respectively (Figure 7A). These spacings corresponded to the β-polymorph, which is organized in an orthorhombic crystal subcell structure20,45,51. Upon spray congealing, the rapid cooling caused the rapid crystallization of GB into the unstable α-polymorph, characterized by a single broad Bragg peak at 21.4° (d-spacing 4.15 Å)12. This unstable α-polymorph reverted to the more stable β-polymorph over the course of a year.

IBU exhibited multiple sharp peaks typical of highly crystalline substances (Figure 7F). Intense Bragg peaks were observed at 12.2°, 16.5°, 16.8°, 17.6°, 19.1°, 20.2° and 22.4°. Upon spray-congealing GB with IBU (Figure 7B), GB itself firstly congealed as the unstable α-polymorph as observed when it was spray-congealed as a pure matrix. This unstable α-polymorph similarly reverted to the more stable β-polymorph within 1 month of storage. As for IBU, sharp peaks corresponding to those of the pure substance were also seen in the physical mixture of GB and IBU (Figure 7B, diffractogram in orange). Specifically, the group of peaks between 16° and 20° and the sharp peak at 22.4° were most apparent. After spray congealing, most of these distinct peaks were lost, leaving behind two broad peaks at 16.2° and 17.8°. This is attributed to a loss of crystallinity of IBU after spray congealing.

Spray congealing GB with 2.5%, w/w (Figure 7D) or 7.5%, w/w PVP/VA (Figure 7E) also resulted in the α-polymorph which reverted to the β-polymorph within 1 month for the lower PVP/VA concentration and 1 week for the higher PVP/VA concentration. This observation suggests that a higher concentration of PVP/VA accelerated the conversion of the unstable α-polymorph to the stable β-polymorph. Conversely, in the presence of 2.5%, w/w EC, the conversion of the α-polymorph to the stable β-polymorph was complete only at the end of 1 year (Figure 7C).

**Discussion**

In the present work, a meltable lipid matrix GB and a model lipophilic drug IBU were characterized for their solid state properties when spray-congealed as SLMs. Properties studied included intermolecular interactions and the nature of solid mixtures of GB and IBU, with and without the inclusion of polymeric additives, PVP/VA or EC. The presence of polymorphs was also investigated and, if any, their stability upon aging for up to a year.
Figure 7. XRD diffraction patterns of (A) unprocessed GB, fresh and aged spray-congealed GB microparticles; (B) 20%, w/w IBU-loaded spray-congealed GB microparticles only; 20%, w/w IBU-loaded spray-congealed GB microparticles with (C) 2.5%, w/w EC; (D) 2.5%, w/w PVP/VA; (E) 7.5%, w/w PVP/VA and the effect of aging (day zero, 1 week, 1 month, 3 months and 1 year) upon storage at 25 °C; (F) pure IBU.
Figure 7. Continued.
Spray congealing was successfully employed to generate GB SLMs. Useful yields of the spray-congealed microparticles were greater than 70%, while total yields exceeded 80%. The losses, which were expected of laboratory-scale batch spray congealing, were mainly due to adherence of the spray droplets to the chamber wall and generation of fines (<10 µm) that were collected in the cyclone by the exhaust system. These fines were not considered useful as they were outside the desired size range. Encapsulation efficiencies of the microparticles exceeded 90%, underscoring the usefulness of spray congealing as a technique to generate lipid microparticles in a highly efficient manner as reported in various studies.  

The presence of a solute is able to depress the melting point of the matrix in a colligative manner, i.e. the depression is proportional to the concentration of solute. When a molecularly dispersed solute in the solid matrix exceeds its solubility limit in the latter, it precipitates or in some cases, crystallizes out as discrete particles or crystals, forming a solid dispersion. Determining the solubility of IBU within solid GB by observing the melting point depression of solid GB caused by the solubilized IBU and thereafter determining the solubility limit of IBU in the solid matrix by means of drug-lipid casts could provide a basis from which to interpret results obtained from other techniques.  

