# Nanoparticles Containing Ketoprofen and Acrylic Polymers Prepared by an Aerosol Flow Reactor Method

*Submitted: April 27, 2004; Accepted: September 23, 2004.*

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## ABSTRACT

The purpose of this study was to outline the effects of interactions between a model drug and various acrylic polymers on the physical properties of nanoparticles prepared by an aerosol flow reactor method. The amount of model drug, ketoprofen, in the nanoparticles was varied, and the nanoparticles were analyzed for particle size distribution, particle morphology, thermal properties, IR spectroscopy, and drug release. The nanoparticles produced were spherical, amorphous, and had a matrix-type structure. Ketoprofen crystallization was observed when the amount of drug in Eudragit L nanoparticles was more than 33% (wt/wt). For Eudragit E and Eudragit RS nanoparticles, the drug acted as an effective plasticizer resulting in lowering of the glass transition of the polymer. Two factors affected the preparation of nanoparticles by the aerosol flow reactor method, namely, the solubility of the drug in the polymer matrix and the thermal properties of the resulting drug-polymer matrix.

**KEYWORDS:** nanoparticles, ketoprofen, aerosol, polymer, Eudragit

## INTRODUCTION

Drug nanoparticles can be defined as drug-containing particles having size smaller than 1 μm.[1,2] These submicron-sized particles consist of the drug and, optionally, a stabilizing or functional biocompatible polymer. Several applications of nanoparticles have been proposed, such as tissue targeting in cancer therapy,[3] controlled release,[4] carrier action for the delivery of peptides,[5,6] and increase in the solubility of drug.[7]

Previously, a method capable of producing drug-polymer nanoparticles, namely, an aerosol flow reactor method, has been presented.[8,9] This method produces spherical, amorphous, matrix-type drug-polymer nanospheres directly as dry powder in a 1-step operation. In the previous study,[9] the properties of nanoparticles consisting of an acrylic polymer, Eudragit L, and drug materials ketoprofen or naproxen were studied. It was observed that crystallization of the drug in the polymer matrix was the limiting factor for drug loading. In this study, the polymeric component is varied, while ketoprofen is used as a model drug.

The polymer nanoparticles prepared by the aerosol flow reactor method have an amorphous solid solution structure.[9] When the polymer glass transition temperature is above the ambient temperature, the polymeric component is in a glassy state, which provides mechanical strength to the particles. Therefore, the mechanical hardness and integrity of the particles can be maintained and coalescence of the particles can be avoided, which allows the collection as dry powder.

The aim of this study was to evaluate how different polymers and interactions between the drug and the various polymers affect the physical state of the nanoparticles. Three acrylic polymers were used in this study. These functional polymers, namely, Eudragit L, Eudragit RS, and Eudragit E, are widely used in the pharmaceutical industry, and are accepted for oral use.[10] These 3 polymers have different chemical compositions and functional groups. For the purposes of this study, first, it was expected that the solubility properties of the nanoparticles could be varied due to different solubilities of the polymers.[10,11] Second, as the functional groups of the polymers are different, interactions between the polymers and the acidic model drug molecule, ketoprofen, were expected to be different.

The structural formulas of the polymer materials used are shown in Figure 1. Eudragit L is a copolymer consisting of methyl methacrylate and methyl methacrylic acid repeating units in a ratio of 1:1.[10] It is soluble when the pH is greater than 6 due to the ionization of the acid groups; below this pH it is insoluble.[11] Eudragit E is a copolymer consisting of a 1:2:1 ratio of methyl methacrylate, dimethylaminoethyl methacrylate, and butyl methacrylate monomers.[10] The tertiary amino groups are ionized at acidic conditions, and this polymer is soluble when the pH less than 5.[11] Eudragit RS is a copolymer consisting of ethyl acrylate, methyl methacrylate, and trimethylammonioethyl methacrylate chloride in a ratio of 1:2:0.1.[10] This polymer has pH-independent permeability.[11]

