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Preparation of microspheres containing low solubility drug compound by electrohydrodynamic spraying

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ABSTRACT

Micro- and nanoparticle formulations are widely used to improve the bioavailability of low solubility drugs. In this study, electrospraying is introduced as a method for producing drug-loaded microspheres at ambient conditions. PLGA microspheres containing celecoxib, a low solubility drug, were prepared with the objective of producing near-monodisperse microspheres with the drug in a stable amorphous form. We found that it is possible to produce near-monodisperse celecoxib-loaded PLGA microspheres at different polymer:drug ratios. The microspheres produced were in the size range 1–5 μm depending on the polymer:drug ratio and had smooth surfaces. Thermal analysis further indicates that celecoxib is present in an amorphous form inside the microspheres. Drug dissolution studies showed an initial burst release followed by a period of sustained release with the dissolution curve depending on the polymer:drug ratio. Electrospraying is thus a promising method for producing amorphous microspheres of low solubility drugs such as celecoxib. The microsphere properties may be further optimized to achieve an appropriate dissolution profile with the aim of increasing oral bioavailability of low solubility drugs.

1. Introduction

Low solubility drugs account for an estimated 40% of all new drugs developed and present a universal challenge for the drug development industry (Lipinski, 2002). A general problem with low solubility drugs is their insufficient bioavailability, which often results in unsatisfactory consequences for patients. It is known from the Noyes–Whitney equation that a reduction in the drug particle size scale increases its dissolution rate and thereby enhances the bioavailability of the drug (Hörter and Dressman, 2001; Noyes and Whitney, 1897). Numerous methods exist for producing such small particles and many of these are used in drug formulation, with the most commonly used methods being solvent evaporation from emulsions, wet/dry milling, precipitation, and spray drying (Billon et al., 2000; Horn and Rieger, 2001; Kesisoglou et al., 2007; Nornoo et al., 2009; Rabinow, 2004). Although these particle generating techniques are successfully used, each of them has their disadvantages and may not be suitable for certain compounds or applications (Kesisoglou et al., 2007; Zgoulli et al., 1999). Another route to increasing the drug dissolution rate is by preparing the drug in an amorphous form. Drugs in the amorphous form have higher Gibbs free energy than stable crystal forms and thereby also have higher drug dissolution rates than the corresponding crystalline drugs. However, amorphous drugs are generally also less stable than crystalline drugs and can be difficult to keep amorphous even under appropriate storing conditions (Yu, 2001).

Electrospraying is an attractive technique for preparing particles in nano- to meso-scale and is suitable for use in drug delivery systems as well as many other applications (Pareta and Edirisinghe, 2006; Reyderman and Stavchansky, 1995; Xie et al., 2006; Xu and Hanna, 2006). Electrospraying makes use of a strong electric field to break up a liquid containing the material of interest into a continuous stream of finely dispersed particles in a one step process. Enayati et al. (2011), Hayati et al. (1986) and Jaworek (2007) provide details on the background of the electrospraying process for producing particles. The size and surface morphology of particles produced by electrospraying can be controlled to some extent, by adjusting the operation and formulation parameters. There are generally notable advantages in using electrospraying in comparison with conventional preparation methods. Firstly, it is a one-step process that does not make use of any template or surfactants and is performed at ambient temperature and pressure. Moreover, near-monodisperse particles can be produced under controlled conditions (Edirisinghe and Jayasinghe, 2004).

Poly-lactic-co-glycolic acid (PLGA) is widely used as a carrier material in drug delivery systems due to its biocompatibility and its degradation into glycolic acid and lactic acid within the body (Klose et al., 2008). PLGA has previously been used together with electrospraying for drug delivery purposes with successful production

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of particles (Enayati et al., 2010). In this article electrospraying is presented as a method for preparing PLGA micro-particles containing the drug celecoxib (CEL), an alternative approach to increase the dissolution rate of low solubility drugs. CEL was used as a model drug in the present work due to its very low aqueous solubility (5 μg/mL) and because it is well described in literature and safe to work with (Chawla et al., 2003). CEL is a non-steroidal, anti-inflammatory drug or, more specifically, a selective cyclooxygenase-2 (COX-II) inhibitor, which is widely used for the treatment of osteoarthritis, rheumatoid arthritis and acute pain (Thakkar et al., 2004). It is weakly acidic with a pKa of 11 and typically comes as a crystalline powder. There are more than 4 types of CEL crystalline polymorphs of which type III with characteristic needle-shaped crystals is the most stable. CEL is associated with undesirable properties such as cohesiveness, low compressibility and bulk density and it is found that increasing the dissolution rate of CEL improves its oral bioavailability (Chawla et al., 2003; Dolenc et al., 2009; Paulson et al., 2001). The purpose of with mixing PLGA and CEL is to try preventing a possible agglomeration and crystal growth of CEL in the produced particles.

There have been many studies in which CEL micro-/nano- particles have been produced using various techniques such as emulsion or milling. However, to our best knowledge CEL particles have never been prepared using electrospraying. Although electrospraying has been used to prepare many types of drugs ranging from peptides to small molecule drugs it is not known whether CEL can be sprayed and stay in amorphous form or if it will precipitate into crystalline structures. Furthermore, it is not known how the CEL will interact with PLGA and how they will be distributed within the prospective particles prepared using electrospraying. The overall objective of this study was to examine whether electrospraying is a suitable technique for preparing near-monodisperse polymer micro-spheres containing a low solubility drug.

2. Materials and methods

2.1. Materials

Celecoxib crystalline powder was acquired from Dr. Reddy, Hyderabad, India (Mw = 381.38 g/mol). Poly(D,L-lactide-co-glycolide) (PLGA; 50:50 Resomer RG503H, Mw = 33 000 kDa) was purchased from Boehringer Ingelheim (Ingelheim, Germany). Acetone (99.9% HPLC grade) and acetonitrile (99.9% HPLC grade) were purchased from Sigma–Aldrich (Poole, UK).

