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Preparation of polymeric nanoparticles containing corticosteroid by a novel aerosol flow reactor method

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Abstract

Polymeric drug-containing nanoparticles were prepared using a novel aerosol flow reactor method. The polymeric drug-containing nanoparticles prepared consist of a poorly water soluble corticosteroid, beclomethasone dipropionate, and polymeric materials Eudragit E 100 or Eudragit L 100. The novel method used in this study allows synthesis of nanoparticles directly as dry powders. The nanoparticles can contain various ratios of drug and polymer, and the use of any additional stabilisation materials is avoided. In this study, nanoparticles with different drug-to-polymer ratios were prepared. Particle size and morphology, crystallinity, and thermal behaviour were determined as a function of particle composition. It was found that all the nanoparticles produced, regardless of particle composition, had geometric number mean diameters of approximately 90 nm, and were spherical showing smooth surfaces. The drug was molecularly dispersed in the amorphous polymeric matrix of the nanoparticles, and drug crystallisation was not observed when the ambient temperature was below the glass transition temperature of the polymer.
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Keywords: Aerosol; Nanoparticles; Beclomethasone dipropionate; Eudragit; Polymeric nanoparticle

1. Introduction

It has been predicted that in the future a growing number of new, potential drugs will have bioavailability problems related to poor water solubility of the drug molecules. Several methods have been used in efforts to increase solubility and thus, bioavailability of poorly water soluble drugs. Examples of the methods used include solubilisation of drug into micelles or liposomes (Humberstone and Charman, 1997), complexation or coating with hydrophilic substances such as poly(ethylene glycols) or cyclodextrins (Hirayama and Uekama, 1999; Yang and Alexandritis, 2000), solid dispersions (Pignatello et al., 1997), using an amorphous modification of the drug (De Jaeghere et al., 2001; Sarkari et al., 2002), and reduction in particle size (De Jaeghere et al., 2001; Müller et al., 2001; Chen et al., 2002).

Nanosized drug particles, i.e. particles having diameters less than 1 μm, have been used to improve solubility and dissolution rates of poorly water soluble drugs. The solubility and dissolution rate of a drug depend on the drug particle surface area, and reducing the particle size results in larger surface area, which thus promotes dissolution (Adamson, 1990; Buckton, 1995; Müller et al., 2001). Various techniques have been used to manufacture nanosized drug particles with size down to hundreds and even tens of nanometres. Dry and wet milling techniques have been widely used to reduce the particle size

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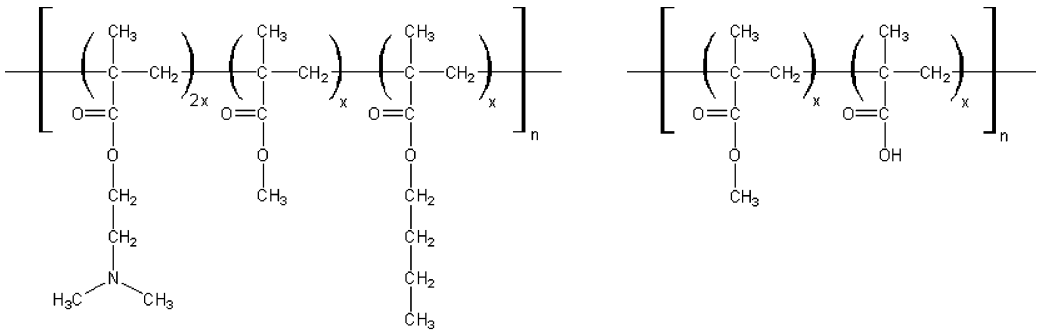
(Liversidge and Conzentino, 1995; Müller and Peters, 1998; Müller et al., 2001). Unfortunately, the nanosized particles cause cake formation in the grinding materials and milling chambers, thus significantly reducing the size reduction efficiency and resulting in broad particle size distribution and non-uniformity in particle size. Furthermore, the milling process can introduce changes in particle morphology, uncontrollable changes in particle crystalline structure (Malcolmson and Embleton, 1998), and possibly contamination, which is absolutely unacceptable in pharmaceutical material processing. To reach the desired nanoscale particle size by wet milling processes, surfactants have to be added into the mixture to prevent the agglomeration of nanosized particles. In addition, long processing times ranging over periods of days are often required to achieve particle sizes of nanometre scale. Solvent-based processes, such as emulsification-solvent evaporation (Bodmeier and Chen, 1990), emulsification-solvent diffusion (Leroux et al., 1995; De Jaeghere et al., 2001) and precipitation method (Couvreur et al., 1995) have also been used to manufacture drug nanoparticles. Generally, these methods require the addition of considerable amounts of surfactants to prevent coalescence during particle formation and hardening in an aqueous suspension. Harsh or pharmaceutically unacceptable solvents are commonly used, which might be considered as a risk regarding scale-up or regulatory issues (Allémann et al., 1993). Furthermore, these commonly used methods for production of nanoparticles result in a suspension of nanoparticles in an aqueous solution stabilised by surfactants. Reported problems of nanosuspensions are drug leakage from the particles into water phase, drug degradation, and physical changes in the suspension during the course of time. These stability problems might be avoided by storing the nanoparticles as dry powder (Bodmeier et al., 1989, 1991; Freitas and Müller, 1998; Schmidt and Bodmeier, 1999). However, to acquire dry powder from a suspension, a separate drying step by, e.g. lyophilisation or spray-drying is necessary.

Further increase in bioavailability and dissolution can be achieved by formulating the drug in an amorphous state (Hancock and Parks, 2000; Sarkari et al., 2002). As the amorphous solid-state form has higher energy than its crystalline counterparts, its saturation solubility is also larger (Hancock and Parks, 2000; Müller et al., 2001). Unfortunately, amorphous drug materials, especially if they consist of nanosized particles, show a strong tendency towards aggregation and crystal growth. This tendency to recrystallise as function of time is governed mainly by thermodynamic factors, as the system tries to reach the most stable crystal state (Buckton and Darcy, 1999; Yu, 2001). One method to overcome this problem in instability is to sterically stabilise the particles using suitable stabilising agents, which will prevent particle coalescence and growth. In addition, if drug molecules present in the amorphous form are embedded in a glassy matrix forming a nanoparticle, the crystallisation of the drug can be possibly prevented, thus making amorphous drugs stable over long periods of time. The stabilising matrix can consist, for example, of polymeric material, which is in glassy state at ambient temperature. Several different film-forming polymers have been widely used in pharmaceutical industry for various coating applications as well as for microencapsulation and nanoparticle synthesis purposes. For example, poly(methacrylate)-based polymers, known under the trade name Eudragits, have been used in microcapsules fabricated by spray-drying, as well as in nanoparticles manufactured by various solvent processes (Dittgen et al., 1997; Pignatello et al., 1997, 2002; De Jaeghere et al., 2001; Esposito et al., 2002). Eudragits have been accepted as pharmaceutical excipients for oral use and are generally regarded as non-toxic.

