Polymeric Drug Nanoparticles Prepared by an Aerosol Flow Reactor Method

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Purpose. Our purpose was to study the possibility of using a novel method, namely, aerosol flow reactor method, for the preparation of drug-containing nanoparticles with varying amounts of drug and polymer. The physical properties of the prepared nanoparticles were analyzed.

Methods. The nanoparticle size distributions were measured using differential mobility analyzer. The structure of the prepared nanoparticles was assessed by x-ray diffraction, differential scanning calorimetry, and electron microscopy. Drug release from the nanoparticles was analyzed.

Results. The spherical particles produced showed a unimodal and lognormal size distribution, and the geometric number mean size of the nanoparticles could be varied between 90 and 200 nm. When the amount of drug in the polymeric matrix was small, the nanoparticles had a homogeneous, amorphous structure. Drug crystals were formed when the amount of drug was increased over the solubility limit of the drug into the polymer. The amounts of drug and polymer controlled the drug release from the nanoparticles.

Conclusions. The aerosol flow reactor method was found to be able to produce homogeneous amorphous matrix-type nanoparticles that can directly be collected as dry powder.

KEY WORDS: amorphous; Eudragit; nanoparticles; nanospheres; polymer.

INTRODUCTION

Drug-containing nanoparticles have recently received considerable interest in the pharmaceutical field. Several methods for manufacturing these submicrometer-sized particles have been described; for instance, micronization and milling (1–3) and various emulsion-based methods such as emulsification-solvent diffusion (4) and emulsification-solvent evaporation (5). However, control of the particle size is commonly inadequate in size-reduction methods, as the achievable particle size depends on the physicochemical properties of the material, such as hardness and thermal properties (1,6,7). In order to achieve submicrometer size, the processing times can be very long, ranging up to several days, thereby increasing the risk of chemical or microbiological contamination. It has also been shown that high-energy milling procedures, which are commonly required to achieve small particle size, can lead to uncontrollable crystal damage resulting therefore in inhomogeneous particle properties (8). Another widely used route to nanoparticles relies on forming a submicrometric emulsion, where the inner phase droplets are hardened to nanoparticles by various methods of solvent evaporation or solvent extraction (9). The final particle size is determined by the emulsion droplet size, which must be maintained constant during particle hardening (9). However, it is a general disadvantage of these methods that chlorinated, harsh, toxic, or pharmaceutically unacceptable solvents are required. Drug incorporation into nanoparticles is greatly dependent on material properties, as drug partitioning between inner and outer phases of the emulsion affects the maximum possible drug loading in the nanoparticles (5). A common drawback of both the size-reduction techniques and the emulsification techniques is that they result in an aqueous nanoparticle suspension stabilized with surfactants. Considerable amounts of surfactants have to be used to stabilize the suspension against particle coalescence and aggregation (9). It has been proposed that the physical and chemical stability can be increased by preparing the nanoparticles as a dry powder (10,11). To manufacture dry powders from nanoparticle suspensions, these have to be subjected to an additional drying step by, for example, lyophilization or spray-drying (7,10).

Recently, methods based on the use of supercritical fluids for nanoparticle synthesis have been described (12,13). These methods are able to produce directly solvent-free dry powders (12) while avoiding the use of surfactants. The particle size and particle morphology are determined by the operating conditions and the solute solubility into the supercritical fluid (12,14). However, the formation of uniform drug-polymer nanospheres has been shown to be difficult due to the different precipitation and crystallization kinetics of drug and polymer molecules (12). The complex ternary system in the supercritical region can lead to the formation of multiple liquid and fluid phases, the prediction and control of which is difficult (15). Drug partitioning into supercritical fluid and swelling of the polymer by the fluid have also been described in some cases (14). Moreover, these methods need special equipment able to withstand high pressures while simultaneously allowing accurate control of pressure and temperature.

Therefore, it is of interest to search for alternative routes for producing drug-containing nanoparticles. In this paper, we present the synthesis of polymeric drug nanoparticles by the aerosol flow reactor method. The aerosol flow reactor method involves preparation of a solution containing the drug and excipients and spraying the solution as nanosized droplets into an inert carrier gas stream followed by solvent evaporation and particle formation in a tubular flow reactor.