2.2. Preparation and characterization of solutions

Spraying solutions with PLGA and CEL were prepared by adding PLGA and/or CEL to acetone and stirring using a magnetic stirrer until a clear solution was formed. Five spraying solutions (S1–S5) with different ratios of PLGA and CEL were prepared, all with a total solute content of 5% (w/v). The spraying solutions were characterized to measure liquid properties such as surface tension, viscosity and density, all at ambient temperature (20–25 °C). Viscosity was measured using a U-tube viscometer (75 mL Cannon-Fenske Routine Viscometer, Cannon Instruments, USA), Surface tension was determined using a Kruss tensiometer (Model-K9, Kruss GmbH, Germany) and densities were calculated from the literature (Smallwood, 1996; Arnold et al., 2007; Chawla et al., 2003). Both the viscometer and tensiometer were calibrated before measurement using either ethanol or distilled water where values are known.

2.3. Particles preparation

Particles were prepared using a single-nozzle electrospraying setup where particles are generated from a single jet (see Fig. 1). The spraying system consisted of three main components, a voltage power source (Glassman Europe Ltd., Tadley, UK) with a high voltage output, a mechanical syringe pump (PHD 4400, Harvard Apparatus, Edenbridge, UK) with a high precision, adjustable flow rate, and a custom built, concentric stainless steel nozzle with outer and inner diameters of 2.34 mm and 1.77 mm respectively. Once the drug and polymer were fully dissolved in the solvent, the solution was loaded into a 5 mL syringe and placed onto the pump. The pump then fed the liquid through silicone tubing and into the nozzle where a jet was formed at the tip of the nozzle by manipulation of the electric voltage. The particles generated from the liquid jet were collected either onto a microscope slide containing distilled water or onto a sheet of aluminium foil, depending on the analysis technique later applied on the particles. The particles were then left to dry in a desiccator under slight vacuum. A video camera with an in-built magnifying lens (Leica S6D JVC-color) was used to observe the nozzle tip at all times during collection of particles in order to ensure a stable cone jet. The system operation parameters; flow rate, collection distance and voltage, were used to partly control particle formation. The flow rate and collection distance influenced particle size and solvent evaporation and the voltage was set at a window where a stable jet was achieved. All samples were sprayed

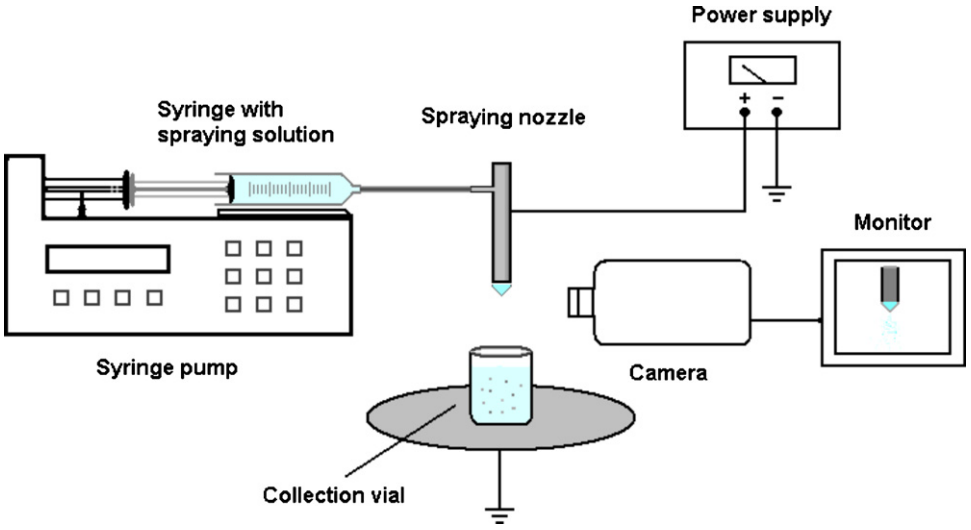

Fig. 1. Schematic illustration of the electrospraying set-up used for particle preparation.

at a flow rate of 20 μL/min, collection distance of 50 mm from the nozzle end and at a voltage between 11 and 13 kV.

2.4. Characterization of particle morphology and size

The structural features of the particles were determined using scanning electron microscopy (SEM) (JEOL JSM-6301F field emission scanning electron microscope) and optical microscopy (Nikon Eclipse ME-600 with a CCD camera JVC KY-F55B). For SEM, the dry particle sample was sputter- coated with gold for 90 s and then viewed under the SEM at an accelerating voltage of 3–10 kV. The images obtained were used to calculate the mean diameter and polydispersivity index of the different particle samples. For each sample 200 particles were measured from different areas of the sample.

2.5. Dissolution studies

A UV spectrophotometer (Perkin-Elmer, model number) was used to measure the UV absorption peak of CEL at 250 nm using appropriate calibration and blanking procedures before the measurements. The CEL loading efficiency of the particles was found by quantifying the entrapped celecoxib. A weighed amount of microspheres was suspended in acetonitrile, mixed thoroughly at ambient temperature for 24 h to dissolve the drug and polymer, and diluted to a concentration of 10 μg/mL CEL in acetonitrile. The CEL UV absorbance was then measured at 250 nm and the leading efficiency was estimated as

$$\%\ \text{loading efficiency} = \frac{\text{amount of drug in the microspheres}}{\text{drug added}} \times 100$$

Dissolution studies were performed by dispersing dry particle samples (6 mg) in 30 mL release medium, kept at ambient temperature and under continuous stirring. A 50:50 volume ratio mixture of ethanol and water was used as release medium. At discrete time intervals 3 mL was removed from the samples and centrifuged at 4000 rpm for 20 min. The supernatant was removed and diluted to give an expected CEL concentration of 10 μg/mL and UV absorbance was measured at 250 nm. Four measurements were done for each particle sample and the mean absorbance value was found. The measurements were done over 10 days and the data were adjusted with appropriate calibration and blanking procedures.