Two different Eudragit materials, namely, Eudragit E 100 and Eudragit L 100 were used as stabilisation materials in this study. The model drug used was beclomethasone dipropionate (BDP), which is an example of a poorly water soluble corticosteroid. It was studied whether the nanoparticle composition, relative amounts of drug and polymer, or Eudragit type used had an effect on the properties of the resulting nanoparticles. Eudragit E 100 is a co-polymer consisting of 1:2:1 ratio of methyl methacrylate, *N*,*N*-dimethylaminoethyl methacrylate, and butyl methacrylate monomers. Due to tertiary amino groups, which are ionised in the acidic pH, Eudragit E is soluble in gastric fluid when pH < 5 (Shukla, 1994; Dittgen et al., 1997). Thus, it has commonly been used as a plain or insulating film-former. Eudragit L 100 consists of 1:1 ratio of methacrylic acid and methyl methacrylate. The acidic groups are resistant



Scheme 1. Structural formulas of Eudragit E 100 and Eudragit L 100.

to gastric fluid, but are ionised when pH > 6, thus this material is soluble in the physiological conditions of small intestine (Shukla, 1994; Dittgen et al., 1997), and accordingly, it has been used as an enteric coating. The structural formulas of the Eudragit materials are shown in Scheme 1.

The aim of the current study was to prepare drug nanoparticles using a novel aerosol flow reactor method. This method is a simple and efficient one-step process that can directly produce particles within a desirable particle size range with consistent and controlled properties. In this method, both the drug and the stabiliser material are dissolved into a common solvent or solvent mixture, which is atomised as small droplets into a carrier gas. The solvent is evaporated in a controlled manner using a heated tubular laminar flow reactor, and the particles produced are collected as dry powder using a low-pressure impactor.

2. Materials and methods

2.1. Materials

2.1.1. Drug solution preparation

The liquid feed stocks containing beclomethasone dipropionate (BDP) (Sicor S.p.A., Italy) and Eudragit E 100 or Eudragit L 100 (Röhm Pharma, Germany) were prepared by separately dissolving materials in ethanol (99.5%; Alko Oyj, Finland) at room temperature with the aid of magnetic stirrer. The ethanolic drug and polymer solutions were then combined at respective amounts. The amount of the solid material was kept constant, i.e. the total solids concentration was 1 g/l while the relative amounts of drug and polymer were varied. The compositions of the nanoparticles and studied experimental conditions are shown in Table 1.

In the experiments using a co-solvent system consisting of 1:1 mixture of water and ethanol, the preparation was done by first dissolving the drug and Eudragit materials to ethanol and combining the solutions at respective amounts. Deionized water was then added into ethanolic solution containing BDP and Eudragit to achieve a final total solids concentration of 1 g/l.

2.2. Methods

2.2.1. Experimental procedure

Experimental laboratory-scale system set-up is presented in Fig. 1. The solution was atomised using a collision-type air jet atomiser TSI 3076 aerosol generator (TSI Inc. Particle Instruments, St. Paul, USA). The liquid solution feed rate was adjusted with a valve to approximately 0.40 ml/min. The resulting aerosol droplets were suspended into a carrier gas, nitrogen. Total carrier gas flow rate through the atomiser was 3.5 l/min to give the atomiser the required operation pressure of 3.5 bar. 2.0 l/min of aerosol was discarded and 1.5 l/min was passed through a heated tubular laminar flow reactor, which was used to evaporate the solvent from the droplets and to allow particle formation to complete. The reactor tube is made of stainless steel, with inner diameter and heated length of 30 and

Table 1
Composition, experimental conditions and drug incorporation of the prepared Eudragit nanoparticles

BDP%:Eudragit% (w/w)	Eudragit type	Drying temperatures studied for particle size distribution (°C)	Amount of BDP incorporated in nanoparticles (synthesised at 80 °C) in comparison to theoretical value
100:0	NA	40, 60, 80, 100, 120, 140, 160, 180	88 ± 2%
80:20	Eudragit E	40, 60, 80, 100, 120, 140, 160, 180	92 ± 1%
60:40	Eudragit E	40, 60, 80, 100, 120, 140, 160, 180	90 ± 7%
50:50	Eudragit E	40, 60, 80, 100, 120, 140, 160, 180	91 ± 6%
40:60	Eudragit E	40, 60, 80, 100, 120, 140, 160, 180	96 ± 5%
20:80	Eudragit E	40, 60, 80, 100, 120, 140, 160, 180	101 ± 2%
0:100	Eudragit E	40, 60, 80, 100, 120, 140, 160, 180	NA
80:20	Eudragit L	80	95 ± 10%
60:40	Eudragit L	80	94 ± 7%
50:50	Eudragit L	80	90 ± 6%
40:60	Eudragit L	80	97 ± 5%
20:80	Eudragit L	80	89 ± 3%
0:100	Eudragit L	80	NA

NA: not applicable.

800 mm, respectively. To study the effects of reactor tube temperature to particle morphology, the drying temperature was varied between 40 and 180 °C. To ensure uniform temperature, the tube is heated with four separately controlled heaters, each at given temperature. The nanoparticle aerosol was diluted with heated nitrogen (50 °C) in a ratio of 1:17 before sampling. In the experiments, where a co-solvent system was used, the reactor tube as well as the dilution gas were set to temperature of 100 °C.

2.2.2. Dry powder collection

Dry powder samples of nanoparticles were collected with a heated (50 °C) Berner-type low-pressure impactor (Hillamo and Kauppinen, 1991) onto aluminium foils using synthesis temperature of 80 °C. Spectrophotometry, DSC analysis, XRD analysis, and scanning electron microscope (SEM) and transmission electron microscope (TEM) observations were performed for these samples. The dry powder samples collected were stored in a refrigerator before analyses.