It was observed that from a concentration of 0–30%, w/w, IBU produced a proportional depression of the melting point of GB. Thereafter, the melting point of GB was no longer depressed but plateaued out at around 60°C. It is believed that from 0 to 30%, w/w of IBU, increasing quantities of IBU could be solubilized within the solid GB matrix, thereby exerting a depression of the latter’s melting point in a colligative manner. Within this concentration range, the GB-IBU system may be thought of as a solid solution, where IBU is molecularly dispersed within the lipid matrix. IBU-loaded spray-congealed GB microparticles exhibited very smooth surfaces, and this observation is typical of solid solutions of drug within its matrix, thus supporting the above conclusion. This solubility of IBU in solid GB was, however, exceeded at 40%, w/w onwards, and explains how the melting point of GB was not further depressed. The GB-IBU system here may be regarded thus as a two-phase solid dispersion where aggregates of insoluble IBU are dispersed within the GB matrix. The GB matrix itself is expected to be saturated with dissolved IBU as well. As both GB and IBU are generally hydrophobic (IBU exists as non-polar dimers), the similar intermolecular forces of attractions are believed to be the driving forces behind the formation of such a homogenous mixture even at high-drug load of 30%, w/w. FTIR also highlighted a small extent of hydrogen bonding between GB and IBU which could have facilitated this. A similar formulation comprising ketoprofen in glyceryl monostearate-hydrogenated castor oil lipid particles has been reported. Another noteworthy point is that from 40 to 60%, w/w IBU, the melting peak of IBU was still not observed (supplementary material). This is most likely due to dissolution of IBU aggregates into the molten GB during the course of heating. At 70%, w/w IBU, the melting peak of the drug was evident, indicating that at this concentration the maximum solubility of IBU in molten GB had been exceeded.  

Unprocessed GB existed in its most stable polymorph (orthorhombic β′-polymorph) before spray congealing. Due to the heterogeneous nature of GB, it exhibited relatively broad Bragg peaks in the X-ray diffractogram. Upon spray congealing with or without 20%, w/w of IBU, the orthorhombic β′-polymorph of GB invariably congealed first as the hexagonal α-polymorph, which was identified by means of its X-ray diffractogram showing a very broad single Bragg peak. This unstable polymorph rearranged itself into the stable orthorhombic β′-polymorph over the course of a month. GB consists of very large glycerides, with an average of 47 carbons per molecule (based on the major dibehenate component), and is therefore expected to require more time in its conversion to the stable polymorph unlike smaller lipids. The above findings underline an important concern about such lipid-based formulations. Significant polymorphic changes in lipids may occur during processing, which may impact upon the physical stability of the formulation and the release profile of the encapsulated drug. GB, being a glyceride, has been widely used in sustained release formulations. It has inherent problems associated with polymorphism, the impact of which on drug release from spray-congealed SLMs is not clear. As for IBU, raw IBU exhibited a typical diffractogram of a crystalline material with multiple sharp and clearly defined peaks. However, these peaks were largely lost upon spray congealing with GB, and the crystallinity of IBU did not recover over the course of a year, highlighting the ability of the GB matrix in stabilizing the amorphous form of IBU.  

The addition of polymeric additives can have profound effects on the polymorphism of the matrices. For example, the addition of poloxamer to glyceryl palmitostearate was found to stabilize the lipid from further polymorphic changes. In this study, the stability of GB polymorphs was profoundly affected by the presence of PVP/VA or EC as revealed by XRD. PVP/VA, at 7.5% w/w, accelerated the conversion of the unstable α-polymorph of GB to its stable β′-polymorph in a week. On the other hand, EC at 2.5% w/w stabilized the α-polymorph such that its conversion to the stable polymorph was complete only after 1 year. This stabilizing effect of EC may be attributed to a partial embedding of the polymeric additive into the matrix or an interaction with the matrix via hydrogen bonding as shown by NMR studies or van der Waals’ interactions. Notwithstanding, the effect of polymeric additives on the stability of lipid polymorphs is relatively unknown, and the contrasting findings here, albeit preliminary, highlight that there may be no straightforward generalization of their effects. As a final note, the addition of either additive had no bearing on the polymorphism of the encapsulated IBU. IBU remained in its amorphous state with no signs of recovery of its crystalline form for up to a year.  