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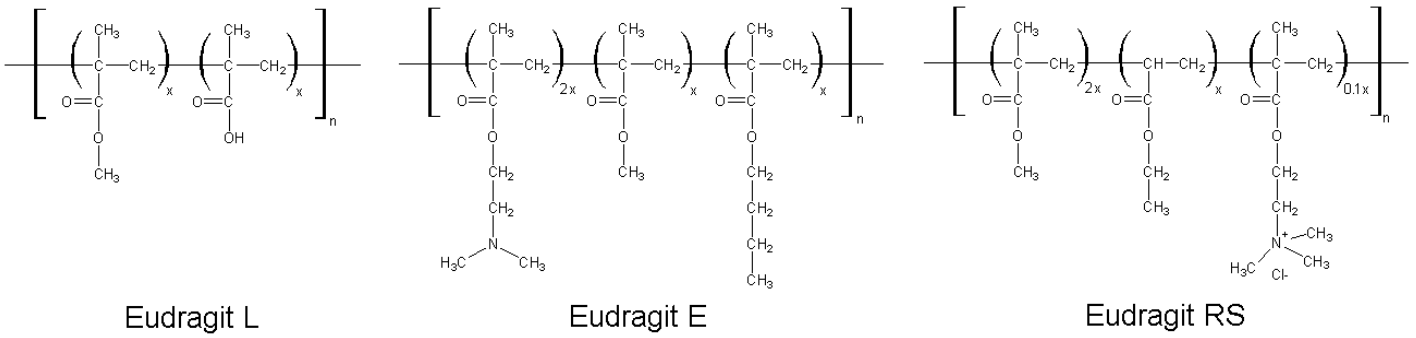


**Figure 1.** Structural formulas of the polymers used.

**Table 1.** Compositions of the Prepared Nanoparticles*

| Amount of drug (wt/wt) | Drug:Polymer | Eudragit L Nanoparticles | Eudragit RS Nanoparticles | Eudragit E Nanoparticles |
|---|---|---|---|---|
| 0% | | + | + | + |
| 5% | 1:19 | + | + | + |
| 10% | 1:9 | + | + | + |
| 25% | 1:3 | + | -‡ | -‡ |
| 33% | 1:2 | + | -‡ | -‡ |
| 50% | 1:1 | +† | -‡ | -‡ |
| 67% | 2:1 | +† | -‡ | -‡ |

*+ indicates successfully collected individual nanoparticles. -, individual nanoparticles could not be collected.

†Drug crystals observed.

‡Coalescence of the particles.

## Materials and Methods

### *Preparation of Particles*

#### *Materials*

Ketoprofen (2-(3-Benzoylphenyl) propionic acid) was purchased from Sigma (St Louis, MO) and was used as received. Eudragit L 100 PO, Eudragit RS 100 PO, and Eudragit E 100 were obtained from Röhm (Röhm Pharma, Darmstadt, Germany), and were used as received.

#### *Preparation of Drug Solution*

The drug-polymer solutions were prepared by separately dissolving the polymer and drug into ethanol (99.6%, Alko Oyj, Rajamäki, Finland) using a magnetic stirrer and combining the solutions at respective amounts. Total solids concentration of the starting solution was fixed at 2 g/L. The compositions of prepared particles are shown in Table 1.

#### *Experimental System Set-up*

The experimental system set-up for the preparation of nanoparticles has been described in detail previously.[8,9] Briefly, the ethanolic solution containing the drug and the polymer was atomized using a collision-type air jet atomizer TSI 3076 as the aerosol generator (TSI Inc Particle Instruments, St Paul, MN). The resulting droplets were suspended into nitrogen, and 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 wall temperature used in this study was kept constant at 80°C and the flow rate of carrier gas was 1.5 L/min. The nanoparticle aerosol was diluted in a porous tube aerosol diluter with nitrogen (20°C) in a ratio of 1:17 before collecting the nanoparticles with a Berner-type low-pressure impactor onto aluminum foil.

#### *Powder Collection*

Dry powder samples of particles were collected after diluting the aerosol (ratio 1:17, dilution gas nitrogen at 20°C) using a Berner-type low-pressure impactor onto aluminum foil. The impactor was kept at room temperature. The impactor classified the aerosol into 11 stages, and for this study, the dry powder samples were formed by combining the material deposited on stages 1 to 9. The dry powder samples were stored in a refrigerator (+2 to +8°C) prior to analyses. Scanning electron microscope (SEM) and transmission electron microscope (TEM) observations, differential scanning calorimetry (DSC) analyses, infrared spectroscopy (IR) analyses, and drug release analyses were performed for these dry powder samples.

