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Microparticle size control and glimepiride microencapsulation using spray congealing technology

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ABSTRACT

Drug-free microparticles were prepared using a spray congealing process with the intention of studying the influence of processing parameters. By varying the atomizing pressure and liquid feed rate, microparticles with median sizes ($d_{(0.5)}$) from 58 to 278 μm were produced, with total process yields ranging from 81% to 96%. An increased liquid feed rate was found to increase microparticle size, and higher atomizing pressures were found to decrease microparticle size. Greater change in microparticle size was achieved by varying atomizing pressure, which can be considered a dominant process parameter regarding microparticle size. In addition, microparticles with glimepiride, a model poorly water-soluble drug, were prepared by spray congealing using three different hydrophilic meltable carriers: Gelucire® 50/13, poloxamer 188, and PEG 6000. Spherical microparticles with relatively smooth surfaces were obtained, with no drug crystals evident on the surfaces of drug-loaded microparticles. XRPD showed no change in crystallinity of the drug due to the technological process of microparticle production. All glimepiride-loaded microparticles showed enhanced solubility compared to pure drug; however, Gelucire® 50/13 as a carrier represents the most promising approach to the dissolution rate enhancement of glimepiride. The influence of storage (30 °C/65% RH for 30 days) on the morphology of glimepiride/Gelucire® 50/13 microparticles was studied, and the formation of leaf-like structures was observed (a "blooming" effect).

1. Introduction

Spray congealing (also known as spray chilling or spray cooling) is one of the methods used to produce microparticles or more specifically microspheres. Microspheres (also called micropellets) are solid, approximately spherical particles with sizes in the micrometer range, in which the drug is evenly distributed within the entire volume of the particle.

The spray congealing process was extensively reviewed by Killeen (1993) and consists of the following steps: (1) The carrier material is melted and the drug is added to the molten carrier. The drug can be either dissolved or mechanically dispersed in the carrier media – both variations are acceptable; however, dispersion systems are more common. (2) The molten material is fed from the heater to the atomizing nozzle, where it is sprayed into the cooling chamber by atomization. (3) Heat transfer between cold air and hot melt is initiated and droplets of molten material should solidify before contact with the wall of the cooling chamber. (4) Solidified and cooled free-flowing powder is collected. Because the process does not involve evaporation of solvents, the microparticles produced are usually dense and non-porous. Spray congealing as a process is very similar to spray drying, with the exception of energy flow. In the case of spray drying, energy is applied to the droplet, forcing evaporation of the media; in spray congealing, energy is removed from the droplet, forcing the melted media to solidify (Killeen, 1993). Simply put, spray congealing is a fusion between hot-melt technology (coating or agglomeration) and spray drying. In spray congealing and spray drying the basic principles are very similar and the same equipment can be used with only minor modifications: feed tubes must be heated to avoid unwanted solidification, atomizing air should be heated, and air flowing through the process chamber should be cooled instead of heated. The most important process variables for spray congealing are the temperature of the molten material, the cooling air temperature, the atomizing air temperature, the atomizing air pressure, and the liquid feed rate.

One of the key elements of a spray congealing process is the atomization efficiency of the molten mixture that can be achieved through different types of atomizers; that is, rotary or centrifugal, airless nozzles, air dual-fluid nozzles, and ultrasonic atomizers (Killeen, 1993). Air atomization using dual-fluid nozzles is widely applied to the spray congealing process because of its versatility.

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A dual-fluid nozzle allows the most control in droplet formation because the orifice opening, atomizing air pressure, and liquid flow rate can be varied independently to obtain a given particle size (Killeen, 1993). All available atomizers have some common drawbacks, such as difficulty in atomizing highly viscous fluids and, consequently, difficulty in achieving drug loadings exceeding 30% (w/w). However, with a change in atomizer design, it is possible to achieve drug loadings up to 50% (w/w) (Albertini et al., 2008).

Spray congealing yields a product that is a solid dispersion of the drug in the carrier. If the drug is poorly water-soluble, the carrier material used should be either highly water-soluble or highly water-permeable, resulting in an improvement of the drug's dissolution rate, which is a recognized characteristic of solid dispersions (Sekiguchi and Obi, 1961). If necessary, the product can be size-separated before further processing (i.e., sieving). Spray congealed microparticles are typically spherical with smooth surfaces; therefore good flow properties can be expected. This is advantageous when such a product is intended for filling into capsules or compressing into tablets.

The advantages of using a spray congealing process are numerous. Generally, no solvent is required in the formulation and manufacturing process, so the environmental requirements of solvent capture and recycling are eliminated. Processing times are often shorter because solvent evaporation is not required. Undesirable drug–solvent interactions are eliminated; for example, highly water-labile drugs can be processed using spray congealing (Turton and Cheng, 2007).

There are also some limitations when using spray congealing processes. The drug must be stable at the temperature required to melt the carrier. For many drugs, the temperature at which degradation takes place is low and may preclude the use of all suitable carrier materials. Processes using hot-melts require careful engineering to avoid feed-line solidification and unwanted agglomeration. Many of the carrier materials used to form dispersions undergo aging changes during storage, which can affect the drug stability and/or drug dissolution profiles (Turton and Cheng, 2007).

Numerous applications of microparticles have been investigated: taste and odour masking (Akiyama et al., 1993; Sjoqvist et al., 1993; Yajima et al., 1999; Uchida et al., 2003; Sheng et al., 2005), protection of the active ingredient from the environment (the body: acidic media, enzymes, etc.; the external environment: humidity, oxygen, light, etc.), enhancement of the dissolution rate of poorly soluble drugs, sustained or controlled drug delivery (Robinson and Swintosky, 1959; Cusimano and Becker, 1968; Akiyama et al., 1993; Savolainen et al., 2002; Savolainen et al., 2003; Park and Yeo, 2007), improvement of flow properties, safe handling of toxic substances (Burgess and Hickey, 2007), cosmetic appearance, and patent circumvention.