2.2.3. Amount of drug in the nanoparticles

The amount of BDP incorporated in the nanoparticles was analysed using spectrophotometry (Pharmacia LKB Ultrospec III, Pharmacia LKB Biochrom Ltd., Cambridge, UK). A suitable amount of dry powder sample was dissolved into ethanol and absorption was observed using wavelength 239 nm (Rohdewald, 1993), and compared to a calibration curve. It was observed that Eudragits also show a small absorption at the same wavelength, so for every sample a background measurement was done with an ethanolic solution containing the same amount and type of Eudragit as the sample. The total error in the determination was estimated by the method of propagation of errors (Parratt, 1961; Bevington and Robinson, 1992).

2.2.4. Particle size analysis

Particle size analysis was performed directly from nanoparticle aerosol with TSI scanning mobility particle sizer (SMPS), equipped with long differential mobility analyser (DMA, model 3071, TSI Inc. Particle Instruments) and condensation particle counter (CPC, model 3027, TSI Inc. Particle Instruments). The particle number size distribution measurements were performed six times at each experimental condition to reduce random error, and an average curve of the six curves was calculated and analysed.

2.2.5. Particle morphology

Particle morphology and structure were studied by field emission SEM (Leo DSM982 Gemini, LEO Electron Microscopy Inc., Oberkochen, Germany) and field emission TEM (Philips CM200 FEG, FEI

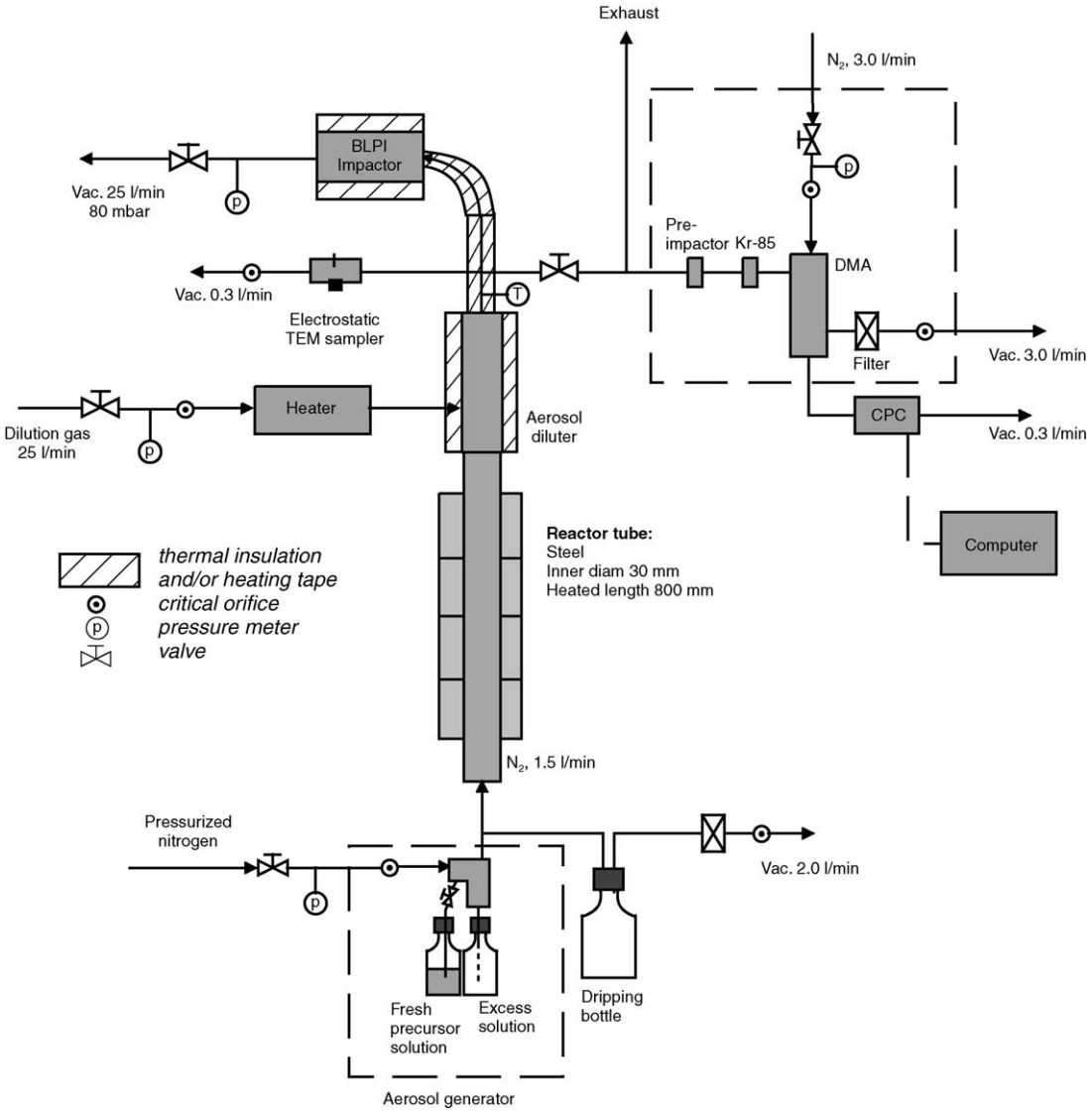


Fig. 1. Experimental set-up. Abbreviations: N_2, clean, dry pressurised nitrogen; Vac., vacuum; l/min, standard litres per minute; Kr-85, aerosol neutraliser using ^{85}Kr β-source; DMA, differential mobility analyser; CPC, condensation particle counter.

Company, Eindhoven, The Netherlands). The samples from the aerosol suspended in the carrier gas were collected directly with a point-to-plane electrostatic precipitator (InTox Products, Albuquerque, NM) onto plain copper grids or onto holey carbon coated copper grids (Agar Scientific Ltd., Essex, UK). The dry powder samples were prepared onto plain copper grids or onto holey carbon coated copper grids by dipping the grid into the sample and carefully blowing excess material off.

2.2.6. X-ray diffraction

Nanoparticle crystallinity was analysed with X-ray diffraction (Philips PW 1710, Philips, Eindhoven and Almelo, The Netherlands) using Cu Kα radiation (α_1 wavelength 0.154060 nm, α_2 wavelength 0.154439 nm

with an α_1/α_2 ratio of 0.5). The XRD patterns were recorded using diffraction angles (2θ) from 3 to 35° (BDP reference powder, step size 0.02°, time per step 10 s; nanoparticle samples, step size 0.03°, time per step 2 s).