2.6. Thermal analysis

Differential scanning calorimetry (DSC) was used here to gain information on the physical state of the drug and polymer components of the prepared particles and any interaction between the two. The DSC analyses were performed using a Netzsch STA 449 C *Jupiter* (Netzsch, USA) instrument together with software, Proteus. Particles were prepared for DSC and the dried samples (~10 mg) were analyzed under a helium purge (50 mL/min) in open aluminium pans. Samples used as reference were the original CEL powder and PLGA powder and a mixture of these at ratios (1:1 and 1:4). The samples were all heated from 10 °C to 200 °C at a rate of 10 °C/min. Thermogravimetric analysis (TGA) was performed simultaneously with the DSC measurement to verify a relatively constant mass over the measurement and no significant amount of remaining acetone in the particle samples.

3. Results and discussion

Previous studies have demonstrated that physico-chemical properties of electrosprayed particles are dependent on both the system operation parameters and formulation of the spraying solution (Enayati et al., 2009; Gañán-Calvo et al., 1997; Lastowa and Balachandran, 2006). Based on known information, some operation parameters (including voltage, flow rate, collection distance) and the total solute concentration of the spraying solution were examined empirically prior to this study in order to optimize the collection of dry, monodisperse particles. After fixing these parameters, electrosprayed PLGA–CEL particle were studied using different ratios of PLGA and CEL to demonstrate how this ratio can influence the properties of the particles.

Table 1
Characteristics of spraying solutions prepared. Values for viscosity indicate mean ± std. dev.

Solution	%CEL	%PLGA	Density (kg/m^3)	Surface tension ($mN\,m^{-1}$)	Viscosity (mPa s)
Acetone	–	–	793	25	0.32 ± 0.005
S1	5	0	814	25	0.37 ± 0.005
S2	2.5	2.5	813	25	0.67 ± 0.011
S3	1	4	813	25	0.93 ± 0.014
S4	0.5	4.5	812	25	1.00 ± 0.009
S5	0	5	812	25	1.10 ± 0.024

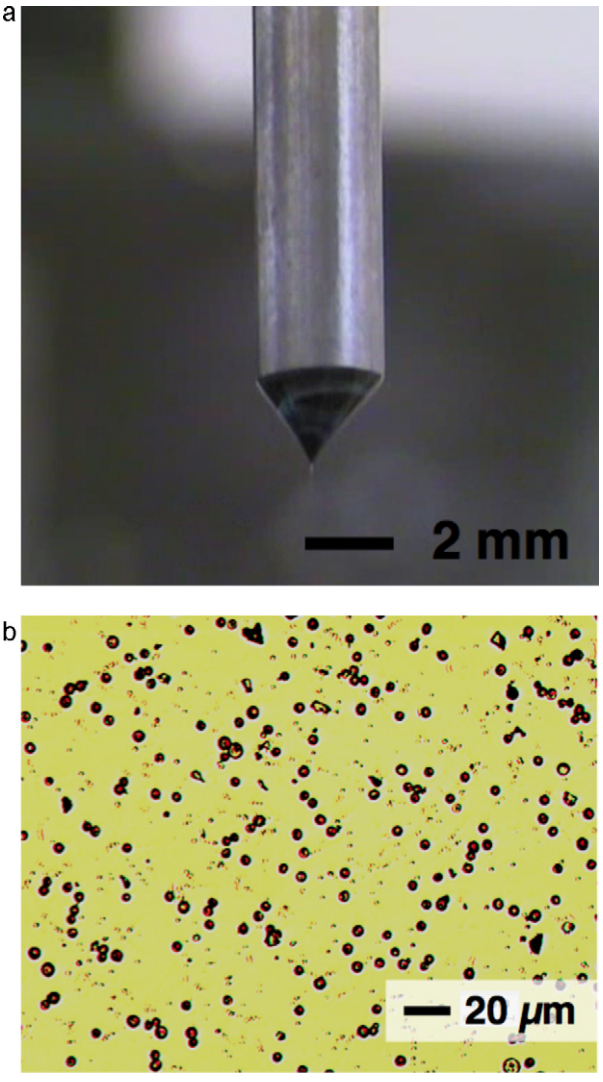

Fig. 2. Image of stable cone-jet taken with high speed camera (a) and optical microscopy image of particle structures produced from S1 (b).