The carriers that can be used in spray congealing are shared with other hot-melt technologies, such as coating materials in hot-melt coating and binders in hot-melt agglomeration. Achanta et al. (1997) defined the ideal characteristics for hot-melt coating materials; however, identical properties are desired in a spray congealing process. Summarized, these characteristics should ensure that (i) the carrier is stable under typical spray congealing conditions; (ii) it should be easy to spray; and (iii) the operating temperatures should be moderate in order to minimize drug degradation.

Suitable commercial excipients that can be used in the spray congealing process can be divided into two basic groups: hydrophilic and hydrophobic carriers. Hydrophilic carriers include polyoxylglycerides (i.e., Gelucire®), poloxamer 188 and 407 (i.e., Lutrol® or Pluronic® F68/F127), polyethylene glycols (PEGs) 2000–20000, and esters of polyethylene glycol (i.e., Stearate 6000 WL1644), whereas hydrophobic carriers include beeswax, carnauba wax, cetearyl alcohol, cetyl palmitate, fats (i.e., glyceryl behenate, glyceryl palmitostearate, glyceryl stearate, glyceryl palmitate), hydrogenated castor oil, microcrystalline wax, paraffin wax, stearic acid, and stearic alcohol (Heng and Wong, 2007).

The selection of a carrier with a hydrophilic/hydrophobic character is crucial for the dissolution behaviour of the drugs. Hydrophobic carriers should be used to control the release of short half-life drugs such as verapamil hydrochloride (Passerini et al., 2003) and theophylline (Albertini et al., 2004). Hydrophilic carriers should be used when enhancement of the dissolution rate of poorly water-soluble drugs is required, like in carbamazepine (Passerini et al., 2002), diclofenac (Cavallari et al., 2005), and praziquantel (Passerini et al., 2006).

Spray congealing was successfully used for preparing microparticles loaded with some other drugs such as clarithromycin (Yajima et al., 1999), indomethacin (Fini et al., 2002), propafenone hydrochloride, α-tocopheryl acetate (Albertini et al., 2008), felodipine (Savolainen et al., 2002; Savolainen et al., 2003), fenbufen (Rodriguez et al., 1999), tetracycline hydrochloride, and lidocaine hydrochloride (McCarron et al., 2008). Recently it was demonstrated that this technology also offers a promising approach for protein drug delivery systems such as insulin (Maschke et al., 2007).

There is limited literature available regarding the effect of various process parameters on the spray congealing process, especially regarding final product particle size. Scott et al. (1964) investigated the influence of process parameters on particle size using a centrifugal wheel atomizer. The particle size was directly proportional to the feed rate and inversely proportional to the liquid feed viscosity and the wheel velocity. Droplet size using a dual-fluid atomization nozzle was studied by Juslin et al. (1995a,b), in which the media were water or aqueous solutions of a binder (polyvinylpyrrolidon) intended for a fluid-bed granulation process. Higher atomizing pressure, lower liquid feed rates, and lower concentrations of binder resulted in smaller droplet sizes during atomization, with atomizing pressure having the greatest influence on droplet size. The addition of binder resulted in larger droplet sizes because of the liquid's increased viscosity. Just recently, a similar relationship was confirmed in the spray congealing process. Increasing the atomizing pressure from 5 bars to 6 resulted in a decrease of the microparticle product size in the spray congealing process (Maschke et al., 2007). An important influence on microparticle size is also associated with the liquid's viscosity, which can be regulated through temperature or the type and amount of solids dispersed in the melt. Lower viscosity (higher temperature) results in smaller product particle sizes (Maschke et al., 2007), whereas higher viscosity (the addition of solids such as Aerosil®) results in larger product particle sizes (Albertini et al., 2008).

When using molten dispersions with higher solid loadings, the flow of the bulk dispersion is reduced due to increased viscosity. An effective countermeasure for this is to increase the temperature of the molten dispersion as well as the temperature of the tubing, if this is allowed from the drug-stability point of view. Alternatively, a change in the formulation can be made by reducing the amount of solids in the dispersion.

The aim of this study was to prepare relatively large batches of microparticulate product and study the influence of process parameters on microparticle size and process yields. This information could be very useful in terms of the industrial applicability of this technology on a larger scale, where optimal process parameters are required and obligatory. Glimepiride was used as a model drug and microparticles were prepared with three different hydrophilic carriers. The drug-loaded microparticles obtained were characterized by XRPD and SEM. Dissolutions of the drug-loaded microparticles were performed with the aim of estimating how the carriers tested improved the dissolution rate of this poorly water-soluble drug.

2. Materials and methods

2.1. Materials

Drug-free microparticles were prepared from Gelucire® 50/13 (polyoxyglycerides or stearyl macrogolglycerides, solid pastilles, Gattefossé, France; lot: 106058). Drug-loaded microparticles were prepared from the following hydrophilic polymers: Gelucire® 50/13, poloxamer 188 (Lutrol F68, BASF, Germany), and PEG 6000 (Clariant GmbH, Germany). The active ingredient used was glimepiride (USV, India), an oral antidiabetic drug.