### *Characterization of Particles*

*Particle Morphology*

Particle morphology was analyzed using a field-emission SEM (Leo DSM982 Gemini, LEO Electron Microscopy Inc, Oberkochen, Germany) using an acceleration voltage of 2 kV. The samples from dry powder particles were prepared by gently dipping a copper grid (for SEM) or lacey carbon-coated copper grid (for TEM) (Agar Scientific Ltd, Essex, UK) into the dry nanoparticles and carefully blowing off excess material. The samples for SEM observations were coated with a thin platinum coating. Particle morphology and internal structure were further analyzed using a field-emission TEM (Philips CM200 FEG, FEI Co, Eindhoven, the Netherlands) using an acceleration voltage of 200 kV.

*Particle Size and Size Distribution*

Particle size distribution analysis was performed directly from the nanoparticle aerosol using a TSI scanning mobility particle sizer (SMPS), equipped with a long differential mobility analyzer (DMA, model 3081; TSI Inc Particle Instruments) and a condensation particle counter (CPC, model 3022; TSI Inc Particle Instruments). For particle size measurements, an additional aerosol diluter (1:10, dilution gas nitrogen at 20°C) was added before the measurements to reduce the particle concentration to a suitable level. The particle number size distribution measurements were performed 6 times at each experimental condition to reduce random error, and an average of the 6 measurements was calculated and used for analysis.

*Differential Scanning Calorimetry*

The thermal behavior of the particles was analyzed using a DSC instrument (Mettler Toledo DSC 822e, 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 punched lid. Temperature range of –50°C 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. The samples were heated above their $T_g$ and studied using a microscope (Zeiss Axioskop, Oberkochen, Germany) equipped with a heating stage (Linkam THMS 600, Surrey, UK). When the samples were heated above glass transition temperature, $T_g$, it was observed that the nanoparticles formed a coalesced drug-polymer matrix and did not consist of single, separate nanoparticles anymore. Therefore, to characterize the thermal behavior of the nanoparticles, $T_g$ values were determined in the first heating cycles in DSC experiments.

*Infrared Spectroscopy*

Infrared absorption spectra of raw materials and nanoparticles in the wavelength region 4000 $cm^{-1}$ to 650 $cm^{-1}$ were recorded using a Fourier transform IR spectrometer (Spectrum One, PerkinElmer Instruments LLC, Shelton, Connecticut) equipped with a Universal ATR sampling accessory (PerkinElmer Instruments LLC, Shelton, Connecticut). Resolution used in the scans was 1 $cm^{-1}$, and the spectra were averaged over 3 scans.

*Drug Release from Nanoparticles*

Drug release tests were performed using a system based on the general drug release standard for delayed-release (enteric-coated) articles, method A.[12] An amount of nanoparticles corresponding to ~2 mg of ketoprofen was weighed and filled into a size 0 gelatin capsule. The capsule was further girdled with a metal wire to ensure that the capsule settled down in the vessel.[13] Round-bottomed cylindrical glass vessels having a total volume of ~150 mL were used as release chambers. The solutions were stirred using a magnetic stirrer at a speed of 50 rpm. The temperature was controlled to 37.0°C ± 0.5°C. In the acid stage, 75 mL of 0.1 N hydrochloric acid was used as the release medium. Aliquots were withdrawn at predetermined time intervals and immediately replaced with fresh medium equilibrated at 37°C. After 2 hours, 25 mL of 0.2 M tribasic sodium phosphate was added to change the pH of the test medium to 6.8, and the test was continued for a further 4 hours. The amount of the drug released was determined using a spectrophotometer (Pharmacia LKB Ultrospec III, Pharmacia LKB Biochrom Ltd, Cambridge, UK) using wavelength of 260 nm. The tests were performed with 2 parallel runs; the values reported are mean values of the 2 runs. The repeatability of the method was evaluated by analyzing 6 parallel samples, and it was found that the results are repeatable. The measured dissolution values have a standard deviation of 6% on average, while the maximum standard deviation was less than 10%. The highest standard deviation values were observed immediately after the pH change, probably due to incomplete mixing and equilibration of the pH in the dissolution vessel.