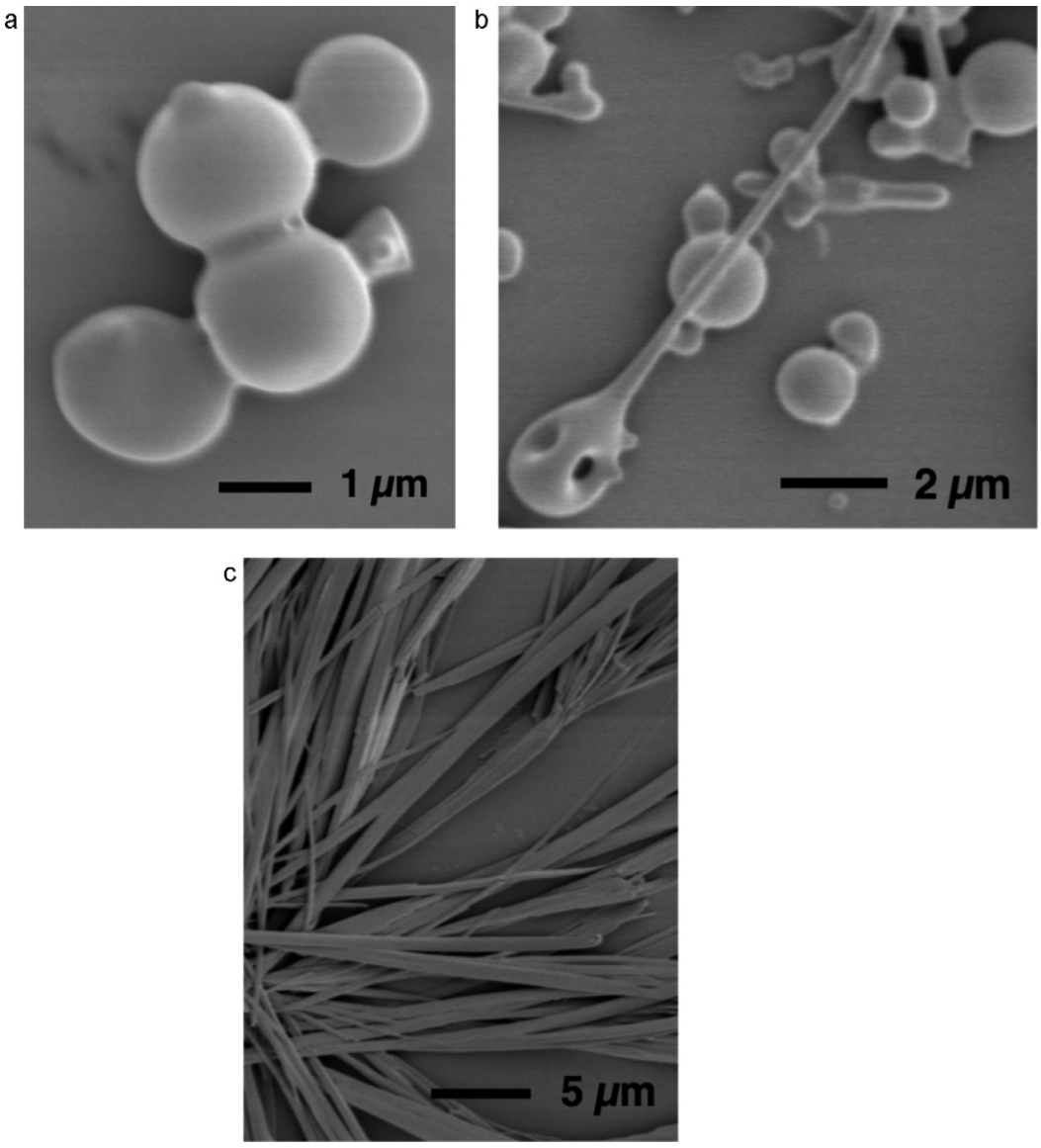

Fig. 3. SEM images of CEL particles (S1) collected in water (a) and without water (b and c).

3.1. Particle formation

The properties of the spraying solutions are shown on Table 1. It is observed that the density and surface tension of the spraying solutions are similar and small differences observed therefore do not seem to play a significant role in the spraying process. However, the viscosity of the solutions varies considerably and differs more than three-fold between the lowest and highest value. An increase in the amount of PLGA added results in an increase in viscosity while the CEL content does not influence the viscosity to the same degree. Properties of the spraying solutions also depend on the solvent used and are therefore linked with the inherent properties of acetone. Some of these properties may have a major influence on the "sprayability" of the solvent and will leave an imprint on the resulting particles. Under a given set of operating conditions, the dielectric constant (and equivalently the electric conductivity) of the solvent can have an influence on the size of the particles produced with a higher dielectric constant resulting in smaller particles (Xie et al., 2006). Acetone has a lower dielectric constant (21 at 20 °C) than other solvents commonly used such as N,N-dimethylformamide (37 at 20 °C) or acetonitrile (38 at 20 °C) and is therefore likely to give slightly larger particles (Smallwood, 1996). However, acetone was chosen because of its ability to dissolve PLGA and CEL in high amounts and its low toxicity (class 3 solvent) compared with many other organic solvents capable of dissolving PLGA and CEL (Center for Drug Evaluation and Research, 1997).

The prepared solutions were sprayed using the setup shown in Fig. 1 and it was demonstrated that a cone-jet (see Fig. 2a) can be obtained and that particles are formed from the jet. By varying the particle collection distance different levels of dryness of the particles could be achieved, with more or less no acetone remaining at collection. Collection of samples was done on glass slides containing distilled water to give a cushioning effect and prevent dissolution of particles. This also enabled suitable drying of samples in a desiccator before capturing images using optical microscopy and SEM.

3.2. Particle characteristics

Images taken with the optical microscope (see Fig. 2b) show successful formation of spherical particles, in the order of few micrometers in diameter, generated immediately after spraying without any post-processing. SEM images in Fig. 3 shows relics of