2.2.7. Thermal analyses

Nanoparticle thermal behaviour was analysed using differential scanning calorimetry instrument (Mettler Toledo DSC 822^e, Mettler Toledo AG, Greifensee, Switzerland) equipped with Star^e computer program. Approximately 3 mg of sample was accurately weighed into a 40 μl aluminium pan and sealed with a punched lid. The temperature range 25–300 °C was scanned using a heating rate of 10 °C/min. Nitrogen purge of 50 ml/min was used in the oven.

The changes of nanoparticles on heating were further analysed visually with optical microscope (Zeiss Axioskop, Oberkochen, Germany) equipped with a hot stage (Linkam THMS 600, Surrey, UK) and a temperature controller (Linkam TMS 92, Surrey, UK). The heating rate used was 20 °C/min. The samples were carefully spread onto glass slides and observed with and without crossed polarisers.

3. Results and discussion

3.1. Amount of drug in the nanoparticles

The amount of drug in the nanoparticles was determined using spectrophotometry, and the results are shown in Table 1. In all cases, the amount of drug in the nanoparticles was close to the theoretical drug loading, in most cases over 90% of the theoretical value. The amount of drug in the nanoparticles is controlled by the amount of drug in the feed solution, and the drug is almost quantitatively incorporated in the nanoparticles. A possible explanation for the deviation in drug content from theoretical value is degradation of BDP in ethanolic solution during solution feeding in particle synthesis, possibly caused by ultraviolet light at normal laboratory conditions. The solution containers were not protected from light in the experiments.

3.2. Effect of temperature on particle size and morphology

The effect of reactor tube temperature on nanoparticle size and morphology was studied using Eudragit

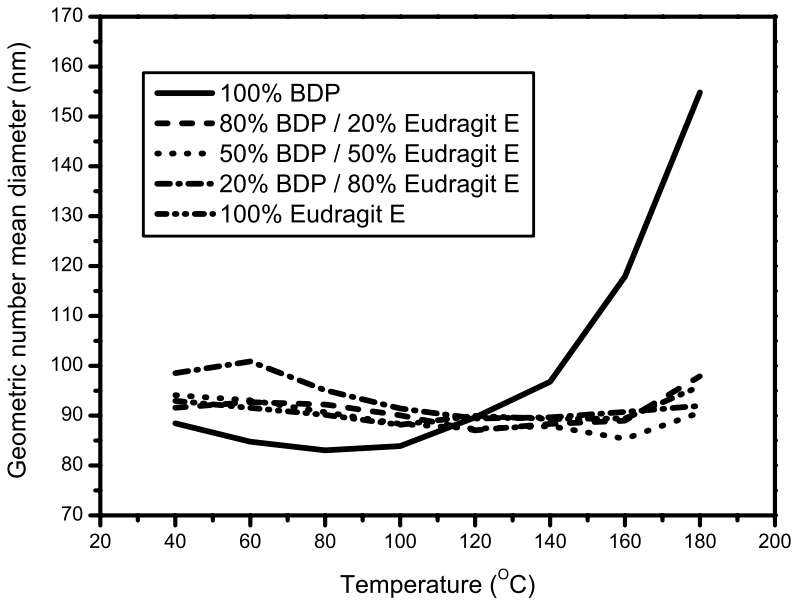


Fig. 2. Geometric number mean particle diameters of BDP–Eudragit E nanoparticles as a function of temperature.

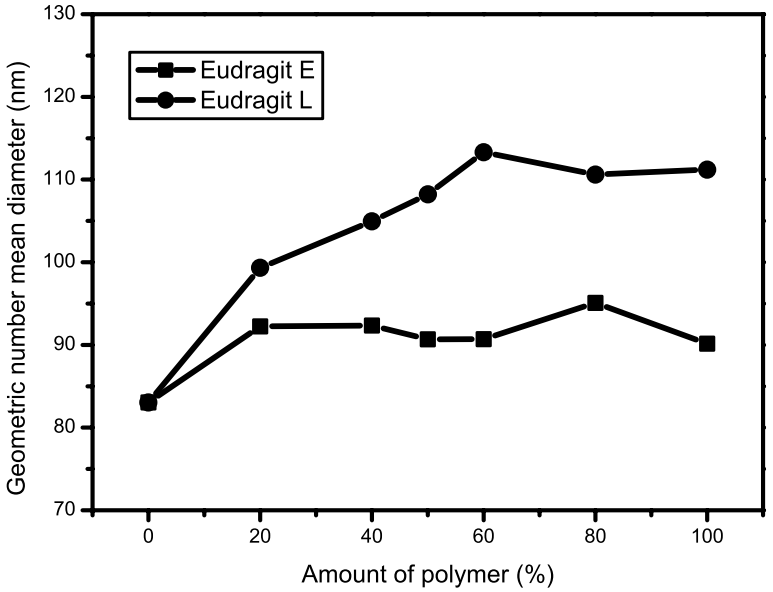


Fig. 3. Geometric number mean particle diameters of BDP–Eudragit E and BDP–Eudragit L nanoparticles as a function of polymer amount. Measurements were performed using a synthesis temperature of 80 °C.

E as the polymer material. The geometric number mean particle diameters are shown in Fig. 2 for various nanoparticle compositions and temperatures. It is observed that the temperature does not have an effect on particle size of the nanoparticles regardless of the amount of Eudragit E, the particle size is fairly constant with geometric mean number diameters of approximately at 90 nm. However, when nanoparticles consisting of only BDP are synthesised, particle size increases as a function of temperature due to formation of hollow particles at high temperatures (Eerikäinen et al., 2003).

The particle size of the nanoparticles was not affected by the composition of the nanoparticles when Eudragit E was used. However, the particles synthesised from Eudragit L had consistently larger particle sizes than those containing Eudragit E (see Fig. 3). The particle size of Eudragit L–BDP particles increased as a function of the amount of the polymer in solution. This increase in particle size is likely to be caused by the higher viscosity of Eudragit L solution in comparison to Eudragit E (Shukla, 1994), which affects the atomisation of the solution. The particle size is increased with increasing viscosity of the solution (Broadhead et al., 1992).

The nanoparticles produced were collected as dry powders using a Berner-type low-pressure impactor, and the morphology of the particles was studied with scanning electron microscopy. SEM image of an exemplary nanoparticle dry powder is given in Fig. 4. The nanoparticles produced are solid, smooth, and spherical having mean diameters around 90 nm. The nanoparticle dry powder collected consists of individual nanoparticles, which touch each other, but retain their original size and shape and do not exhibit major necking. It was observed that the morphology of the particles was not affected by Eudragit type or the amounts of polymer and drug.