2.2. Preparation of microparticles

2.2.1. Drug-free microparticles

The microparticles were prepared by spray congealing using a Büchi Mini Spray Dryer B-290 (Büchi, Switzerland). A dual-fluid nozzle with a 0.7 mm nozzle tip and a 1.5 mm nozzle cap was used to atomize the melt into the cooling chamber. The original glassware of the apparatus was used, consisting of the process chamber (15 cm diameter and 60 cm length), a high-performance cyclone, an aspirator, and an outlet filter. A continuous flow of cooled air with temperatures ranging between 0 and 5 °C was used for solidification of particles in the process chamber. Processing air was cooled with a B-296 dehumidifier (Büchi, Switzerland) coupled to the spray dryer at the air inlet. Airflow through the chamber was set to the equipment maximum. The nozzle was thermostated with water to 60 °C using the nozzle's inner loop to prevent solidification in the nozzle. The atomizing air was heated by use of a capillary sunk in the water bath at 60 °C. Batch sizes of the prepared drug-free microparticles were between 42 and 97 g, typically around 70 g. Gelucire® was melted and thermostated to 70 °C, then it was fed to the nozzle using a peristaltic pump (Flocon 1B.1003-R/65, Petro Gas, Germany) via tubing heated by a temperature controller (Digi-Sense, Cole Parmer, USA) to prevent solidification. Atomizing pressure was measured at the T-junction after the spray dryer's built-in rotameter with a GDH 13 AN digital manometer (Greisinger electronic, Germany). The influence of atomizing pressure and liquid feed rate was studied on drug-free microparticles. The liquid spray rate used ranged from 6.0 to 23.4 ml/min. Various atomizing air pressures between 1.090 and 1.590 bar were tested.

2.2.1.1. Spray congealing total process yield and useful yield. Total yield was calculated by dividing the mass of final product by the mass of starting material (%, w/w). The final product was then sieved using a vibrating shaker (AS200 basic, Retsch, Germany) through 125 μm and 500 μm sieves (Retsch, Germany) – the fraction between the sieves was designated the useful fraction. Larger microparticles are expected to have better flow properties compared to smaller microparticles, which could be advantageous if the microparticles are compressed into tablets. Microparticles larger than 500 μm are expected to be agglomerates. This was the justification for choosing a size interval of 125–500 μm as the useful fraction. The useful yield was calculated from the mass of a useful fraction by dividing it by the mass of the starting material (%, w/w). The mass of starting material consumed was determined by weighing the beaker of molten material before and after the process.

2.2.1.2. Particle size and morphology. Particle size distribution was measured by laser diffraction (Mastersizer S, Malvern Instruments Ltd., UK) using the following parameters: 300RF lens; small volume dispersion unit (1000 rpm); true density 1.110 g/cm^3 (AccuPyc 1330, Micromeritics, USA); and refractive index of Gelucire® 50/13 1.439. The refractive index was determined by extrapolation (Saveyn et al., 2002) to 100% of the solids from Gelucire® 50/13 solutions in water (4 points; 0.184% (w/w) – 1.880% (w/w); R^2 of 0.997) using a Jena J78 refractometer (Carl Zeiss, Germany). The dispersion medium used was 96% ethanol, in which Gelucire® 50/13 is insoluble. The particle size of each batch was measured in triplicate.

The size, shape, and surface of drug-free microparticles were examined by scanning electron microscope (EHT = 1.00 kV, SE2 detector, Zeiss SUPRA35 VP, Germany).

2.2.2. Glimepiride-loaded microparticles

Glimepiride-loaded microparticles were prepared using the following carrier materials: Gelucire 50/13®, poloxamer 188, and PEG 6000. The same equipment and setup as with drug-free microparticles was used. The carrier material was melted to an appropriate temperature (Gelucire® to 70 °C, poloxamer and PEG 6000 to 80 °C), then glimepiride was added (1.7%, w/w) and the molten media was sonicated for 1 min. The molten dispersion was put on the thermostated heater and mixed using a magnetic stirrer before it was fed to the nozzle via heated tubing. The liquid feed rate used was 6.0 ml/min, whereas the atomizing pressures used were 1.4, 2.0, and 1.8 bar for Gelucire®, poloxamer 188, and PEG 6000, respectively. Batch sizes of glimepiride-loaded microparticles were around 25 g.

2.2.2.1. Morphology of glimepiride-loaded microparticles. The size, shape, and surface of glimepiride-loaded microparticles were examined by scanning electron microscope (EHT = 1.00 kV, secondary electron detector, JSM 7001-F, JEOL, Japan).

2.2.2.2. X-ray powder diffractometry (XRPD). An X'Pert PRO MPD (PANanalytical, NL) diffractometer using Cu Kα radiation was employed. The scanning angle ranged from 2° to 40° of 2θ, scan steps were 0.033 of 2θ, and the counting time was 50 s/step. Samples of pure drug, physical mixtures of drug and carriers and drug-loaded microparticles were evaluated.

2.2.2.3. Determination of drug content. Approximately 20 mg of drug-loaded microparticles were weighted into a 100 ml flask using appropriate solvent of acetonitrile and water (80:20, v/v) mixture. The content was gently mixed for 120 min and analyzed with a Waters Alliance 2690 Analytical HPLC system (Waters, USA) in binary mode (flow rate of 1.5 ml/min), a column oven (30 °C), and a diode array detector (λ = 230 nm). An RP C18 column was used for content determination. The HPLC data acquisition and analysis were performed with Millennium 32 software (Waters). The measurements were performed in triplicate. Results were expressed as percent of theoretical content.

2.2.2.4. In vitro dissolution studies of drug-loaded microparticles. In vitro dissolution tests were performed using the USP paddle apparatus (VK7000, VanKel, USA) rotating at 50 rpm. As a dissolution medium, 900 ml of pH 6.8 phosphate buffer thermostated at 37 °C was used. Samples of pure drug and drug-loaded microparticles containing 6 mg of glimepiride were added to the dissolution medium. Samples were taken at predetermined time points and filtered through PVDF (0.45 μm) filter. Amount of dissoluted drug was determined spectrophotometrically at 228 nm against polymer carrier as blank. The measurements were performed in triplicate.