Two model drugs were used in this study, namely ketoprofen and naproxen, both of which are nonsteroidal antiinflammatory drugs (NSAIDs). Ketoprofen and naproxen have been widely used as model drugs for preparation of various nano- and microcapsule systems (3,16,17). Common side-effects of NSAIDs are ulceration and irritation and damage of gastric mucosa. It has been shown that these adverse side-effects are at least partly dependent on the route of administration; oral administration of NSAIDs resulting in

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more irritation (3). Irritation and mucosal damage might be reduced by tailoring the release of the drug close to the site of absorption. The aim of this study was to synthesize controlled release, namely, pH-dependent nanoparticles. These pH-dependent particles are tailored to release the drug rapidly in the intestine (18).

The polymer chosen for the preparation of these nanoparticles, Eudragit L 100, is a copolymer consisting of methacrylic acid and methyl methacrylate monomers in a ratio of 1:1 (19). This polymer has two functions in the nanoparticle synthesis. First, it retards drug release from the nanoparticles due to its pH-dependent solubility. Secondly, it is expected to stabilize the structure of drug nanoparticles by preventing drug crystal growth as well as increasing mechanical hardness of the nanoparticles.

MATERIALS AND METHODS

Synthesis of Nanoparticles

Materials

Ketoprofen [2-(3-benzoylphenyl) propionic acid] and naproxen [(*S*)-2-(6-methoxy-2-naphthyl) propionic acid] were purchased from Sigma (St. Louis, MO, USA) and were used as received. Eudragit L 100 was obtained from Röhm (Röhm Pharma, Darmstadt, Germany) and was used as received.

Preparation of the Drug Solution

Solutions containing drug and polymer solutions were prepared by separately dissolving the polymer and the drug into ethanol (99.6%, Alko Oyj, Rajamäki, Finland) at room temperature using a magnetic stirrer and combining the solutions in various ratios. The compositions of synthesized nanoparticles are shown in Table I.

The effect of solution concentration on particle size was studied using a 50% Naproxen 50% Eudragit L solution with concentrations 1 g/l, 2.5 g/l, 5 g/l, 10 g/l, and 25 g/l. For the purposes of particle synthesis and collection, however, a concentration of 1 g/l was chosen, as the risk of atomizer blockage due to solvent evaporation in the air jet during the course of experiment increases with increasing concentration.

Experimental System Set-Up

The experimental system set-up is shown in Fig. 1. The solution was atomized using a collision-type air jet atomizer TSI 3076 as the aerosol generator (TSI Inc. Particle Instruments, St. Paul, MN, USA). The liquid solution feed rate was adjusted with a crimped injection needle to approximately 0.30 ml/min. The resulting droplets were suspended into nitrogen, which acts as an inert carrier gas. The carrier gas flow rate through the atomizer was measured to be 1.5 l/min. The aerosol generated 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 800 mm, respectively. To ensure uniform temperature, the tube was heated with four separately controlled heaters. The reactor wall temperature used in this study was kept constant at 80°C. The nanoparticle aerosol was diluted in a porous tube aerosol diluter with heated nitrogen (50°C) in a ratio of 1:17 before sampling.

Powder Collection

Dry powder samples of nanoparticles were collected with a heated (50°C) Berner-type low-pressure impactor (20) onto aluminium foils. The impactor used classifies the aerosol into 11 stages, and for the purposes of this study, the powder samples deposited on stages 1 to 9 were combined. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) observations, differential scanning calorimetry (DSC) analysis, x-ray diffraction (XRD) analysis, spectropho-

Table I. Ketoprofen Nanoparticles Synthesized from 1 g/l Ethanolic Solution Using Synthesis Temperature 80°C

Drug:polymer ratio	Theoretical drug % (w/w)	Nanoparticles collected	Measured drug % (w/w)	Geometric number mean diameter (nm)
(a)				
1:0	100%	–	n.a.	76
3:1	75%	–	n.a.	81
2:1	67%	–	n.a.	89
1:1	50%	–	n.a.	94
1:2	33%	+	36%	99
1:3	25%	+	24%	102
1:9	10%	+	12%	103
0:1	0%	+	n.a.	104
(b)				
1:0	100%	–	n.a.	81
3:1	75%	–	n.a.	92
2:1	67%	–	n.a.	92
1:1	50%	–	n.a.	93
1:2	33%	–	n.a.	101
1:3	25%	–	n.a.	99
1:9	10%	+	10%	102
0:1	0%	+	n.a.	104

n.a. = not applicable.