Conclusions  

The effects of spray congealing and additives on the solid state characteristics of GB were investigated by a combination of calorimetric and spectroscopic techniques. GB was found to incorporate 20%, w/w of IBU as a solid solution. Spray congealing resulted in GB polymorphic changes to the unstable α-polymorph. Presence of polymeric additives can either speed up or slow down the polymorphic changes. Such additives may be employed as agents to either stabilize an unstable polymorph or to hasten its conversion to the stable polymorph. Clearly, from this study, spray congealing presented itself to be an efficient manufacturing process for preparing lipid-based microparticles containing a drug.  

Declaration of interest  

The authors report no declarations of interest. The authors would like to acknowledge the financial support from GEA-NUS PPRL fund (N-148-000-008-001). Priscilla Wong Chui Hong is a recipient of the National University of Singapore Graduate Research Scholarship.  

References  

1. Das S, Chaudhury A. Recent advances in lipid nanoparticle formulations with solid matrix for oral drug delivery. AAPS PharmSciTech 2011;12:62–76.
2. Thomsen LJ, Schafer T, Kristensen HG. Prolonged release matrix particles prepared by melt pelletization II. Hydrophobic substances as meltable binders. Drug Dev Ind Pharm 1994;20:1179–97.

3. Qi S, Deutsch D, Craig DQM. An investigation into the mechanisms of drug release from taste-masking fatty acid microspheres. J Pharm Sci 2008;97:3842–54.

4. Pouton CW. Self-emulsifying drug delivery systems: assessment of the efficacy of emulsification. Int J Pharm 1985;27:335–48.

5. Chauhan B, Shimihi S, Paradkar A. Preparation and characterization of etoricoxib solid dispersions using lipid carriers by spray drying technique. AAPS PharmSciTech 2005;6:405–12.

6. Kumar MK, Shah MH, Ketkar A, et al. Effect of drug solubility and different excipients on floating behavior and release from glyceryl monooleate matrices. Int J Pharm 2004;272:151–60.

7. Barker SA, Yap SP, Yuen KH, et al. An investigation into the structure and bioavailability of 3-tert-cocopherol dispersions in Gelucire 44/14. J Control Release 2003;91:477–88.

8. Trotta V, Goios F, Monteiro H, et al. Influence of lipid microparticle encapsulation on in vitro efficacy, photostability and water resistance of the sunscreen agents, octyl methoxycinnamate and butyl methoxydibenzoylmethane. Drug Dev Ind Pharm 2014;40:1233–39.

9. Cortesi R, Esposito E, Luca G, Nastruzzi C. Production of liposomes as carriers for bioactive compounds. Biomaterials 2002;23:2283–94.

10. Sanna V, Kirschvink N, Gustin P, et al. Preparation and in vivo toxicity study of solid lipid microcapsules as carrier for pulmonary administration. AAPS PharmSciTech 2004;5:Article 27.

11. Brasseur S, Amighi K, Moes AJ, eds. Evaluation of solid lipid microcapsules for controlled delivery to the pulmonary tract. Proceedings of the 9th Forum of Pharmaceutical Sciences, Spa, Belgium; 2000.

12. Killeen MJ. Spray drying and spray congealing of pharmaceuticals. In: Swarbrick J, Boylan JC, eds. Encyclopedia of pharmaceutical technology. Vol. 14. New York (NY): Marcel Dekker; 1996:207–21.

13. Passerini N, Perissutti B, Moneghini M, et al. Characterization of carbamazepine-Gelucire 50/13 microcapsules prepared by a spray-congealing process using ultrasounds. J Pharm Sci 2002;91:699–707.

14. Savolainen M, Khoo C, Glad H, et al. Evaluation of controlled-release polar lipid micro particles. Int J Pharm 2002;244:151–61.

15. Hamdani J, Moes AJ, Karim A. Development and evaluation of prolonged release pellets obtained by the melt pelletization process. Int J Pharm 2002;245:167–77.