2.2.2.5. Determination of solubility enhancement of glimepiride. An excess of microparticles, corresponding to 12 mg dose of the drug was added into a beaker containing 100 ml of pH 6.8 phosphate buffer. The samples were magnetically stirred at 25 °C for 120 min, then filtered through PVDF filter (0.45 μm). The filtrates were analyzed spectrophotometrically at 228 nm against polymer carrier as blank. In case of drug-loaded microparticles with Gelucire 50/13 the

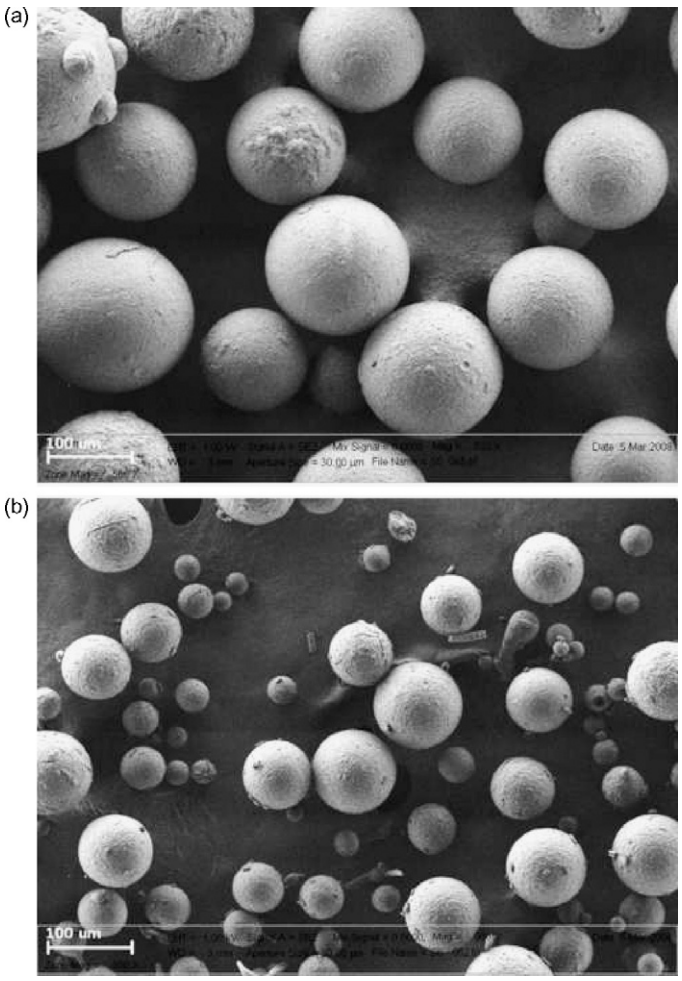

Fig. 1. SEM picture of microparticles: (a) with particle size from 125 to 500 μm (useful fraction; sample A2); (b) with particles smaller than 125 μm (bottom fraction; sample A2).

samples were centrifuged at 20.000 rpm for 15 min before filtration. The measurements were performed in triplicate.

3. Results and discussion

3.1. Study of the influence of atomizing pressure and liquid feed rate on drug-free microparticle size

3.1.1. The influence of atomizing pressure on microparticle size distribution and process yield

Fig. 1 represents SEM pictures of the useful fraction (Fig. 1a; microparticle size 125–500 μm) and bottom fraction (Fig. 1b; microparticles smaller than 125 μm). The SEM pictures show that the product microparticles have an ideal spherical shape with relatively smooth surfaces. Most of the product consists of primary particles. The SEM pictures also confirm that the particle sizes of the useful and bottom fractions are consistent with the sieve mesh sizes

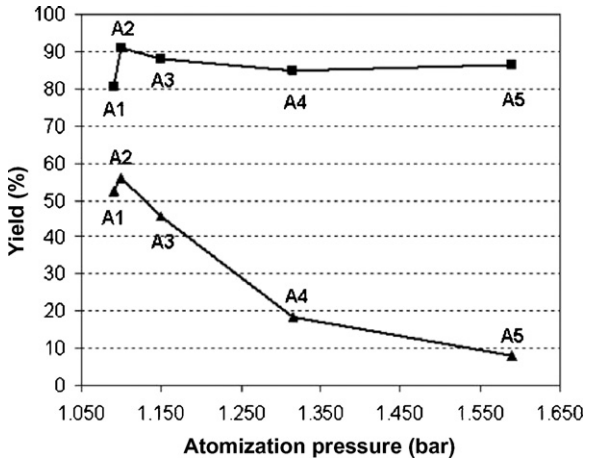

Fig. 2. Influence of atomization pressure on total and useful yield at a liquid feed rate of 6.0 ml/min: (■) total yield; (▲) useful yield.

used for sieve analysis. This means that sieving is an appropriate method for separating microparticles.

The influence of atomizing pressure was studied in a series of five batches produced under the same conditions (liquid feed rate 6.0 ml/min) except for varying atomizing pressures: 1.090, 1.100, 1.150, 1.315, and 1.590 bar in experiments A1, A2, A3, A4, and A5, respectively. The particle size measurements of these batches using laser diffraction are given in Table 1. Median particle size measured as $d_{(0.5)}$ is reduced from approximately 280 to 60 μm with an increase of atomizing air pressure from approximately 1.1 to 1.6 bar, respectively. This means that higher atomizing pressures lead to the production of smaller microparticles. Higher atomizing pressures result in higher air velocities at the exit of air through the nozzle orifice. This increases the input of kinetic energy to the liquid and the increase of shear-stress resulting in a smaller microparticle size. Some authors refer to this as the air-to-liquid mass ratio (Schaefer and Worts, 1978; Wan et al., 1995), whereby higher atomizing pressures increase the air-to-liquid mass ratio.