Transmission electron microscopy studies were performed to examine the internal structure of the particles more closely. An example of TEM observations is given in Fig. 5. The samples studied showed no indication of any internal structure or crystal grain boundaries, instead the particles consisted of a homogeneous matrix having no sign of phase separation of the drug and the polymer. Besides, the crystallinity of the particles was studied with electron diffraction, and the samples studied showed an amorphous diffraction halo.

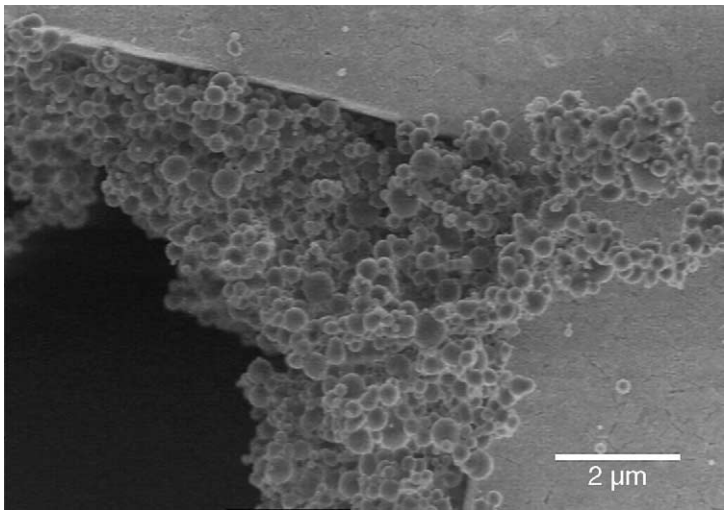


Fig. 4. SEM image of nanoparticle dry powder containing 40% of BDP and 60% Eudragit E synthesised at 80 °C. Magnification: 10,000×.

3.3. Effect of composition on crystallinity and thermal behaviour

X-ray diffraction analyses were performed to verify the TEM observations of amorphous structures. Untreated, original BDP powder shows distinct peaks and a low background intensity, and can, therefore, be classified as crystalline material (see Fig. 6a). The diffractograms of nanoparticles consisting of BDP and Eudragit E or Eudragit L (see Fig. 6b), however, show only an amorphous halo without any indication of crystalline structures. These results confirm the formation of homogeneous particles consisting of molecularly dispersed drug and polymer.

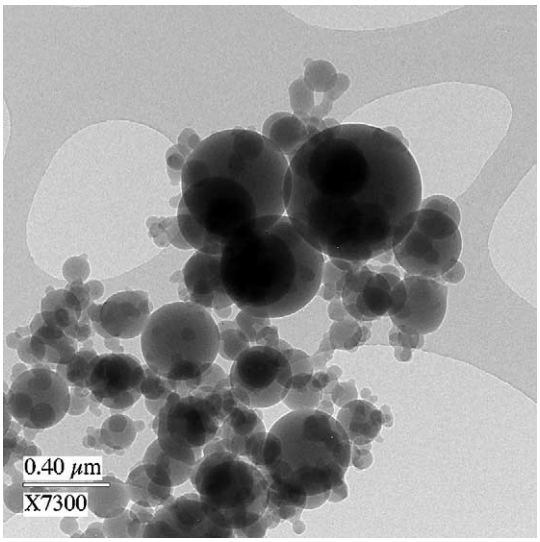


Fig. 5. TEM image of nanoparticle dry powder containing 60% of BDP and 40% Eudragit L synthesised at 80 °C. Electron optical magnification: 7300×.

Differential scanning calorimetry has been shown to be a powerful tool in analysis of interactions in polymer–drug systems, especially in the case where the particles are manufactured from a single solution (Dubernet, 1995). It can be used to prove the existence of a solid solution, where the drug and polymer are molecularly dispersed, and the interactions between the drug and the polymer are strong enough to keep the system thermodynamically stable. However, if the interactions between the two components are not strong enough to give good solubility of drug to the polymer, but the storage temperature is below the glass transition temperature of the polymer, the particles will stay stable due to high viscosity of the vitreous polymer preventing the drug from crystallising (Dubernet, 1995). In this case, a molecular dispersion is formed. When the system is heated above the glass transition temperature of the polymer, the viscosity of the polymer matrix is lowered and crystallisation of the drug takes place, which can be observed as an exotherm in the DSC curve (Dubernet, 1995).