16. Ostwald W. The formation and changes of solids. Z Physik Chem 1918;1897;22:289–300.

17. Verma AR, Krishna P. Polymorphism and polytypism in crystals. Kristall und Technik 1966;1:665–6.

18. Yoshioka M, Hancock BC, Zografii G. Crystallization of indomethacin from the amorphous state below and above its glass transition temperature. J Pharm Sci 1994;83:1700–5.

19. Westesen K, Bunjes H, Koch MJH. Physicochemical characterization of lipid nanoparticles and evaluation of their drug loading capacity and sustained release potential. J Control Release 1997;48:223–36.

20. Souto E, Mehnert W, Muller RH. Polymorphic behaviour of Compritol 888 ATO as bulk lipid and as SLN and NLC. J Microencapsul 2006;23:417–33.

21. Gamboa OD, Goncalves LG, Grosso CF. Microencapsulation of tocopherols in lipid matrix by spray chilling method. Procedia Food Sci 2011;1:1732–9.

22. Felder CB, Blanco-Prieto MJ, Hiezmann J, et al. Ultrasound atomization and subsequent polymer desolvation for peptide and protein microencapsulation into biodegradable polyesters. J Microencapsul 2003;20:553–67.

23. Li LC, Zhu L, Song JF, et al. Effect of solid state transition on the physical stability of suspensions containing bu-capivance lipid micro-particles. Pharm Dev Technol 2005;10:309–18.

24. Rodriguez L, Albertini B, Passerini N, et al. Hot air coating technique as a novel method to produce microparticles. Drug Dev Ind Pharm 2004;30:913–23.

25. Albertini B, Passerini N, Pattarino F, Rodriguez L. New spray congealing atomizer for the microencapsulation of highly concentrated solid and liquid substances. Eur J Pharm Biopharm 2008;69:348–57.

26. Mackaplow MB, Zarraga IE, Morris JF. Rotary spray congealing of a suspension: effect of disk speed and dispersed particle properties. J Microencapsul 2006;23:793–809.

27. Passerini N, Albertini B, Perisutti B, Rodriguez L. Evaluation of melt granulation and ultrasonic spray congealing as techniques to enhance the dissolution of praziquantel. Int J Pharm 2006;318:92–102.

28. Emas M, Nyqvist H. Methods of studying aging and stabilization of spray-congealed solid dispersions with carnauba wax. 1. Microcalorimetric investigation. Int J Pharm 2000;197:117–27.

29. Di Sabatino M, Albertini B, Kett VL, Passerini N. Spray congealed lipid micro-particles with high protein loading: preparation and solid state characterisation. Eur J Pharm Sci 2012;46:346–56.

30. Guo QY, Chan LW, Heng PW. Investigation of the release of aspirin from spray-congealed micro-pellets. J Microencapsul 2005;22:245–51.

31. Scott MW, Robinson MJ, Pauls JF, Lantz RJ. Spray congealing: particle size relationships using a centrifugal wheel atomizer. J Pharm Sci 1964;53:670–5.

32. Maschke A, Becker C, Eyrich D, et al. Development of a spray congealing process for the preparation of insulin-loaded lipid micro-particles and characterization thereof. Eur J Pharm Biopharm 2007;65:175–87.

33. Burton R, Cheng XX. Cooling processes and congealing. In: Swarbrick J, ed. Encyclopedia of pharmaceutical technology. 3rd edn. New York (NY): Informa Healthcare; 2007:761–73.

34. Menjoge A, Kulkarni M. Pharmaceutical composition for improving palatability of drugs and process for preparation thereof. Patent 7,378,109; 2008.

35. Brossard C, Ratsimbazafy V, Lefort des Ylouses D. Modelling of theophylline compound release from hard gelatin capsules containing Gelucire matrix granules. Drug Dev Ind Pharm 1991;17:1233–9.

36. Zhang YE, Schwartz JB. Melt granulation and heat treatment for wax matrix-controlled drug release. Drug Dev Ind Pharm 2003;29:131–8.

37. Ashland. Plasdone S-630 copovidone product overview; 2013.

38. Sadeghi F, Ford JL, Rubinstein MH, Rajabi-Siahboomi AR. Study of drug release from pellets coated with surelease containing hydroxypropylmethylcelullose. Drug Dev Ind Pharm 2001;27:419–30.