Span ($(d_{(0.9)} - d_{(0.1)})/d_{(0.5)}$) represents a measurement of the width of size distribution, whereby a higher span indicates a wider distribution. The span values for all batches are around 2.0 except for batch A3, for which the microparticle size distribution seems to be slightly narrower. No significant difference in span (*t*-test with $\alpha = 0.05$) can be observed between batches A1 and A5, which are the batches in which the lowest and the highest atomizing pressures were used. This means that the width of microparticle distribution does not change with varying atomizing pressures; only median particle size is influenced by these variations.

The influence of atomizing pressure on the total and useful process yield is presented in Fig. 2. A steady drop in useful yield is observed with increasing atomizing pressure. According to the results of particle size determination, higher atomizing pressure as a process parameter results in smaller droplets and, consequently, microparticle size, which contributes to the drop in the useful yield. The total yield of the process depends on the process parameters and conditions during spray congealing; however, it also depends on product loss, which is more or less constant. This constant loss

Table 1
Influence of atomizing pressure on particle size distribution of microparticles (average ± *SD*; *n* = 3).

	Batch				
	A1	A2	A3	A4	A5
$d_{(0.1)}$ (μm)	64.7 ± 3.7	72.5 ± 14.2	47.9 ± 3.9	25.0 ± 2.7	20.1 ± 1.3
$d_{(0.5)}$ (μm)	278.2 ± 12.0	256.4 ± 28.2	126.5 ± 4.6	78.6 ± 5.6	58.3 ± 7.7
$d_{(0.9)}$ (μm)	607.3 ± 37.3	574.9 ± 45.7	260.1 ± 14.9	181.8 ± 9.7	141.6 ± 26.4
Span	1.95 ± 0.06	1.97 ± 0.10	1.68 ± 0.06	2.00 ± 0.11	2.07 ± 0.17

Fig. 3. Worm-like or needle-like particles produced at unsatisfactorily low atomization pressure (at 1.050 bar).

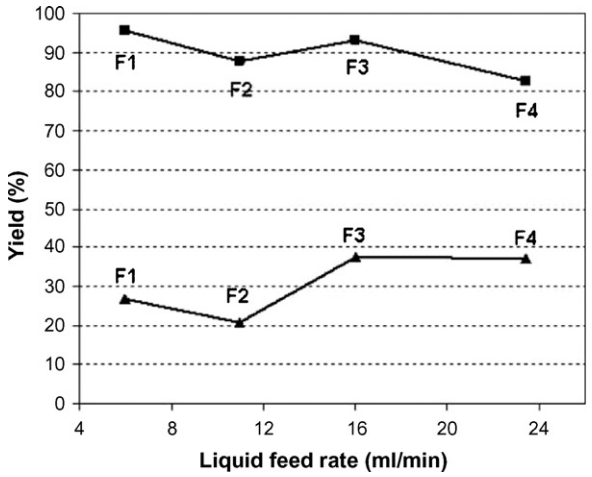

Fig. 4. Influence of liquid feed rate on total and useful yield at atomizing pressure of 1.440 bar: (■) total yield; (▲) useful yield.

is associated with the mass of molten material that is not atomized into the cooling chamber. Part of the molten material is always left in the feed tubing and liquid feed line in the nozzle. The mass of this material is roughly estimated at 5–10 g in our experiments. One of the parameters influencing total yield is the droplet size. For a given liquid feed rate and composition, the cooling capacity is fixed. The amount of energy that needs to be removed from molten droplets is equal to the latent heat of solidification, which depends only on the liquid feed rate at a certain composition. Smaller droplets have larger contact surfaces with the cooled air in the process chamber, so the heat transfer that is required to solidify droplets is expected to be faster. In the case of larger droplets, the heat transfer is expected to be slower and cooling residence time must be prolonged (i.e., larger chamber dimensions); otherwise the molten liquid will not completely solidify before contact with the cooling chamber wall. Large droplets of molten material at given chamber dimensions lead to the formation of undesired product in the form of a crust on the inside of the chamber wall, which decreases the total process yield value. This is evident when atomizing pressure is decreased below 1.1 bar (batch A1, Fig. 2). If atomizing pressure is decreased further (below 1.070 bar), a rapid drop in total process yield can be expected due to the formation of a thicker crust. At such conditions the formation of worm-like or needle-like non-spherical product was observed (Fig. 3).

Ideally, atomizing pressure should be optimized for best manufacturing performance; this is also supported by the literature (Maschke et al., 2007). When large particles are preferred, atomizing pressure should be a compromise between particle size and total process yield value.

3.1.2. Influence of liquid feed rate on microparticle size distribution and process yield

The influence of the liquid feed rate was studied in a series of four batches produced under the same conditions (atomizing pressure of 1.440 bar) except for varying liquid feed rates: 6.0 ml/min, 11.0 ml/min, 16.0 ml/min, and 23.4 ml/min in experiments F1, F2, F3, and F4, respectively. The particle size measurements of these batches are shown in Table 2. Median particle size increases from approximately 84 to 140 μm with the increase of liquid feed rate from 6.0 to 23.4 ml/min, respectively. All other parameters being equal, a higher liquid feed rate increases microparticle size in the spray congealing process as the air-to-liquid mass ratio decreases. However, the influence of the liquid feed rate on microparticle size is not as pronounced as the influence of atomizing pressure, for which larger differences in microparticle size were observed.