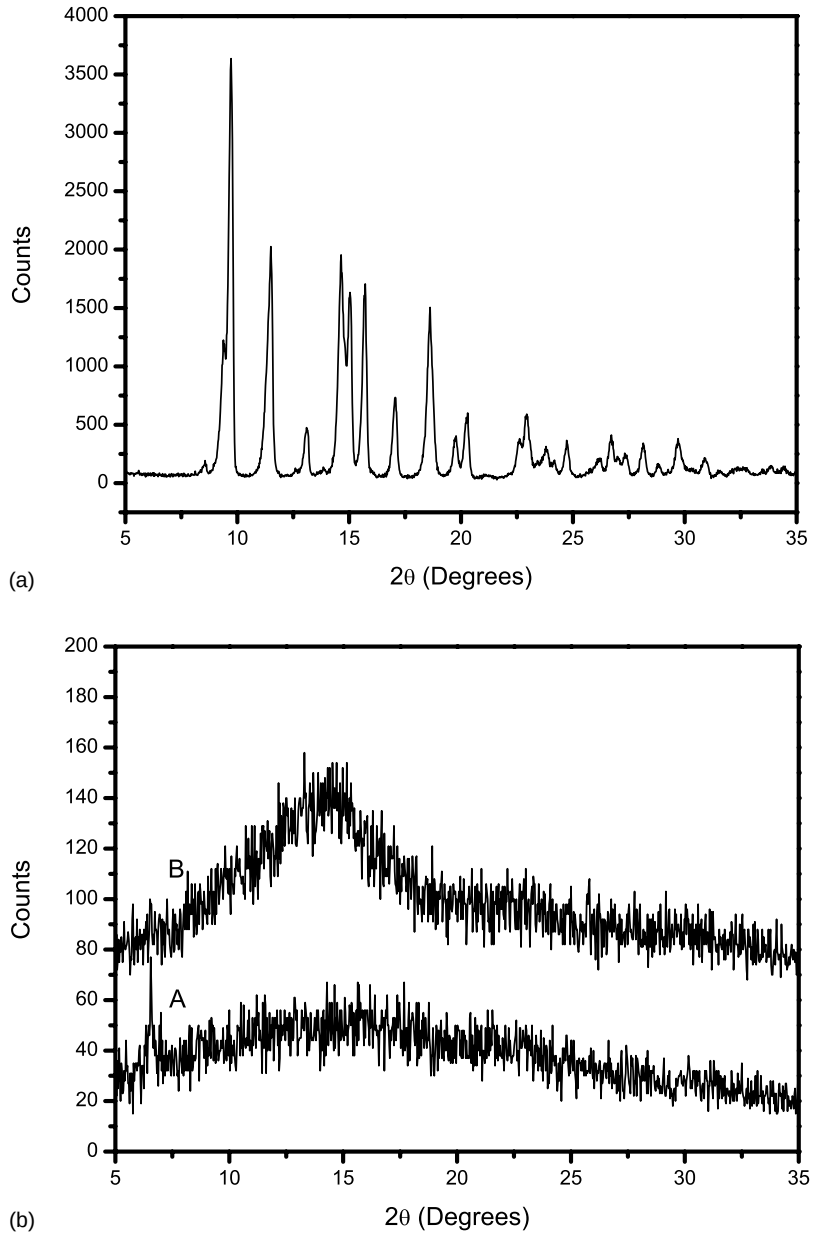


Fig. 6. (a) XRD pattern of original BDP powder. (b) XRD patterns of BDP nanoparticles synthesised at 80 °C: (A) 60% BDP/40% Eudragit E; (B) 60% BDP/40% Eudragit L.

BDP–Eudragit nanoparticles were studied with differential scanning calorimetry to observe the thermal behaviour of the samples. Firstly, the prepared 100% BDP nanoparticles were studied and compared to original, untreated BDP powder (see Fig. 7). The BDP nanoparticles show an exothermic peak at 141 °C, which is not present in the original powder. This peak can be attributed to crystallisation of the amorphous drug, as the appearance of birefringence was also confirmed with microscopy observations.

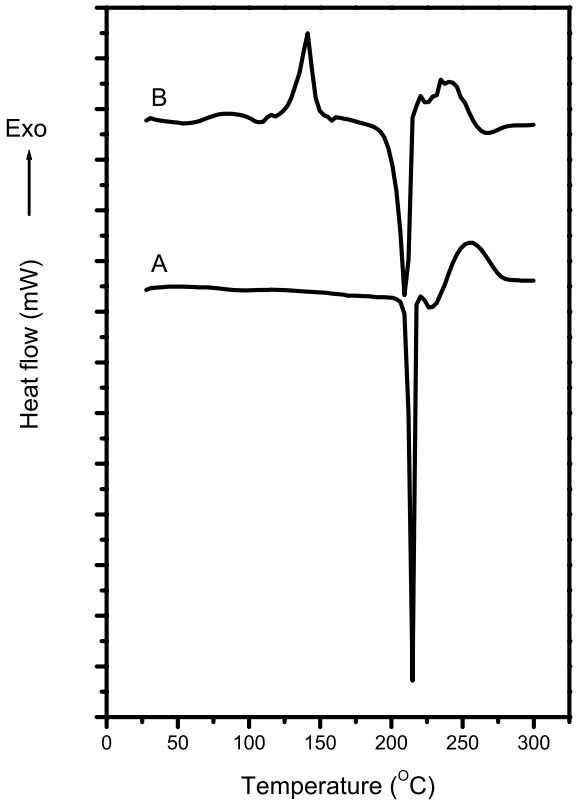


Fig. 7. DSC scans of (A) original BDP powder and (B) synthesised BDP nanoparticles.

The melting of the recrystallised BDP is observed at 210 °C, at the same temperature as the melting of the original powder. The finding of an amorphous structure by DSC is in good agreement with the TEM and electron diffraction observations showing amorphous drug particles.

100% Eudragit E and 100% Eudragit L nanoparticles were also compared to untreated powders. Original, untreated Eudragit E shows a glass transition temperature at 46 °C. Eudragit E nanoparticles show very similar thermal behaviour, the measured glass transition temperature of the nanoparticles was 45 °C, which is slightly lower than of the original powder. These values are in good agreement with the previously reported values (Lovrecich et al., 1996; Lin et al., 1999). Untreated Eudragit L shows two phase transitions between 25 and 300 °C, first of which takes place over a wide temperature range and has previously been attributed to glass transition of the polymer (Yüksel et al., 1996). The nature of the second phase transition is not as clear, but dissociation of intermolecular hydrogen bonds and anhydride formation has been suggested (Lin et al., 1995). Similarly to Eudragit E, the treatment to nanoparticles did not change the DSC curve significantly for Eudragit L nanoparticles. On the basis of these experiments, it is concluded that as the Eudragit starting materials are already in an amorphous form, the treatment to nanoparticles does not change the crystallinity of the materials.

The thermal behaviour of drug-containing BDP–Eudragit E nanoparticles differs greatly from both Eudragit E nanoparticles and BDP nanoparticles, as shown in Fig. 8 for various compositions of

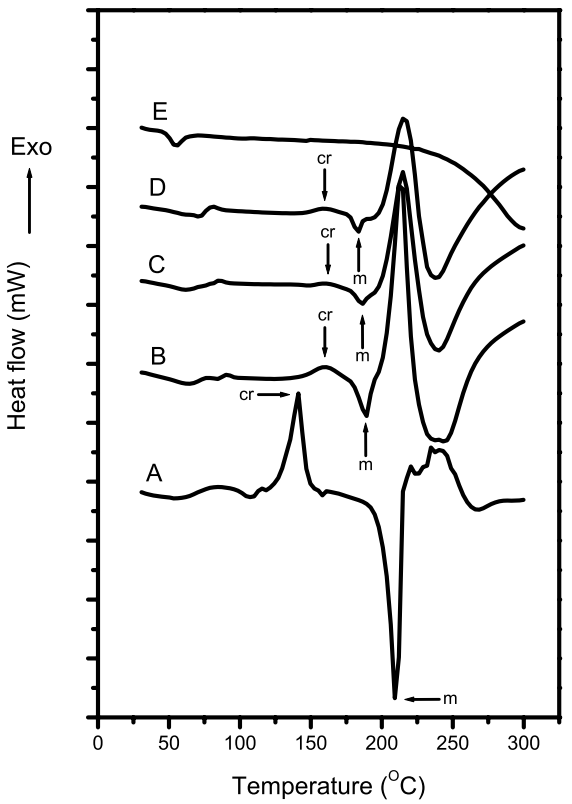


Fig. 8. DSC scans of nanoparticles containing various amounts of BDP and Eudragit E synthesised at 80 °C: (A) 100% BDP; (B) 60% BDP/40% Eudragit E; (C) 50% BDP/50% Eudragit E; (D) 40% BDP/60% Eudragit E; (E) 100% Eudragit E. Observed crystallisation and melting of the crystals are marked with cr and m, respectively.