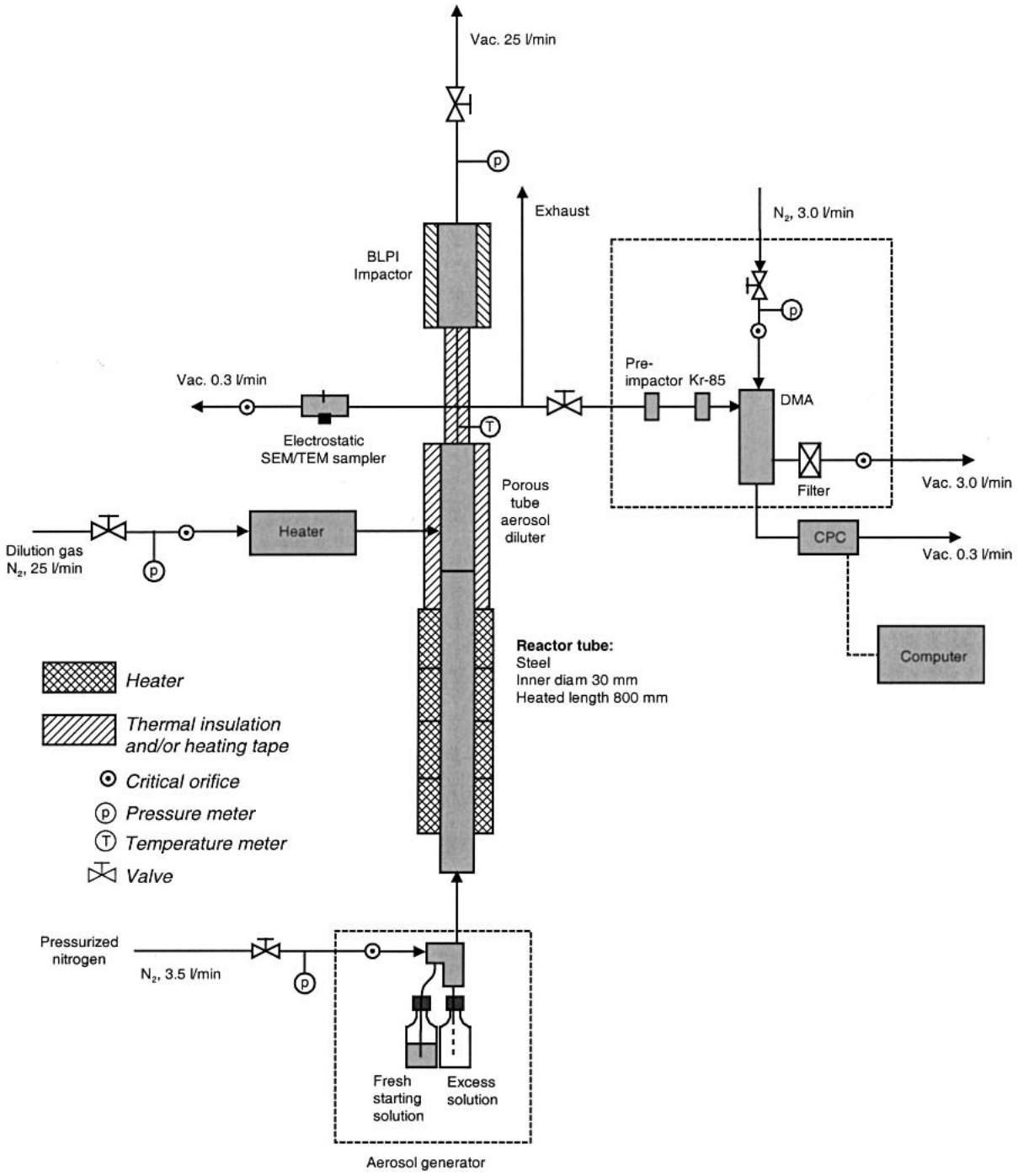

Fig. 1. Experimental system set-up (N_2 = clean, dry pressurized nitrogen, Vac. = vacuum, l/min = standard liters per minute, Kr-85 = aerosol neutralizer using ^{85}Kr β-source, DMA = differential mobility analyzer, CPC = condensation particle counter).

tometry, and drug release analysis were performed for these samples. The dry powder samples were stored in a refrigerator before analyses.