The influence of the liquid feed rate on the total and useful process yield values is presented in Fig. 4. An increase in the liquid feed rate shows a trend of increasing useful yield from 27% to 37% for batches F1 and F4, respectively. Regarding the influence of the liquid feed rate on the total yield, a decreasing trend is observed as the feed rate is increased. A similar conclusion as for atomizing pressure can be made. At higher liquid feed rates using constant atomizing pressure, the droplets are larger and some of them are unable to solidify before contact with the chamber wall. Furthermore, a greater amount of molten material must be solidified with an increased liquid feed rate, while the air cooling capacity is kept at its maximum in all the experiments. A crust of unsatisfactory product is created on the inside of the cooling chamber, which lowers the total process yield. It was noticed that the crust was wider and thicker at higher feed rates, which is the reason for lower total yield values at these conditions.

Our results lead to the conclusion that greater variation and control of microparticle size can be obtained by changing the atomizing pressure at a fixed liquid feed rate rather than by changing the feed rates at a constant atomizing pressure.

3.2. Characterization of glimepiride-loaded microparticles

3.2.1. Particle size and morphology of glimepiride-loaded microparticles

SEM pictures of glimepiride-loaded microparticles show that the product consists of primary and agglomerated particles with spherical shapes and relatively smooth surfaces (Fig. 5). No drug

Table 2
Influence of liquid feed rate on particle size distribution of microparticles (average ± *SD*; *n* = 3).

	Batch			
	F1 (6.0 ml/min)	F2 (11.0 ml/min)	F3 (16.0 ml/min)	F4 (23.4 ml/min)
$d_{(0.1)}$ (μm)	21.1 ± 1.4	30.4 ± 2.2	32.0 ± 4.6	38.0 ± 2.1
$d_{(0.5)}$ (μm)	84.2 ± 5.4	107.7 ± 9.7	126.0 ± 8.3	139.6 ± 2.1
$d_{(0.9)}$ (μm)	308.8 ± 27.3	357.0 ± 40.5	434.2 ± 38.6	450.5 ± 7.4

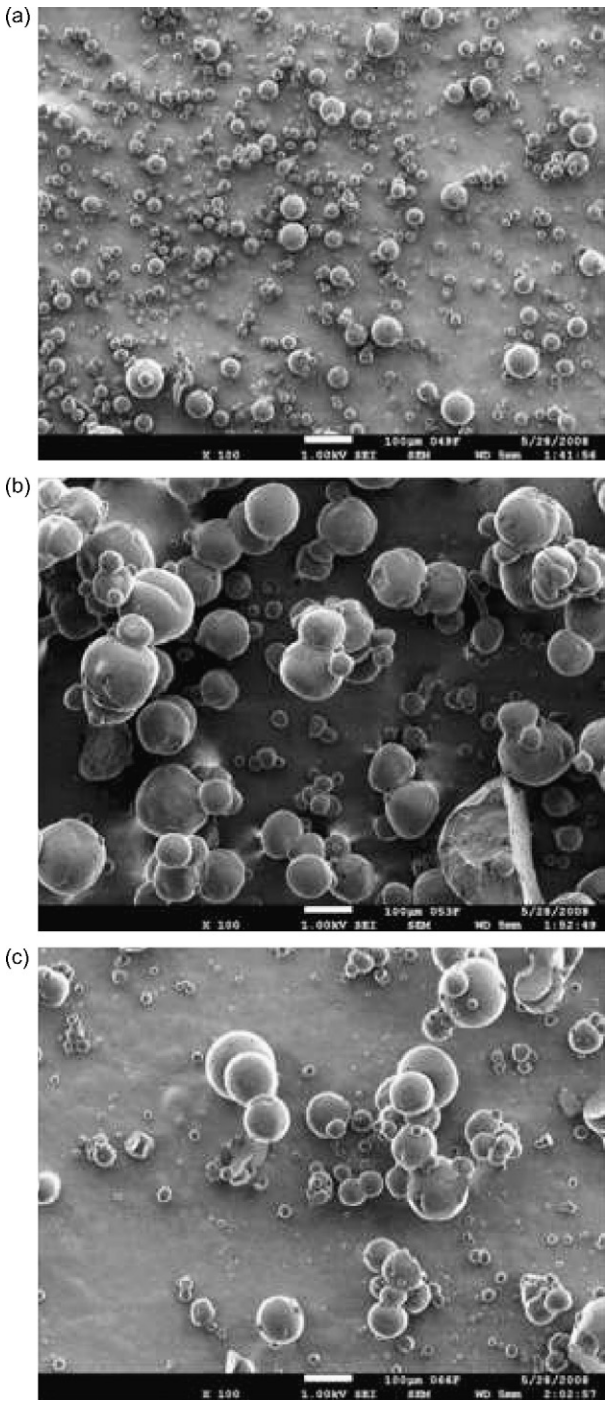

Fig. 5. SEM pictures of glimepiride-loaded microparticles with: (a) Gelucire® 50/13; (b) poloxamer 188; and (c) PEG 6000 as carrier materials.

crystals of glimepiride have been identified on the surface of drug-loaded microparticles. Microparticles made with poloxamer 188 and PEG 6000 as carriers were larger, despite higher air-to-liquid mass ratios used for their production compared to Gelucire® microparticles. This can be attributed to higher viscosity of molten poloxamer 188 and PEG 6000 compared to Gelucire® 50/13 melt (Vilhelmsen et al., 2005).