BDP–Eudragit E nanoparticles. Instead of drug crystallisation and subsequent melting as observed for pure BDP nanoparticles, the BDP–Eudragit E nanoparticle DSC scans show a wide exotherm ranging from 130 to 180 °C, after which a small endotherm appears. Immediately after this endotherm, a large, dominating exotherm is observed at 214 °C, which is again followed by a wide endotherm. The BDP–Eudragit E samples were further examined with optical microscopy to observe possible crystallisation on heating using polarised light. On heating above T_g of the polymer, the nanoparticles coalesced, and the particle boundaries were no longer visible. The samples also turned optically clear at this point. It was observed that crystals appeared in the samples on heating at a temperature range extending from 130 to 180 °C, after which the crystals melted at approximately 190 °C. These observations of crystallisation and subsequent melting are in good agreement with the DSC scans. No visible physical changes were, however, observed at the temperature of the large exotherm, at 214 °C and thus, it is suggested that this exotherm might be due to some chemical reaction taking place at high temperatures between BDP and Eudragit E.

The behaviour of drug-containing Eudragit L nanoparticles is different from drug-containing Eudragit E nanoparticles (see Fig. 9). The nanoparticles containing 50% or less of drug do not show any additional phase transitions, but instead the thermal behaviour of these drug-containing nanoparticles is fairly similar to pure Eudragit L nanoparticles. No phase transitions attributed to BDP are present. This was also confirmed with optical microscopy, as no crystals appeared on heating. When the amount of BDP is increased up to 60%, the crystallisation of the drug followed by melting of the formed crystals become detectable. The crystallisation of the drug was also clearly observed in the microscopy experiments as appearance of birefringence. The crystallisation of the drug takes place, however, at a higher temperature than for the pure drug nanoparticles, the crystallisation temperatures of nanoparticles containing 60 and 80% of BDP are 164 and 155 °C, respectively, in comparison to 141 °C observed for pure BDP nanoparticles. The retarded crystallisation might be due to viscous polymer matrix hindering the movement and organisation of drug molecules. The melting temperature

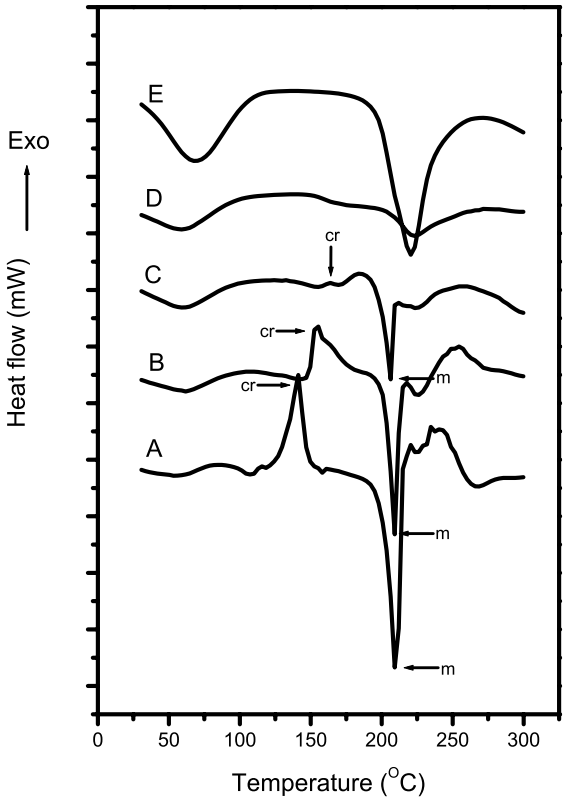


Fig. 9. DSC scans of nanoparticles containing various amounts of BDP and Eudragit L synthesised at 80 °C: (A) 100% BDP; (B) 80% BDP/20% Eudragit L; (C) 60% BDP/40% Eudragit L; (D) 50% BDP/50% Eudragit L; (E) 100% Eudragit L. Observed crystallisation and melting of the crystals are marked with cr and m, respectively.

of the crystals does not change, but is 210 °C in all the cases.

Obviously, the thermal behaviour of drug nanoparticles containing Eudragit E and Eudragit L differ from each other. The drug can crystallise in the latter case on heating above the glass transition temperature of Eudragit L, and it can, therefore, be considered as an indication of formation of a molecular dispersion (Dubernet, 1995) when the drug amount exceeds 50%. It can be deduced that in this case the crystals formed consist most likely of pure BDP, as the melting of the crystals takes place at the same temperature as of the pure drug. Below 50% the drug is soluble in the Eudragit L polymer, giving a solid solution, and no phase changes attributed to BDP are

observed. The behaviour of BDP–Eudragit E nanoparticles is different, as the crystallisation as well as melting of the crystals take place at lower temperatures than of the pure drug. Lowering of drug melting point in microparticles consisting of a drug and Eudragits has been observed previously, and was taken as an indication of formation of solid solution (Pignatello et al., 2001). However, to further clarify this behaviour and the nature and origin of the interactions between the drug and Eudragit E require more detailed studies with different methods. More importantly, these DSC observations show that the drug is molecularly dispersed in the polymer matrix, when the temperature is below the T_g of the polymer. As the nanoparticles are heated, the mobility of the drug is increased followed by crystallisation, provided that the relative amount of the drug is above its solubility limit to the polymer.