Characterization of Nanoparticles

Particle Morphology

Particle morphology was analyzed using a field-emission scanning electron microscope (Leo DSM982 Gemini, LEO Electron Microscopy Inc., Oberkochen, Germany) with an acceleration voltage of 2 kV. The samples from nanoparticle dry powders were prepared by gently dipping a copper grid (Agar Scientific Ltd., Essex, England) or lacey-carbon coated copper grid (Agar Scientific Ltd.) into the powder and carefully blowing off excess material. The samples for SEM observation were coated with a thin platinum coating when instability of the particles in the electron beam was detected. Particle morphology and internal structure were further analyzed using a field-emission transmission electron microscope (Philips CM200 FEG, FEI Company, Eindhoven, The Netherlands) with an acceleration voltage of 200 kV.

Particle Size and Size Distribution

Particle size distribution analysis was performed directly from the nanoparticle aerosol using a scanning mobility particle sizer (SMPS) (TSI Inc. Particle Instruments) equipped with a long differential mobility analyser (DMA; model 3071, TSI Inc. Particle Instruments) and a 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 of the six measurements was calculated and used for analysis.

Differential Scanning Calorimetry

Nanoparticle thermal behavior was analyzed using a DSC instrument (Mettler Toledo DSC 822^e, Mettler Toledo AG, Greifensee, Switzerland) equipped with a Star^e computer program. Approximately 3 mg of sample was accurately weighed into a 40-μl aluminum pan and sealed with a perforated lid. The temperature range –50 to 200°C was scanned using a heating rate of 10°C/min. A nitrogen purge of 50 ml/min was used in the oven.

X-Ray Diffraction

Nanoparticle crystallinity was analyzed using XRD (control unit Philips PW 1710, Philips, Eindhoven and Almelo, The Netherlands). Cu Kα radiation was used (generator PW 1830, 40 kV, 50 mA, 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 at diffraction angles (2θ) from 3° to 40° (goniometer PW 1820).

Drug Incorporation

The amount of drug in the nanoparticles was analyzed using a spectrophotometer (Pharmacia LKB Ultrospec III, Pharmacia LKB Biochrom Ltd., Cambridge, England). A suitable amount of nanoparticles was dissolved into methanol (Methanol PA ACS, >99.8%, J. T. Baker, Mallinckrodt Baker, Deventer, The Netherlands), and the concentration in the solution was analyzed using wavelengths 255 nm for ketoprofen (21) and 271 nm for naproxen (21).

Drug Release

Drug release from the nanoparticles was studied using a method based on general drug release standard for delayed-release (enteric-coated) articles (22). An amount of nanoparticles corresponding to approximately 2 mg of drug was weighed into an Erlenmeyer flask. In the acid stage, 75 ml of 0.1 N hydrochloric acid was used as the release medium. The solutions were stirred at 100 rpm using a magnetic stirrer at ambient temperature. Samples were withdrawn at predetermined time intervals, and the amount of sampled liquid was immediately replaced with the release medium. The stirring was stopped 2 min before the sampling to allow the nanoparticles to settle and thus to minimize the amount of intact nanoparticles sampled. After two hours, 25 ml of 0.2 M tribasic sodium phosphate was added, and the test was continued for a further 3 h. The amount of the drug released was determined using a spectrophotometer (Philips PU 8620 Series UV/VIS/NIR, Pye Unicam Ltd., Cambridge, England) using wavelength 260 nm for ketoprofen and 270 nm for naproxen. Before the spectrophotometry analysis, the samples were filtrated (0.22 μm PVDF, Millipore Corporation, Bedford, MA, USA). As no surfactant is used in the dissolution medium, the nanoparticles exist as large aggregates in the suspension due to hydrophobic interactions. The filtration efficiency in removing these aggregates was verified with TEM observations of the samples before and after the filtration.