## RESULTS AND DISCUSSION

### *Effect of the Polymer and the Amount of Drug on Particle Size*

The atomizer used to spray the nanosized droplets produced a unimodal and lognormal droplet size distribution. After drying the droplets, the particle size distribution of the solid nanoparticles reflected the droplet size distribution produced by the atomizer. The geometric standard deviation of the distributions was less than 2.0 for all the studied drug-polymer particles, which was in good accordance with the atomizer

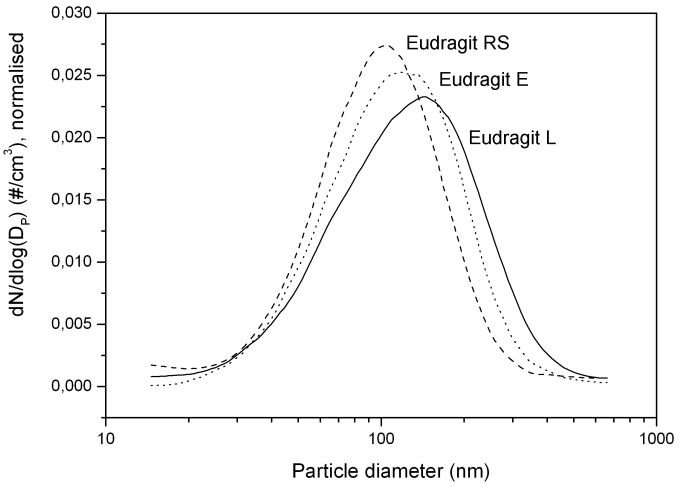


**Figure 2.** Particle size distributions of ketoprofen nanoparticles containing 10% (wt/wt) ketoprofen and 90% (wt/wt) different Eudragits.

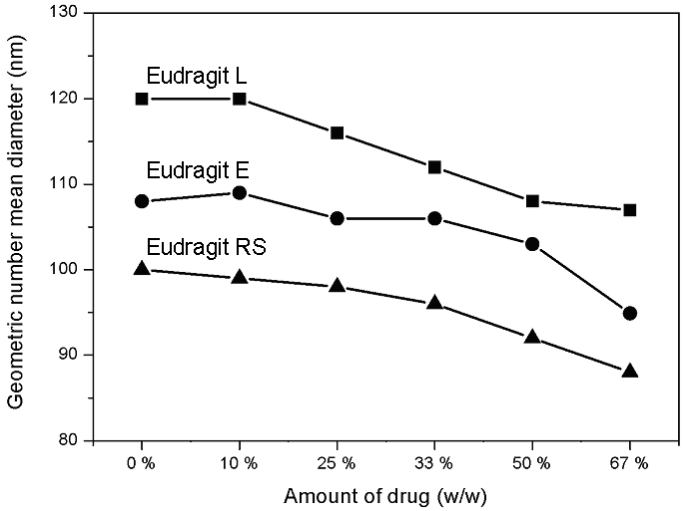


**Figure 3.** Number of mean geometric particle sizes as a function of drug (ketoprofen) amount in the nanoparticles.

specifications.[14] In Figure 2, particle size distributions of nanoparticles containing 10% (wt/wt) ketoprofen are shown. The number mean geometric particle size was calculated from the size distribution curve. In Figure 3, the number mean particle sizes are plotted as a function of drug amount. As a general trend, the particle size slightly decreased as the amount of drug was increased in the nanoparticles. It was observed that Eudragit L produced larger particles than either Eudragit E or Eudragit RS, and that Eudragit RS produced the smallest particles. This was most likely caused by different viscosities and surface tensions of the solutions, which affected the atomization and the droplet size.[15]

### *Collection of the Nanoparticles*

The different polymers used led to different stability of the nanoparticles during collection. Powders could be collected when the amount of drug was equal to or less than 50% (wt/wt) for Eudragit L nanoparticles, whereas for Eudragit E and Eudragit RS nanoparticles, nanoparticles containing 33% (wt/wt) or less drug could be collected. When higher amounts of drug were incorporated to these polymers, the product collected was tacky and transparent, and seemed not to consist of individual particles.