3.2.2. XRPD analysis of glimepiride and glimepiride-loaded microparticles

Fig. 6 shows the XRPD patterns of pure glimepiride, drug-loaded microparticles with all carriers and their corresponding physical

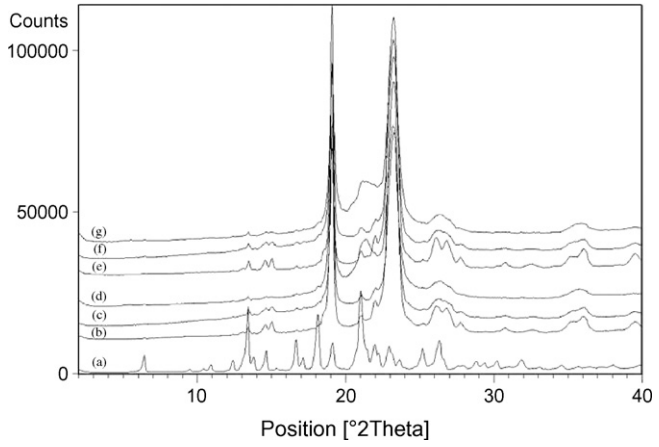

Fig. 6. XRPD diffractograms of: (a) pure glimepiride; (b) glimepiride/PEG 6000 microparticles; (c) glimepiride/poloxamer 188 microparticles; (d) glimepiride/Gelucire® 50/13 microparticles; (e) glimepiride/PEG 6000 physical mixture; (f) glimepiride/poloxamer 188 physical mixture; and (g) glimepiride/Gelucire® 50/13 physical mixture.

mixtures. Pure glimepiride is in crystalline form, as demonstrated by the sharp and intense diffraction peaks (Fig. 6a) corresponding to form I of the drug (Iwata et al., 1997). Diffractograms of glimepiride-loaded microspheres exhibited typical signals for carriers and are in agreement with the literature (Perissutti et al., 2000; Fini et al., 2005). Low-intensity peaks (at 13.4°, 16.6°, 18.2°, and 21.1° of 2θ) in diffractograms of physical mixtures and microparticles correspond to form I of glimepiride. The low intensity of these peaks reflects the low drug concentration in measured samples. Comparison of diffractograms of microparticles (Fig. 6b–d) with their physical mixtures (Fig. 6e–g) shows that they have analogous low-intensity peak patterns with comparable intensity of the peaks. Peak diffraction angles of microparticles were substantially identical to those of physical mixtures. It can be assumed that the crystallinity of the drug was not essentially reduced by the technological procedure used.

3.2.3. Drug content, dissolution and solubility enhancement

The actual drug content of glimepiride in microparticles was 99.7% ± 0.1%, 99.7% ± 0.2% and 101.4% ± 0.1% of theoretical drug content (1.7%, w/w) for microparticles with Gelucire 50/13, PEG 6000 and poloxamer 188, respectively. This means that during microparticle preparation using spray-congealing process the drug distribution in molten dispersion is uniform and that actual drug content can be expected to be equal to theoretical value.

The dissolution of drug-loaded microparticles was performed to evaluate the influence of the carrier used on the improvement of dissolution of glimepiride (Fig. 7). The highest amount of dissolved glimepiride was obtained using Gelucire 50/13 at 35.6% after 120 min, followed by poloxamer 188 and PEG 6000 with 29.0% and 28.6%, respectively. Amount of pure glimepiride dissolved stayed just below 10%. Gelucire 50/13 was also the carrier which offered fastest dissolution rate by reaching the maximum release in the dissolution profile at 5 min. In case of poloxamer 188 and PEG 6000 maximum release was obtained after 15 and 30 min. All microparticles exhibited noticeably better dissolution profiles than pure glimepiride, regarding both the amount of dissolved drug as well as dissolution rate. From the three carrier materials tested, Gelucire 50/13 has the best dissolution improvement results, while poloxamer 188 and PEG 6000 do not differ much between each other. In the dissolution profiles decrease of dissolved drug can be observed in case of all three carriers. This can be attributed to supersaturation effect with consequent partial precipitation of the drug. Amounts of dissolved drug then slowly increase with time to the

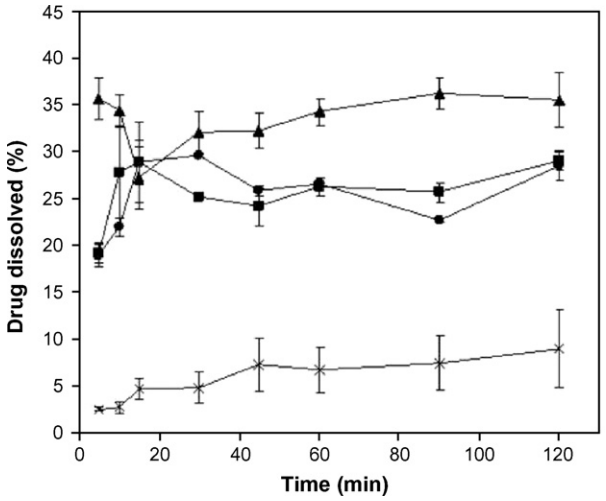

Fig. 7. Dissolution profiles for: (▲) glimepiride/Gelucire® 50/13 microparticles; (●) glimepiride/poloxamer 188 microparticles; (■) glimepiride/PEG 6000 microparticles; (×) pure glimepiride in phosphate buffer pH 6.8.

peak concentrations of drug which were achieved at early sampling times.