RESULTS AND DISCUSSION

Particle Size as a Function of Nanoparticle Composition

In the aerosol flow reactor method, each droplet of solution converts into one particle by evaporation of the solvent. The particle size distribution of the nanoparticles is determined by the droplet size distribution generated by the atomizer. Particle size distributions were measured for the nanoparticles synthesized and the geometric number mean diameters of the particle size distributions are listed in Table I. In good accordance with the droplet size distribution produced by the atomizer, the particle size distributions measured were unimodal, lognormal, and had geometric standard deviations less than 2 (23). As a general trend, the particle size decreased as the amount of drug in the nanoparticles increased. The reduced concentration of the polymer in the solution leads to a decrease in the viscosity of the solution. Viscosity affects the atomization; a less viscous solution produces smaller droplets and therefore leads to smaller particles.

Particle Size as a Function of Solution Concentration

As each particle is formed by the evaporation of the solvent from a droplet, it was assumed that the solution concentration should have an effect on particle size. Specifically, the particle volume should increase as a function of increasing solute concentration in the solution. This assumption was verified using a solution containing 1:1 mass ratio (50%:50%) of naproxen and Eudragit L with various total concentrations. The lowest measured concentration was 1 g/l and the highest 25 g/l. Higher concentrations than this could not be prepared due to solubility problems. Measured particle size distribution curves for various concentrations are shown in Fig. 2a. The particle size distributions measured were unimodal and lognormal, in good accordance with the droplet size distribution produced by the atomizer.

The dependence of geometric number mean diameter and calculated particle volume on the solution concentration are shown in Fig. 2b. The geometric number mean diameter increases from 93 nm for 1 g/l to 201 nm for 25 g/l. However, the particle volume increase is linear, as expected. Slight deviations from a perfect linear behavior are most probably caused by an increase in solution viscosity as a result of increasing solute concentration, which affects the atomization of the solution. The atomizer used in this study has a nominal number mean droplet size of 300 nm (23), and therefore, this sets an upper limit to the achievable particle size. To further control the particle size, different types of atomizers can be used.

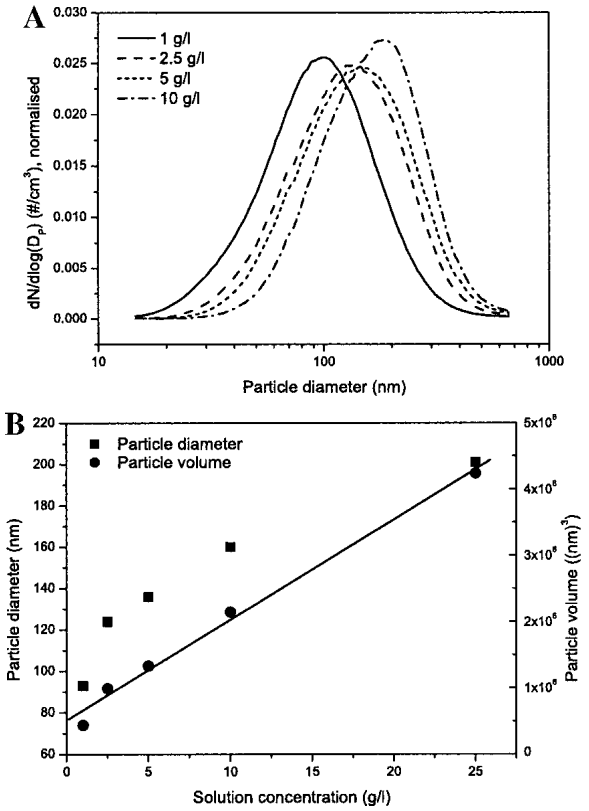

Fig. 2. (a) Particle size distribution curves for various solution concentrations. (b) Geometric number mean diameter and calculated particle volume as a function of solution concentration.

Success of Particle Synthesis and Particle Morphology

The nanoparticles produced were collected with an impactor. The dry powder samples collected were studied with scanning electron microscopy. It was found that nanoparticles containing 33% or less ketoprofen or 10% naproxen could be collected as individual, spherical nanoparticles. Typical SEM images of the collected powders are shown in Fig. 3 as images A and B. It was observed that the nanoparticles containing 50% or more ketoprofen or 25% or more naproxen were unstable in collection, resulting in coalescence of the particles and drug crystal growth (see Fig. 3, images C and D).