3.4. Effect of solvent system on particle morphology and particle crystallinity

In some applications, it would be desirable to be able to modify the morphology of the nanoparticles,

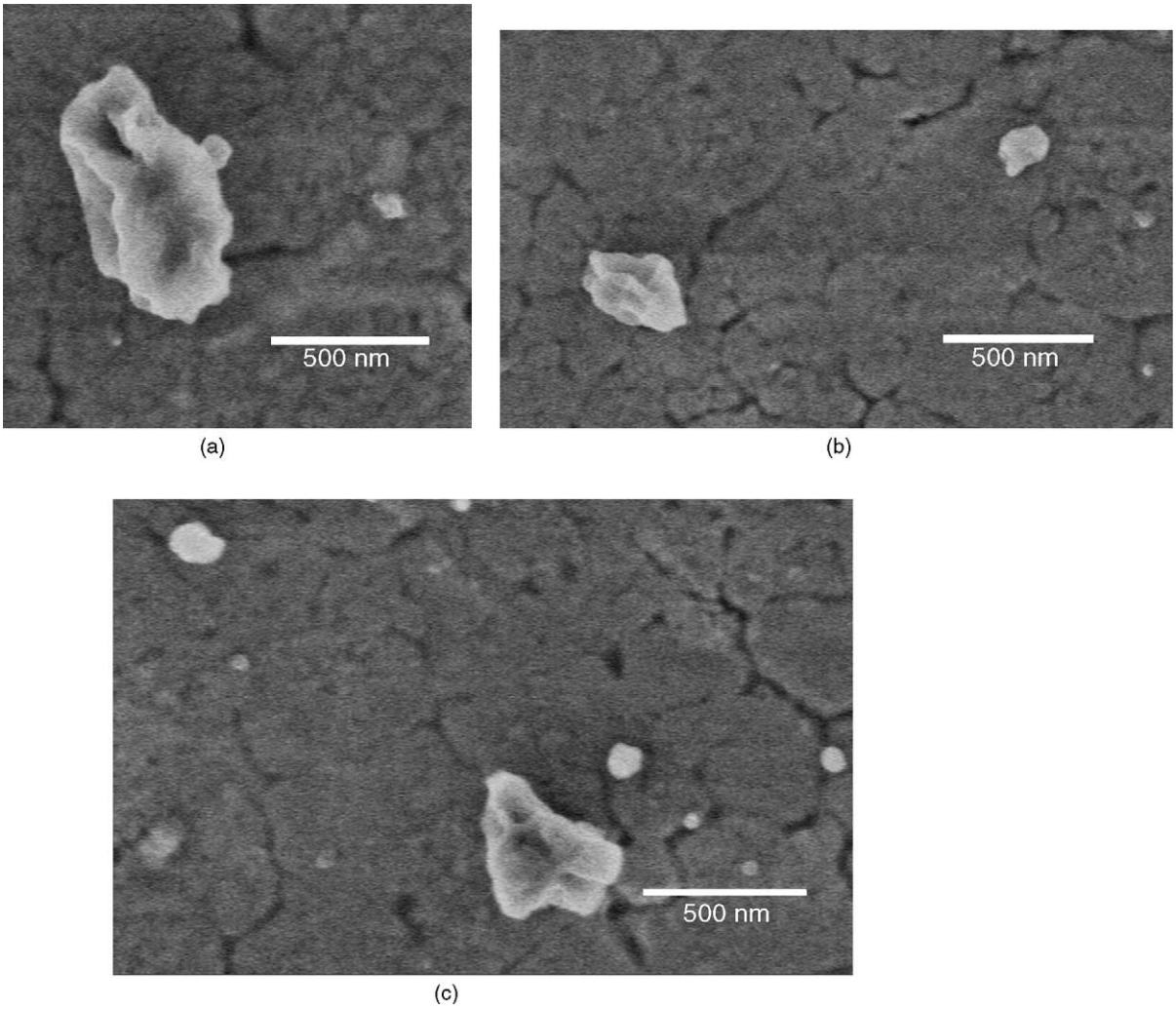


Fig. 10. SEM images of nanoparticles containing 50% of BDP and 50% Eudragit L prepared from 1:1 ethanol:water solvent mixture synthesised at 100 °C. Magnification: 50,000×.

e.g. to further increase the surface area of the particles available for solvent. As the experimental variables studied did not change the morphology of the BDP–Eudragit nanoparticles, a co-solvent system was examined. It was anticipated that by adding a co-solvent, which is a poor solvent for the components of the nanoparticles, the drying of the droplets might be changed due to solubility differences in the two solvents. The co-solvent has to be miscible with the ethanolic solution containing the drug and Eudragits to ensure uniform droplet formation in the atomisation of the mixture. In addition, it was assumed that it would be advantageous, if the co-solvent had a higher boiling point than ethanol. When the ethanol evaporates, the material in the droplet is forced to precipitate due to its poor solubility in the solvent left in the droplet. Based on these limits, water was chosen as the co-solvent, as both Eudragits and BDP are poorly water soluble and water has a higher boiling point than ethanol. In our studies, we found that the ethanolic solutions of Eudragit and BDP could incorporate at least 50% water without visible flocculation or turbidity of the solutions. On the basis of these preliminary experiments, solutions consisting of a solvent system of 50% water and 50% ethanol, and containing 50% Eudragit E or Eudragit L and 50% of BDP with a total solids concentration of 1 g/l were prepared. The solutions were subjected to similar procedure as the ethanolic BDP–Eudragit solutions, with the exception that a drying temperature of 100 °C was used to ensure complete evaporation of water. Based on SEM observations, the co-solvent system did not have an effect on BDP–Eudragit E nanoparticles, but the particles are similar to the nanoparticles produced from an ethanolic solution, showing a spherical, smooth appearance. However, a change in morphology was observed for BDP–Eudragit L nanoparticles, as shown in Fig. 10. The nanoparticles prepared from a co-solvent mixture have a wrinkled or faceted appearance in comparison to spherical, smooth particles produced without the use of co-solvent. Also these nanoparticles were studied with electron diffraction, and were shown to be amorphous. A possible explanation for the difference in the behaviour of the two Eudragit types might be in varying glass transition temperatures of the materials. Eudragit E has a lower glass transition temperature than Eudragit L. At the temperature of the drying, Eudragit E is well in the rubbery region, and thus the diffusion and movement of the molecule chains in the droplet is possible during drying. On the contrary, at 100 °C, the Eudragit L material is only slightly above T_g, so the movement of the chains might still be somewhat restricted. When the droplets are dried at this temperature, the solid material precipitated cannot reorganise into a sphere. It is, therefore, suggested that the different morphologies created using a co-solvent system are due to different thermal properties of the polymers.

4. Conclusions

In this study, it was demonstrated that homogeneous, amorphous matrix-type nanoparticles can be produced from a poorly water soluble corticosteroid drug and different types of Eudragits by an aerosol flow reactor method, using only ethanol, a pharmaceutically acceptable solvent. The composition of the nanoparticles and drying temperature did not affect the particle size distribution, particle morphology or structure. Thus, it is possible to operate within wide experimental conditions with this method without phase separation of the drug and stabiliser. The problems of drug leaking and uneven drug distribution, which are commonly encountered in emulsion processes, are avoided using this novel method.

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