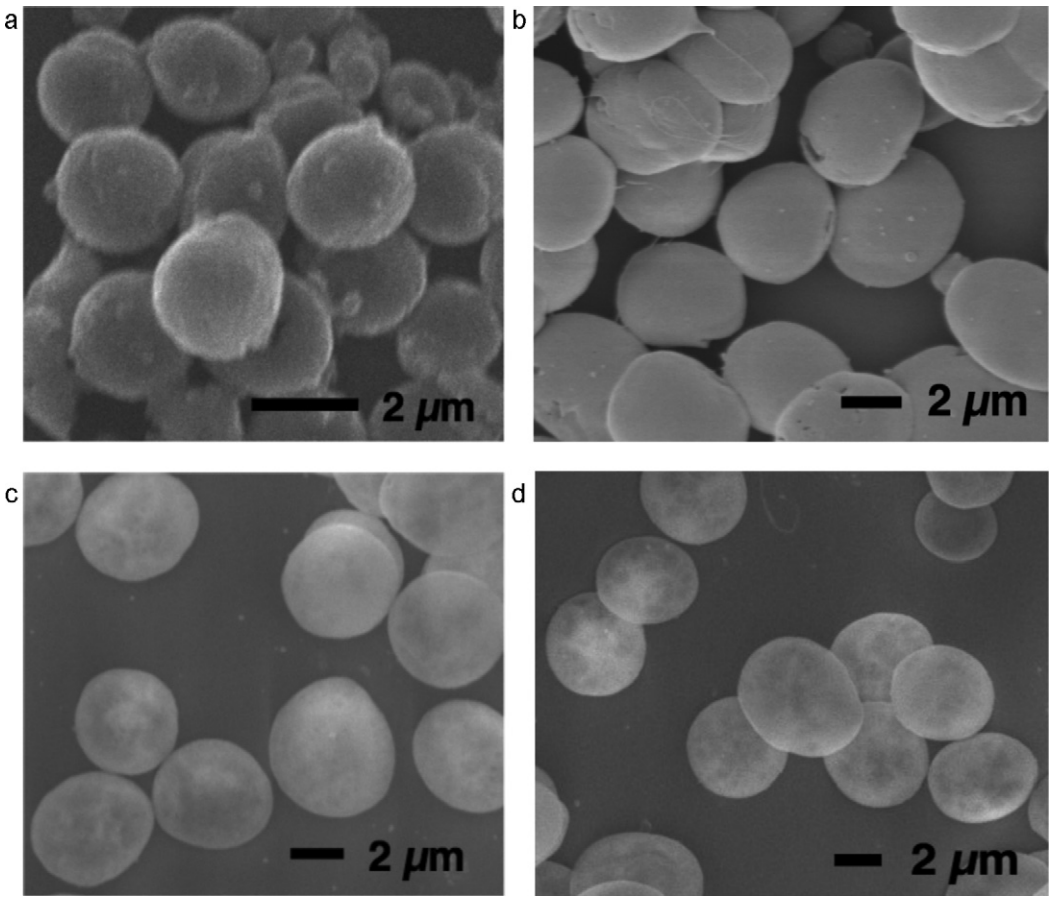

Fig. 4. SEM images of microspheres from samples S2 (a), S3 (b), S4 (c) and S5 (d) collected in water.

CEL sprayed alone and either collected in water (Fig. 3a) or without water (Fig. 3b and c). When collected in water it is seen that the initially particular CEL has crystallized and formed needle-shaped structures. When collected without water some areas showed spherical particles with a smooth surface and other areas showed a combination of spherical particles and particles with fibre-like structures propagating along them, suggesting that crystallization gradually takes place.

Fig. 4 shows SEM images of samples S2 (Fig. 4a), S3 (Fig. 4b), S4 (Fig. 4c) and S5 (Fig. 4d). All of these images show microspheres with smooth surfaces and only few defect structures are present. The characteristic needle-shaped crystal structures of CEL were not observed at the presence of PLGA in the studied ratios. This could be a result of interactions between PLGA and CEL that keeps CEL from mixing with water and crystallizing. PLGA is known for its ability to form interactions with drug molecules and in this case likely through hydrophobic interaction of CEL with hydrophobic segments of the polymeric chains in PLGA (Jeon et al., 2000).

The sizes of the microspheres produced were measured and the values for the mean microsphere diameters are shown in Table 2. Microspheres in S1 have the smallest diameter at 1.2 μm and the largest diameter is found for microspheres in S5 at 4.4 μm. The particle size increases as a function of %PLGA added relative to CEL and is consistent with what is observed for the viscosity of the solutions. An increase in particle size is thus likely to be a result of increase in viscosity of the spraying solution. This result is consistent with what was found by Jayasinghe and Edirisinghe (2002). All particle samples generated were found to be nearly monodisperse with a degree of polydispersity between 7% and 9% except for S1, which was less homogenous. Monodisperse microspheres are desirable in order to achieve a consistent dissolution of the microspheres as well as a reliable release of the drug (Sansdrap and Moës, 1993). Fig. 5a–e shows the size distribution for microspheres of samples S1–S5 and it is seen that all samples have an approximate bell-curve distribution. Based on the observations of SEM images in Fig. 4 PLGA and CEL remain mixed and do not divide into separate particles. Needle-shaped CEL crystals were not visible on the SEM images of samples S2–4 indicating that PLGA inhibits such crystal formation of CEL.

Table 2
Particle sizes obtained and their respective degree of polydispersivity. Number of particles = 200.

Sample	Mean particle diameter (μm)	Degree of polydispersivity (%)
S1	1.2	21.2
S2	2.3	8.6
S3	3.6	9.0
S4	4.3	9.0
S5	4.4	7.4

An additional sample S6 was studied to demonstrate that the collection liquid could have an impact on the surface morphology of the microspheres. Sample S6 has the same material composition as sample S5 but the particles were collected in ethanol instead of distilled water. SEM images of S6 show microspheres that have irregular pores in the nano to submicrometer range on the surface due to a difference in evaporation of the solvent from the polymeric and drug material when collected in ethanol (see Fig. 6). The presence of such pores may aid to further increase the effective surface area of the microspheres and hence increase the dissolution rate of the drug. By changing the system operation parameters, the surface porosity could be tailored to suit the given application and optimize the drug dissolution profile.