The collected powders were analyzed by electron microscopy to observe the morphology of the nanoparticles. The nanoparticles made of polymer Eudragit L and containing 33% (wt/wt) or less of drug were spherical, had smooth surfaces, and showed no crystallites (see Figure 4A). When the amount of drug was 50% (wt/wt), some crystallites were also observed. For Eudragit E, the nanoparticles containing 10% (wt/wt) or less drug were spherical, separate nanoparticles. When the drug amount was increased to 25% (wt/wt), the nanoparticles showed coalescence, and separate nanoparticles could not be detected (see Figure 4C). Similarly to Eudragit E, the Eudragit RS nanoparticles were separate, distinct nanoparticles when the amount of drug was 10% (wt/wt) or less (see Figure 4B). Also for these nanoparticles, coalescence and loss of integrity was found when the amount of drug was 25% (wt/wt), as shown in Figure 4D. The compositions and observed appearances of the nanoparticles prepared are summarized in Table 1.

TEM observations were performed for the successfully prepared nanoparticles. Transmission electron microscopy (see Figure 5) showed solid, homogeneous drug-polymer particles. Grain boundaries or crystals were not detected and, therefore, it was concluded that these nanoparticles had a matrix-type structure.

### *Thermal Behavior of the Nanoparticles*

To explain the reason for the coalescence of the nanoparticles, the thermal behavior of the particles was analyzed with DSC. Specifically, the glass transition temperature of the composite nanoparticles was determined. The $T_g$ values are listed in Table 2. For the nanoparticles prepared from Eudragit L, the glass transition was slightly lowered as a function of drug amount (see Table 2). However, the glass transition of all Eudragit L nanoparticles was clearly above room temperature. When the drug amount was equal to or less than 33% (wt/wt), the DSC curves showed no signal attributable to melting peak of the drug (see Figure 6). Therefore, it could be concluded that the drug was incorporated in these nanoparticles in an amorphous form.[16-20] For the nanoparticles containing 50% (wt/wt) drug, however, an endothermic transition attributable to the melting of drug crystals was observed at 94°C. Pure ketoprofen showed a distinct crystal melting peak at 96°C (see Figure 6). For the nanoparticles containing 50% (wt/wt) drug, the solubility