Glimepiride is a poorly water-soluble drug with reported solubility in aqueous media with pH 7.0 of 0.0012 mg/ml (Frick et al., 1998; Endo et al., 2003). Our measured solubility of pure glimepiride in pH 6.8 buffer was 0.00087 mg/ml. Solubility of glimepiride using drug-loaded microparticles was also measured, because it is expected that solubilizing carrier materials may improve concentration of the drug in the solution. Measured concentrations of glimepiride from Gelucire 50/13, poloxamer 188 and PEG 6000 microparticles were 0.0084 mg/ml, 0.0047 mg/ml and 0.0048 mg/ml, respectively. These improvements in solubility represent about 10-fold increase of solubility using Gelucire and about 5-fold increase using poloxamer 188 and PEG 6000.

All microparticles exhibited an improvement in solubility compared to pure glimepiride, which can be attributed to the effect of the carriers: improved wetting and solubilization of glimepiride. Display of surface-active properties seems to be more expressed with Gelucire® 50/13 compared to the other two carriers because this carrier increases the solubility more than PEG 6000 and poloxamer 188. Therefore, microparticles with Gelucire® 50/13 represent the most promising approach to increasing nonequilibrium solubility and enhancing the dissolution rate of glimepiride in the future development of solid dosage forms.

3.2.4. Influence of storage on morphology of glimepiride/Gelucire® 50/13 microparticles

The surface morphology of glimepiride/Gelucire® 50/13 microparticles was examined using SEM after storage in an open container at 30 °C and 65% relative humidity for 30 days. The microparticle surface structure before storage (Fig. 8a) and after storage (Fig. 8b) was found to be distinctively different: before storage the surfaces of the microparticles were homogeneous and smooth, but after 30 days of storage leaf-like structures were found on the surfaces. This may be attributed to the polymorphic transformation of crystallized triglycerides on the surface of microparticles; that is, the α to β transformation of fats upon storage which was reported by Garti and Sato (1988). This is not unusual because Gelucire® is a lipid-based excipient composed of mixtures of polyethylene glycol esters of fatty acids and glycerides. In the literature this phenomenon is referred to as "blooming" and has already been reported to occur with Gelucire® 50/13 during storage at elevated temperatures (Khan and Craig, 2004).

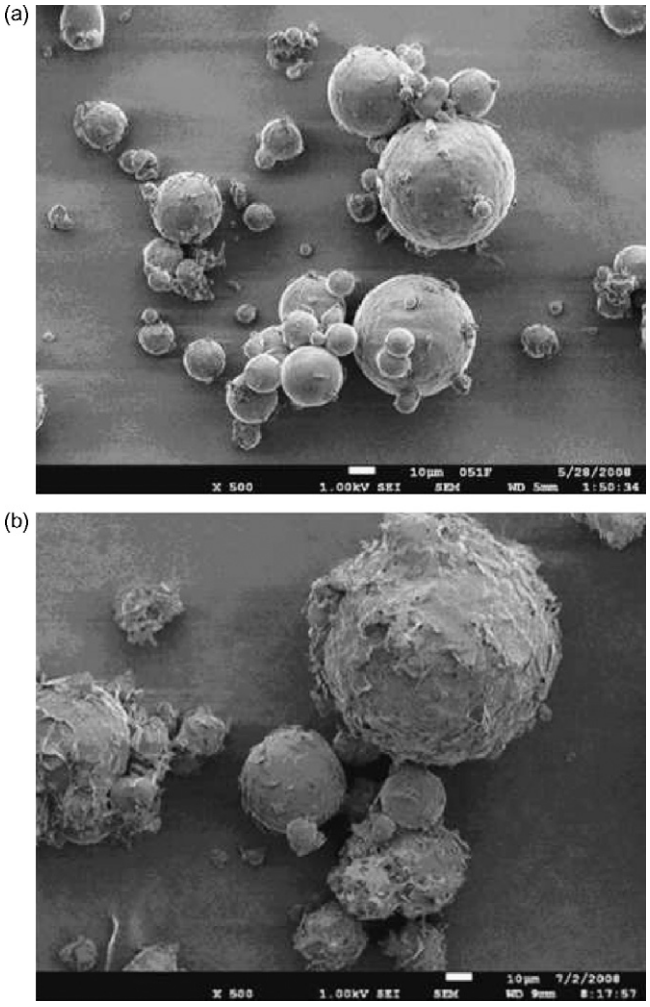

Fig. 8. SEM pictures of: (a) freshly prepared glimepiride/Gelucire® 50/13 microparticles; (b) glimepiride/Gelucire® 50/13 microparticles stored in open container at 30 °C and 65% relative humidity.

4. Conclusion

Reasonably large batches (up to 100 g) of drug-free microparticles from Gelucire® 50/13 were successfully prepared with relatively high total process yields (up to 95%) using laboratory equipment and the spray congealing process. SEM showed that the product consists mainly of primary microparticles of ideal spherical shape with smooth surfaces. The influence of the liquid feed rate and atomizing pressure on microparticle size showed that higher atomizing pressures decrease the microparticle size and vice-versa. A higher liquid feed rate was also found to increase particle size; however, greater control of microparticle size can be obtained by changing the atomizing pressures.

It has been shown that spray congealing could be used to prepare glimepiride-loaded microparticles of spherical shape and smooth surfaces with various hydrophilic carrier materials – Gelucire® 50/13, poloxamer 188, and PEG 6000. XRPD of pure glimepiride and microparticles show the presence of form I polymorph of the drug and no evident change in crystallinity was detected due to the technological process of microparticle preparation. Dissolution and solubility enhancement tests showed that Gelucire® 50/13 is the most suitable carrier for improvement of dissolution rate and solubility of this poorly water-soluble drug. Spray congealing is a promising manufacturing method to be employed and developed for industrial-scale microparticle preparation. It is expected to gain

widespread use due to the recent growing interest in melt technologies, especially for taste masking, sustained and controlled release, and API solubility enhancement.

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