The successfully prepared nanoparticle dry powders were also examined with transmission electron microscopy to study the internal structure of the nanoparticles. The nanoparticles synthesized were spherical and had a homogeneous structure (Fig. 4). Crystals or grain boundaries were not detected. Therefore, these synthesized nanoparticles can be classified as matrix-type nanoparticles, also termed nanospheres in the literature (24). The electron diffraction patterns showed a diffuse pattern attributable to amorphous structure. To further study the internal structure of the nanoparticles, thermal analyses and x-ray diffraction analyses were carried out.

Thermal Properties and Crystallinity of the Nanoparticles

Thermal properties of the nanoparticles were studied using DSC. Untreated, pristine ketoprofen drug powder shows a distinct endotherm attributable to crystal melting at 96.1°C (Fig. 5a.). The crystalline structure of pure ketoprofen is further evidenced by distinct peaks and low background intensity in the XRD pattern (Fig. 6), and consequently, this starting material can be classified as being highly crystalline. The thermograms of the prepared ketoprofen–Eudragit L nanoparticles are also shown in Fig. 5a. The nanoparticles containing no drug, but only polymer (curve F), show a typical pattern of amorphous materials. A broad glass transition can be identified in the temperature region of 20–75°C. The DSC analyses of the nanoparticles containing 33% or less drug show similar scans to the polymeric nanoparticles containing no drug. A broad glass transition can be observed, but peaks attributable to drug crystallization or drug melting are not found for these samples. Therefore, the DSC analyses imply the existence of the drug in an amorphous form in the nanoparticles. The amorphous structure of the nanoparticles was further confirmed by x-ray diffraction showing an amorphous pattern for nanoparticles containing 33% or less ketoprofen (see Fig. 6). The drug interacts with the polymer, leading to

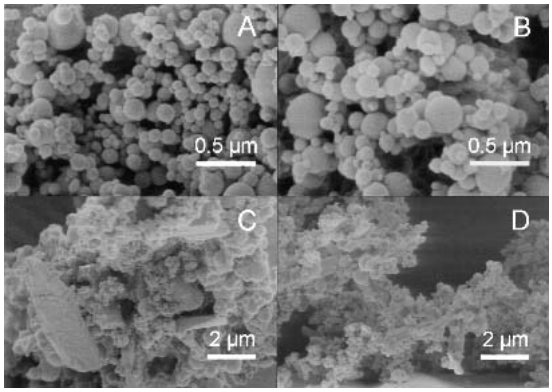

Fig. 3. Exemplary SEM images of the collected nanoparticle powders: (A) 33% ketoprofen/67% Eudragit L nanoparticles (magnification 50,000×); (B) 10% naproxen/90% Eudragit L nanoparticles (magnification 50,000×); (C) 67% ketoprofen/33% Eudragit L nanoparticles (magnification 10,000×); (D) 67% naproxen/33% Eudragit L nanoparticles (magnification 10,000×).

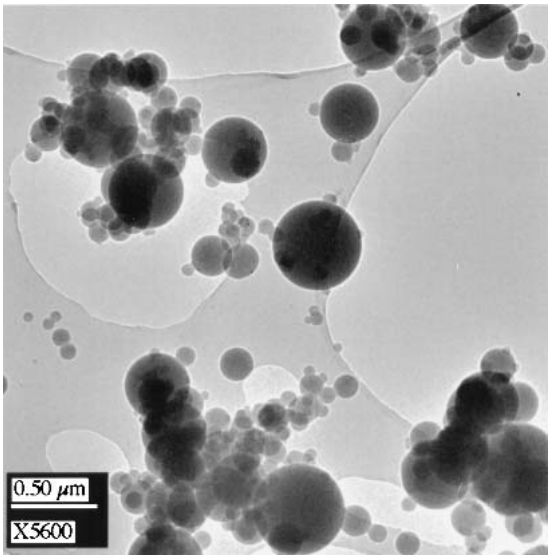

Fig. 4. Exemplary TEM image of the collected nanoparticle powder. Nanoparticles containing 25% ketoprofen and 75% Eudragit L. Electron optical magnification 5600×.