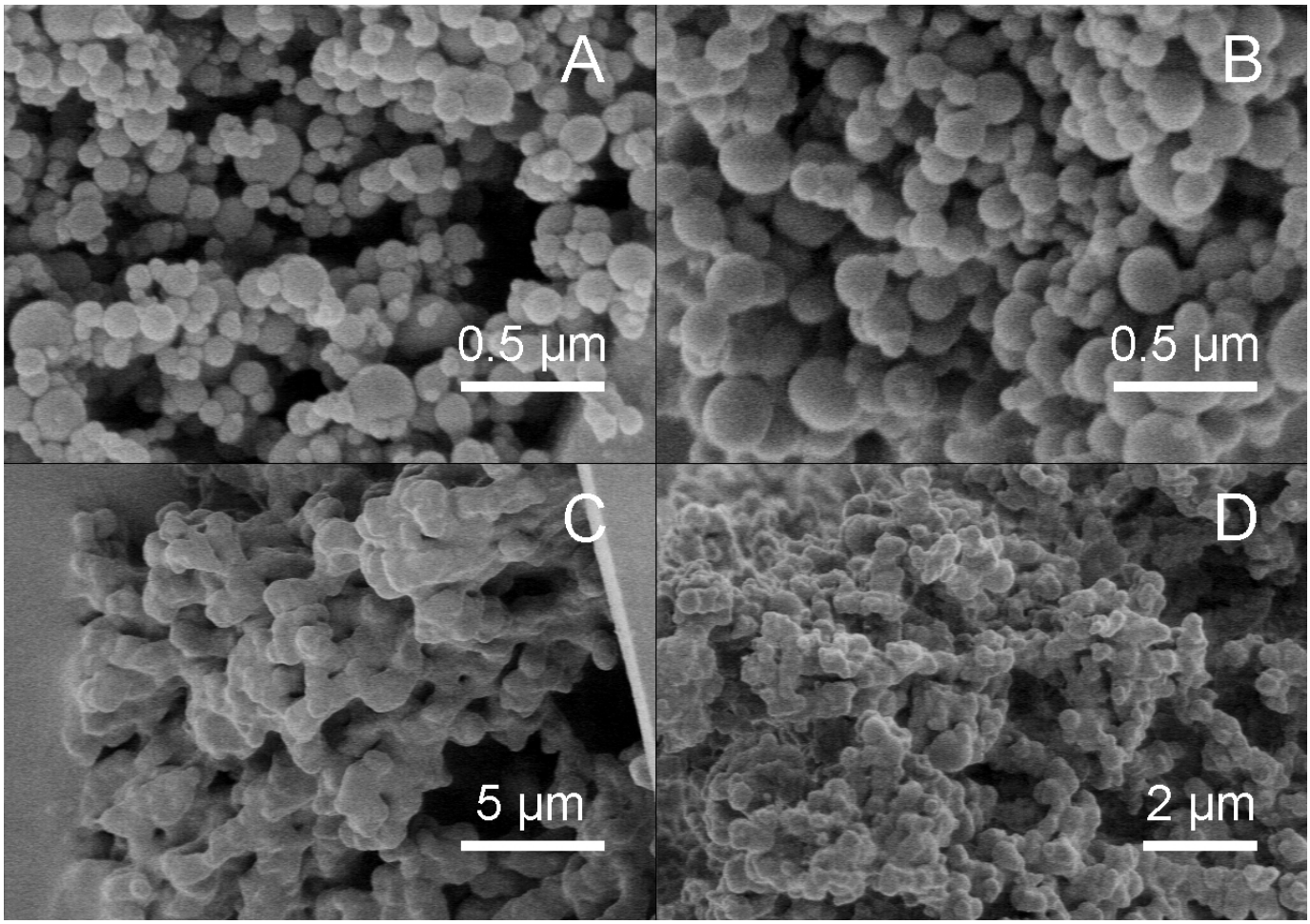


**Figure 4.** Exemplary SEM images of the nanoparticles produced. Images show nanoparticles containing the following: A, 25% (wt/wt) ketoprofen and 75% (wt/wt) Eudragit L (nominal magnification ×50000); B, 10% (wt/wt) ketoprofen and 90% (wt/wt) Eudragit RS (nominal magnification ×50000); C, 25% (wt/wt) ketoprofen and 75% (wt/wt) Eudragit E (nominal magnification ×5000); and D, 25% (wt/wt) ketoprofen and 75% (wt/wt) Eudragit RS (nominal magnification ×10000).