39. USP. Ibuprofen Tablets. United States Pharmacopeia and National Formulary (USP 29-NF 24). Vol. 2., p. 1102.

40. Rasenack N, Muller BW. Ibuprofen crystals with optimized properties. Int J Pharm 2002;245:9–24.

41. Vilhelmsen T, Eliasen H, Schaefier T. Effect of a melt agglomeration process on agglomerates containing solid dispersions. Int J Pharm 2005;303:132–42.

42. Zaky AA, Abdel-Raheem IT. Solubility enhancement of meloxicam prepared via binary and ternary phases using spray congealing. Asian J Pharm Hea Sci 2011;1:196–203.

43. Florio GM, Zwier TS, Myshakin EM, et al. Theoretical modeling of the OH stretch infrared spectrum of carboxylic acid dimers based on first-principles anharmonic couplings. J Chem Phys 2003;118:1235–45.

44. Martins RM, Siqueira S, Machado MO, Freitas LA. The effect of homogenization method on the properties of carbamazepine micro-particles prepared by spray congealing. J Microencapsul 2013;30:692–700.

45. Brubach JB, Jannin V, Mahler B, et al. Structural and thermal characterization of glycerol behenate by X-ray diffraction coupled to differential calorimetry and infrared spectroscopy. Int J Pharm 2007;336:248–56.

46. Elfordy AA, Essa EA. Dissolution of ibuprofen from spray dried and spray chilled particles. Pak J Pharm Sci 2010;23:284–90.

47. Goto M, Takiguchi T. The crystal structure of the β form of α-monolaurin. Bull Chem Soc Jpn 1985;58:1319–20.

48. Hagemann JW, Garti IN, Sato K. Crystallization and polymorphism of fats and fatty acids. New York (NY): Marcel Dekker; 1988.

49. Hernqvist L. On the structure of triglycerides in the liquid state and fat crystallization. Fette Seifen Anstrichm 1984;86:297–300.

50. Sydow E. On the phase transitions in normal chain carboxylic acids with 12 up to including 29 carbon atoms between 30 °C and melting point. Arkiv Kemi 1953;6:309–16.
51. Gunstone FD, Harwood JL, Dijkstra AJ. The lipid hand-book with CD-ROM. 3rd ed. Boca Raton (FL): CRC Press; 2007.

52. Hamdani J, Moës AJ, Amighi K. Physical and thermal characterisation of Precirol® and Compritol® as lipophilic glycerides used for the preparation of controlled-release matrix pellets. Int J Pharm 2003;260:47–57.

53. García-González CA, Argemi A, Sampaio de Sousa AR, et al. Encapsulation efficiency of solid lipid hybrid particles prepared using the PGSS® technique and loaded with different polarity active agents. J Supercrit Fluids 2010;54:342–7.

54. Jaspart S, Bertholet P, Piel G, et al. Solid lipid microparticles as a sustained release system for pulmonary drug delivery. Eur J Pharm Biopharm 2007;65:47–56.

55. Obaidat AA, Obaidat RM. Controlled release of tramadol hydrochloride from matrices prepared using glyceryl behenate. Eur J Pharm Biopharm 2001;52:231–5.

56. Roberts M, Vellucci D, Mostafa S, et al. Development and evaluation of sustained-release Compritol® 888 ATO matrix mini-tablets. Drug Dev Ind Pharm 2012;38:1068–76.

57. Jannin V, Pochard E, Chambin O. Influence of poloxamers on the dissolution performance and stability of controlled-release formulations containing Precirol ATO 5. Int J Pharm 2006;309:6–15.

58. Van den Mooter G, Wuyts M, Blaton N, et al. Physical stabilisation of amorphous ketoconazole in solid dispersions with polyvinylpyrrolidone K25. Eur J Pharm Sci 2001;12:261–9.

59. Boldyrev VV. Mechanochemical modification and synthesis of drugs. J Mater Sci 2004;39:5117–20.

Supplementary material available online
Supplementary Figure S1.