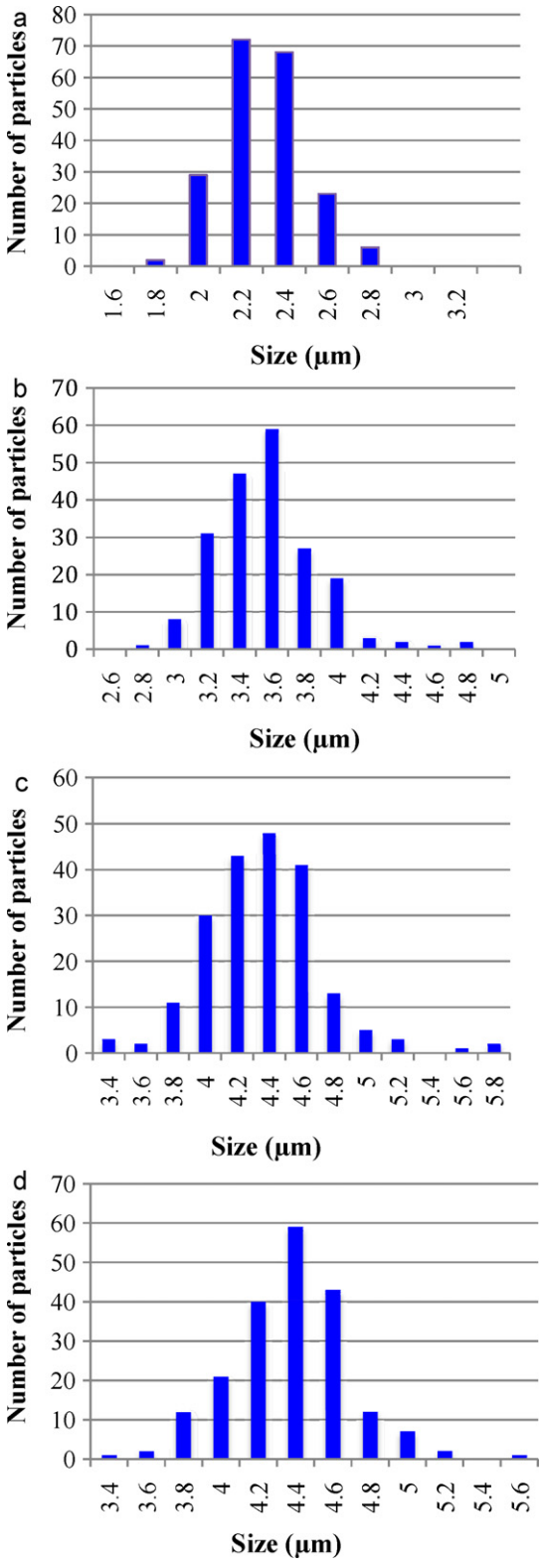

Fig. 5. Size distribution of microspheres from samples S2 (a), S3 (b), S4 (c) and S5 (d).

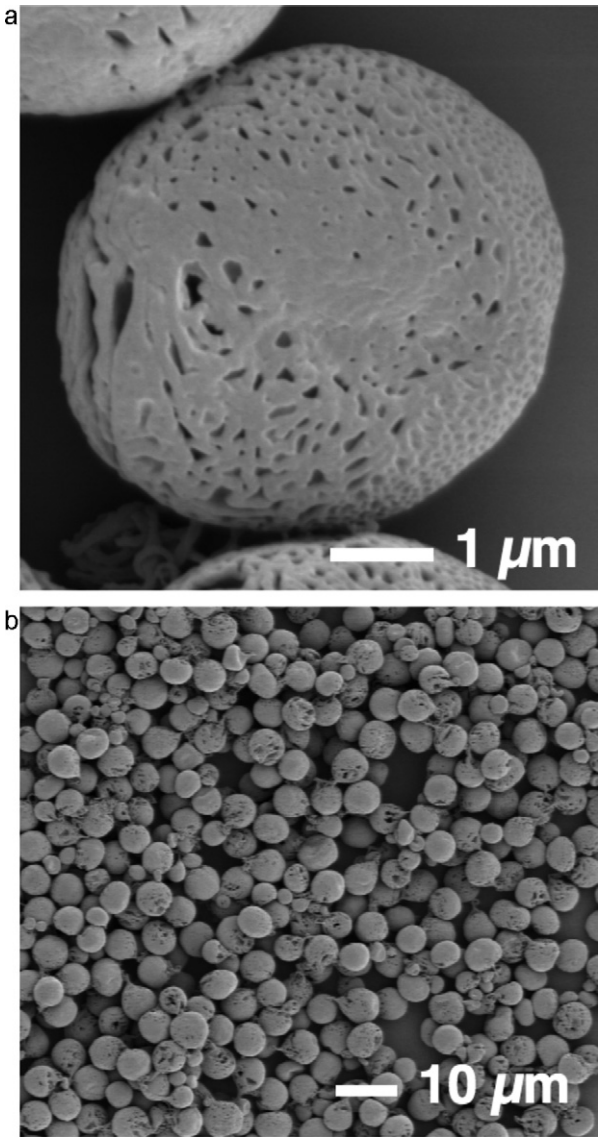

Fig. 6. SEM images of microspheres from sample S6.

3.3. Dissolution studies

Drug release from biodegradable polymeric particles takes place by several mechanisms, which together control the drug release rate. Assuming the particles have a matrix structure, drug release takes place predominantly through (a) desorption of surface bound drug, (b) diffusion of drug through the polymer matrix and (c) erosion of the polymer matrix (Soppimath et al., 2001). For PLGA particles specifically, the surface bound drug results in an initial rapid release due to the large surface area of the particles. Subsequently, diffusion of drug through the PLGA matrix and release of drug from the degradation of PLGA take place (Schliecker et al., 2003).