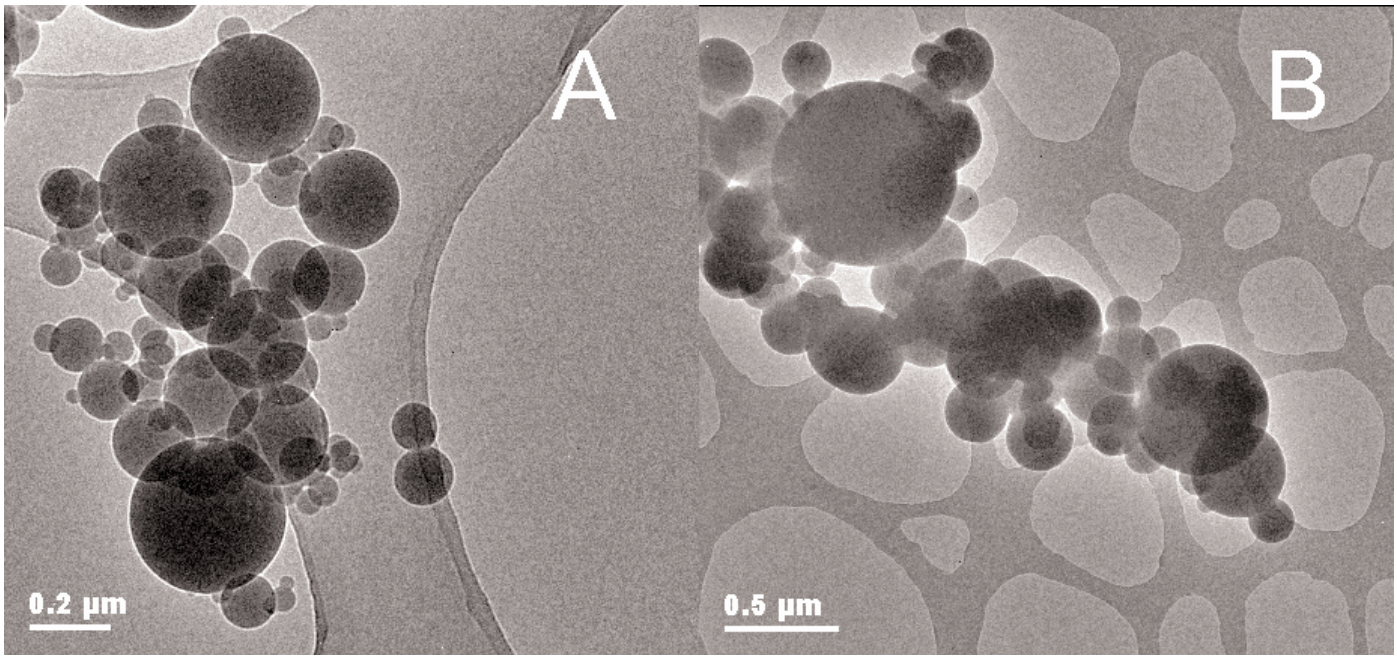


**Figure 5.** Exemplary TEM images of the nanoparticles produced. Images show nanoparticles containing the following: A, 10% (wt/wt) ketoprofen and 90% (wt/wt) Eudragit L (electron optical magnification ×9600); and B, 5% (wt/wt) ketoprofen and 95% (wt/wt) Eudragit E (electron optical magnification ×5600).

**Table 2.** Glass Transition Temperatures of the Polymer Nanoparticles*

| Amount of Ketoprofen (wt/wt) | Eudragit L, °C | Eudragit E, °C | Eudragit RS, °C |
|---|---|---|---|
| 0% | 54 | 49 | 53 |
| 5% | 52 | 45 | 50 |
| 10% | 50 | 41 | 50 |
| 25% | 50 | 24 | 28 |
| 33% | 48 | 23 | 20 |
| 50% | 40† | NA | NA |
| 67% | NA | NA | NA |

* NA indicates not applicable.

† A melting peak corresponding to ketoprofen crystals was observed at 94°C.

limit of drug in the polymer matrix was exceeded, and the excess drug formed crystals. The ketoprofen melting peak appeared at a lower value in the nanoparticles, most likely due to small, imperfect drug crystals formed in the polymer matrix.[21] Also, interaction with the polymer could lead to lowering of the melting point.[18,21,22]

On the contrary, for the nanoparticles prepared from Eudragit RS or Eudragit E, crystallization of drug could not be detected within the composition range studied (see Figure 6). As no crystals were observed, the amount of ketoprofen was below the solubility limit of ketoprofen in these polymer matrices. Instead, a significant lowering in the glass transition temperature of the polymer was observed, as shown in Table 2. The glass transition temperatures of Eudragit E and Eudragit RS composite nanoparticles were much lower than of Eudragit L nanoparticles. For Eudragit E and Eudragit RS nanoparticles, when the drug amount was 25% (wt/wt), the glass transition temperatures were close to room temperature. The glass transition temperatures measured were 24°C and 28°C for the Eudragit E and Eudragit RS nanoparticles, respectively. The glass transition temperatures were close to the collection temperature (room temperature) of the nanoparticles. Consequently, the nanoparticles were softened and the mechanical strength was not sustained. Ketoprofen drug molecule acted as an effective plasticizer for these polymers, lowering the glass transition temperature.[23,24]

### *IR Spectroscopy*

Infrared spectroscopy was used to study the interactions between the drug and the polymers. Ketoprofen has a carboxylic acid group, which can interact with the functional groups of the polymers. The carbonyl peaks in the IR spectra of ketoprofen were recorded at 1694 $cm^{-1}$ and 1654 $cm^{-1}$, and have previously been assigned to dimeric carboxylic acid carbonyl group and ketonic carbonyl group stretching vibrations, respectively.[25,26]