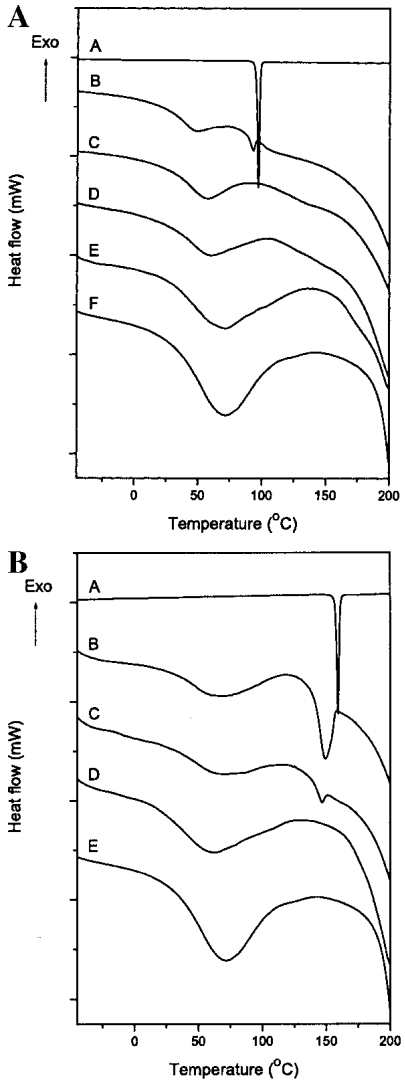

Fig. 5. (a) Differential scanning calorimetry thermograms of the nanoparticles: (A) pure ketoprofen, (B) 50% ketoprofen/50% Eudragit L nanoparticles, (C) 33% ketoprofen/67% Eudragit L nanoparticles, (D) 25% ketoprofen/75% Eudragit L nanoparticles, (E) 10% ketoprofen/90% Eudragit L nanoparticles, (F) 100% Eudragit L nanoparticles. Curve A was reduced by a factor of 20 to fit in the same image. (b) Differential scanning calorimetry thermograms of the nanoparticles: (A) pure naproxen, (B) 33% naproxen/67% Eudragit L nanoparticles, (C) 25% naproxen/75% Eudragit L nanoparticles, (D) 10% naproxen/90% Eudragit L nanoparticles, (E) 100% Eudragit L nanoparticles. Curve A was reduced by a factor of 20 to fit in the same image.

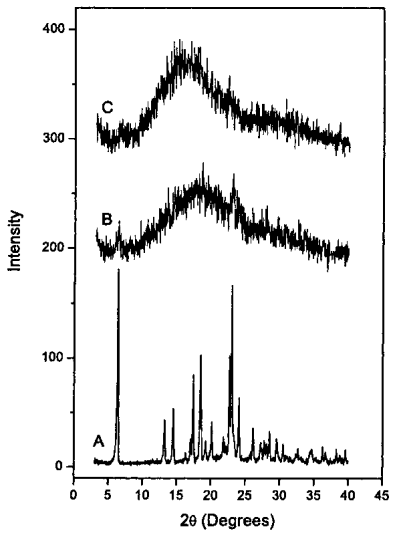

Fig. 6. X-ray diffraction patterns of the nanoparticles: (A) pure ketoprofen, (B) 50% ketoprofen/50% Eudragit L nanoparticles, (C) 25% ketoprofen/75% Eudragit L nanoparticles. Curve A was reduced by a factor of 4 to fit in the same image.

formation of an amorphous solid solution where the drug is evenly incorporated into the polymer matrix. The formation of an amorphous solid solution in systems consisting of ketoprofen and acrylic polymers has previously been observed by other authors (16,25), and therefore, our findings of amorphous structures are in good agreement with these previous studies. A small shift in the polymer glass transition temperature to lower values was observed in the thermograms of drug-containing nanoparticles. For pure Eudragit L nanoparticles containing no drug, the T_g value was determined to be 50.3°C whereas for nanoparticles containing 10%, 25%, and 33% ketoprofen, the evaluated T_g values were 49.5°C, 43.7°C, and 43.6°C, respectively. The addition of drug into the nanoparticles decreases the glass transition of the polymer as the drug acts as a plasticizer to the polymer (26–28). Incorporation of a small molecule in-between the polymer chains increases the mobility and flexibility of the chains, resulting in a lowering of the glass transition (26–28).