Measurement of UV absorbance showed that CEL is present in the microspheres and that it seemingly does not take damage from the spraying process. Absorbance could be measured at 250 nm with a linear relationship between the concentration of CEL and the resulting absorbance measured. The measured drug loading of samples S2, S3, and S4 dissolved in acetonitrile was found to deviate ±10% from the originally added amount and this data was used to find the cumulative release of drug from the microspheres. Due to the very poor solubility of CEL in water a release media containing 50:50 ethanol:water was used, where sink conditions presumably applies (McCarron et al. (2006) used 50:50 methanol:water to achieve sink conditions). Release of CEL from the microspheres was measured under sink conditions assuming that difficulties associated with release from colloidal delivery systems under sink conditions do not apply for the rela-

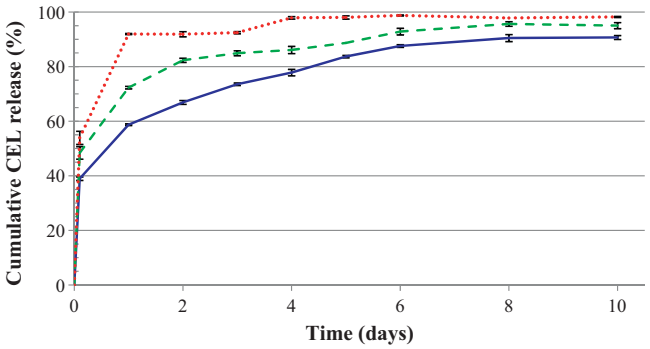

Fig. 7. Release of CEL from microspheres for samples S2 (red/dots), S3 (green/dashes) and S4 (blue/solid line). Error bars indicate std. dev. from UV measurements. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

tively large particle sizes found in this study (Piñón-Segundo et al., 2005).

The drug release profile for the microspheres in Fig. 7 shows a time-dependent release of CEL for all three samples, S2, S3 and S4. A burst release between 39 and 54% is seen for all microsphere samples within the first hour indicating the large amount of CEL bound on the surface of the microspheres. Subsequently all samples experience continued CEL release until almost all CEL was released. Sample S2 is the quickest to reach plateau level after 4 days while S4 is the slowest at 8 days. Piñón-Segundo et al. (2005) have shown that by increasing the drug content in similar matrix type particles a faster release of drug is seen due to a higher amount of porosity created in the matrix and a reduction in the thickness of matrix the drug must diffuse through (the polymer diffusion barrier). This also seems to be the case here where samples S2 and S3 release more than 80% of their CEL content within the first two days. Sample S4 and to a lesser extent S3 show a bi-phasic release pattern where a more sustained release is experienced after the initial burst release. For S4 this sustained release is approximately linear between day 1 and day 6, suggesting that CEL is partly dispersed inside the microspheres. However, for all three samples a high burst release was seen suggesting a somewhat irregular distribution of CEL in the PLGA matrices with a higher drug density at the surface of the microspheres. This could be explained by differences in the solubility of polymer and drug in the solvent leading to displacement of drug to a superficial region during solvent evaporation.

By changing the PLGA:CEL ratio it was possible to modulate the release profile of the microspheres. Further control of microsphere composition could enable a release profile with a more constant release over a shorter time. Although the curves in Fig. 7 show CEL release taking place over several days, they do not predict the release profile of CEL *in vivo*. The biodegradable nature of PLGA will result in a faster degradation of PLGA *in vivo* and an increase in release rate (Zolnik and Burgess, 2008). Dissolution studies in biorelevant media, containing relevant enzymes, are therefore necessary to obtain better resemblance to the *in vivo* performance of the microspheres.

3.4. Structural features

Thermal analysis was done to examine the physical state of CEL and PLGA in the prepared microspheres. The physical state of both CEL and PLGA has an influence on the dissolution and drug release profiles of the microspheres as well as the stability of the drug. After microsphere fabrication, CEL may exist in a crystalline or amorphous state within a crystalline or amorphous PLGA matrix. The presence of interactions between CEL and PLGA will also result in changes in the observed thermal peaks. In all DSC measurements the samples were heated from 10 °C to 200 °C above the melting point of CEL to capture thermal events within this range. Fig. 8a and b shows DSC thermograms for unprocessed CEL powder (Fig. 8a) and sample S1 (Fig. 8b). The unprocessed CEL shows characteristic melting endotherm at 162 °C while S1 shows both an endotherm peak at 162 °C and an exotherm peak at 90 °C. The exotherm peak observed is likely to indicate the recrystallization of partly amorphous CEL in the microspheres. It seems that the glass transition temperature (T_g) here may have been too small to detect if present. Measurements on physical mixtures of CEL and PLGA at ratios 1:4 and 1:1 (figures not included) showed an endotherm peak at 54 °C on both samples indicating the T_g of PLGA and possibly CEL. The mixture with 1:1 ratio also showed a broad endotherm peak at 154 °C indicating a shifted melting point of CEL. The absence of a melting peak at ratio 1:4 could be explained by the miscibility of CEL in PLGA, which may mask for the detection of crystallinity. The

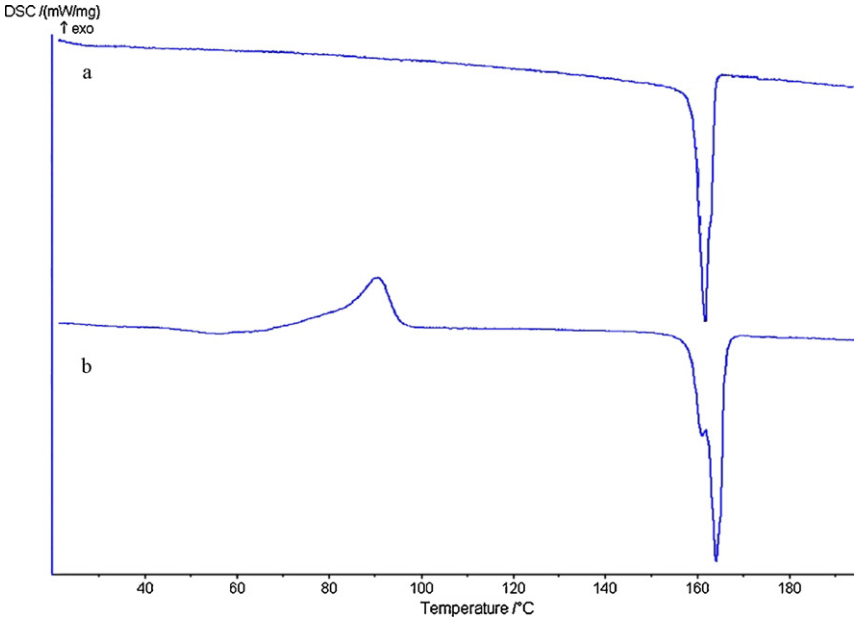

Fig. 8. DSC thermograms of microspheres of CEL powder (a) and sample S1 (b).

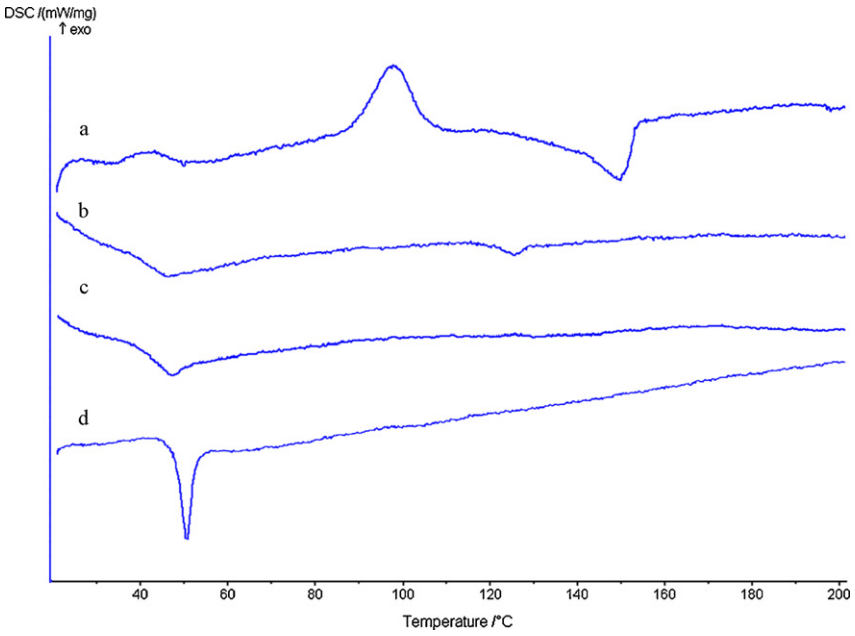

Fig. 9. DSC thermograms of microspheres from samples S2 (a), S3 (b), S4 (c) and S5 (d).

shift in CEL melting peak to 154 °C could be a result of interactions between polymer and drug.

Fig. 9b–d shows DSC thermograms of samples S2, S3, S4 and S5 respectively. For all of these samples thermogravimetric analysis was performed simultaneously with DSC and showed no significant loss in mass, indicating that the samples did not contain measurable amounts of acetone. Sample S2 shows an exotherm peak at 97 °C and an endotherm peak at 149 °C indicating recrystallization of CEL at 97 °C and a shifted CEL melting peak. No distinct T_g was observed in S2 although the presence of PLGA T_g peak seems likely. Sample S3 shows an endotherm peak at 47 °C and another one at 126 °C indicating a T_g of PLGA at 47 °C and a shifted melting peak on CEL at 126 °C. Sample S4 shows an endotherm peak around 47 °C and no melting endotherm indicating again a T_g of PLGA at 47 °C. Generally, shifts in the T_g and T_m peaks were observed for S2, S3, and S4. The melting endotherms for CEL was broadened and shifted down or disappeared. This is likely due to interactions between PLGA and CEL in the microspheres. Recrystallization in S2 and the absence of a distinct melting endotherm in S3 and S4 suggest that CEL is molecularly dispersed or in an amorphous form but could also be a result of dissolution of CEL in PLGA. On S3 and S4 the T_g seems to be shifted downwards compared with the T_g on S5.

It has been reported by Dubernet (1995) that a reduction in the polymer T_g and an absence of drug melting peak takes place when a drug is in a solid solution inside a polymer matrix. This finding indicates that CEL is molecularly dispersed in the PLGA matrix, although with an uneven distribution within the microsphere structures suggested by the *in vitro* dissolution studies. This will be investigated in more detail in further work. It is possible that a molecular dispersion of CEL in the PLGA matrix results in disturbances in CEL crystal formation.

4. Conclusions

It was demonstrated that PLGA microspheres in the size range 1–4 μm containing large amounts of CEL could be produced using electrohydrodynamic spraying. This was found at various drug:polymer ratios, all giving a narrow size distribution. Further, microspheres with pores on the surface could be formed increasing the surface area of the microspheres. Drug dissolution data showed that different release profiles can be obtained by changing the CEL:PLGA ratio, with faster release as CEL loading is increased. Moreover, dissolution studies showed that after an initial burst, release was controlled by degradation of PLGA. Thermal analysis of the samples indicates that the crystalline structure of CEL is disrupted by microsphere formation or inhibition by PLGA and that CEL is therefore in an amorphous form inside the microspheres. To conclude, electrospraying was used as a novel method to produce drug microspheres with the purpose to increase the dissolution rate of low solubility drugs such as CEL. Based on the findings of this study electrospraying is a potentially attractive method for preparation of microspheres containing low solubility drugs. Yet, further studies, including different solvents, polymers and drug compounds are needed to elucidate these findings.

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