However, when the amount of ketoprofen in the nanoparticles was increased to 50%, an endothermic transition, attributable to drug crystal melting, was visible in the thermogram at 93.1°C (see Fig. 5a). It can be deduced that the drug solubility in the polymer matrix is exceeded and the drug crystallizes (29,30). This was also shown in the x-ray diffraction pattern of nanoparticles containing 50% ketoprofen, as the broad background diffraction pattern of the amorphous structure became overlapped by peaks corresponding to diffraction from the drug crystal lattice (see Fig. 6). The strongest diffraction peaks of crystalline ketoprofen at 6.4° (2θ) and 23.0° (2θ) can be identified in the diffraction curve of the nanoparticles containing 50% ketoprofen.

Similar behavior was observed also for naproxen nanoparticles. In this case, however, the drug formed an amorphous structure with the polymer only when the drug amount was 10%, and drug crystal melting peak can be observed in the DSC measurements already when the amount of drug was 25% or more (see Fig. 5b). The formation of crystals was also observed in the x-ray diffraction patterns. On the basis of these results, it is suggested that the solubility of naproxen in the polymer matrix is lower than that of ketoprofen, and also, the maximum possible drug loading in the amorphous nanoparticles is lower.

Drug Incorporation

The amount of incorporated drug in the nanoparticles was measured using spectrophotometry, and the results are shown in Table I. It was found that the drug incorporation in nanoparticles is almost quantitative, showing drug amounts close to theoretical values. The encapsulation efficiency (measured drug amount vs. theoretical value) was calculated

to be well above 90% in most cases, regardless of the drug used. The drug nanoparticles are formed in the aerosol flow reactor by solvent evaporation, each droplet of solution drying into a particle leading to effective drug encapsulation in the nanoparticles. The solid material in a droplet precipitates to form a particle. Problems such as drug partitioning commonly encountered in processes based on formation of an emulsion are avoided.

Drug Release

The release of ketoprofen from the nanoparticles is shown in Fig. 7. First, it was found that pristine ketoprofen drug powder was dissolved completely even at acidic conditions (see Fig. 7) in less than 2 h. The release of the drug from the polymeric nanoparticles was found to be dependent on the amounts of drug and polymer in the nanoparticles. When the nanoparticles contained 33% ketoprofen, 90% of the drug content was released at acidic conditions. The nanoparticles containing 25% ketoprofen released 80% of their drug content at acidic conditions whereas nanoparticles containing 10% ketoprofen released 70% of the incorporated drug at acidic conditions. It is assumed that the drug at or close to the nanoparticle surface can diffuse to the release medium at the acidic conditions, even though the particles did not dissolve. Ketoprofen is a molecule having a carboxylic acid group, and at acidic conditions, most of the ketoprofen molecules will not have an ionic charge. A small amount of molecules can still dissolve in the acidic media, even though ketoprofen is classified as being poorly water soluble. After the pH change, complete dissolution of the nanoparticles took place rapidly, in less than 15 min, for all samples. At buffer conditions, the Eudragit L polymer is ionized and soluble in the medium, thereby releasing the drug.

CONCLUSIONS

The aerosol flow reactor method was shown to be able to produce spherical, smooth, amorphous matrix-type nanoparticles consisting of a pH-dependent acrylic polymer and ketoprofen and naproxen drugs. The nanoparticles could be collected directly as dry powder, without the need to use surfactants or other stabilizers. The maximum loading of ketoprofen and naproxen in the amorphous nanoparticles was found experimentally to be 33% (w/w) and 10% (w/w), respectively. When the amount of drug was over this limit, the stability of the nanoparticles was not good enough to allow collection as dry powder due to drug crystal growth in the agglomerated particles. The release of the drug from the nanoparticles was controlled by the amounts of polymer and drug in the nanoparticles.

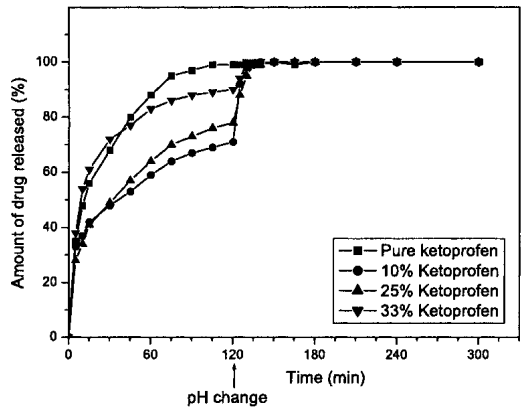

Fig. 7. Drug release for various nanoparticle compositions.

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