Exemplary IR spectra of the nanoparticles are shown in Figure 7. For clarity and stronger absorptions arising from ketoprofen, materials containing 33% (wt/wt) ketoprofen are shown as

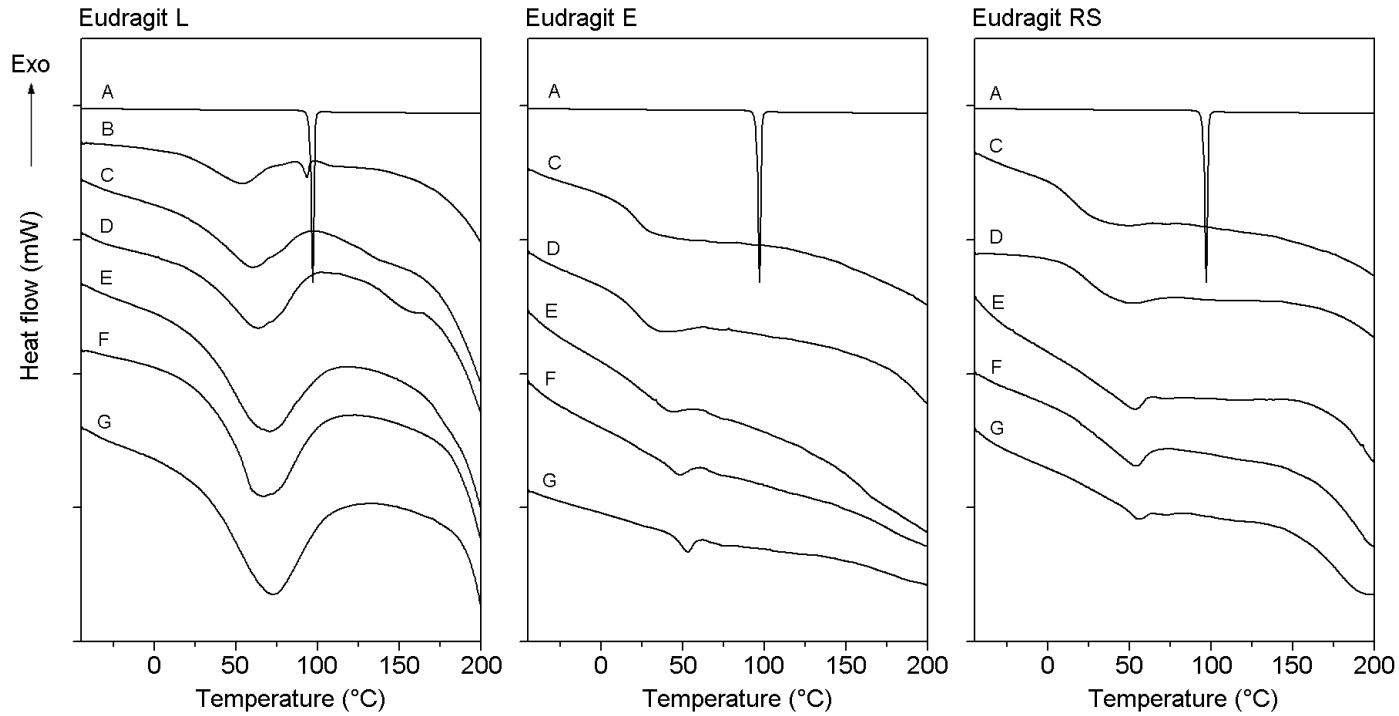


**Figure 6.** DSC thermograms of the following: A, pure ketoprofen; and nanoparticles containing B, 50% (wt/wt) ketoprofen; C, 33% (wt/wt) ketoprofen; D, 25% (wt/wt) ketoprofen; E, 10% (wt/wt) ketoprofen; F, 5% (wt/wt) ketoprofen; and G, 0% (wt/wt) ketoprofen (placebo nanoparticles). Curve A was reduced by a factor of 20 to fit in the same image.

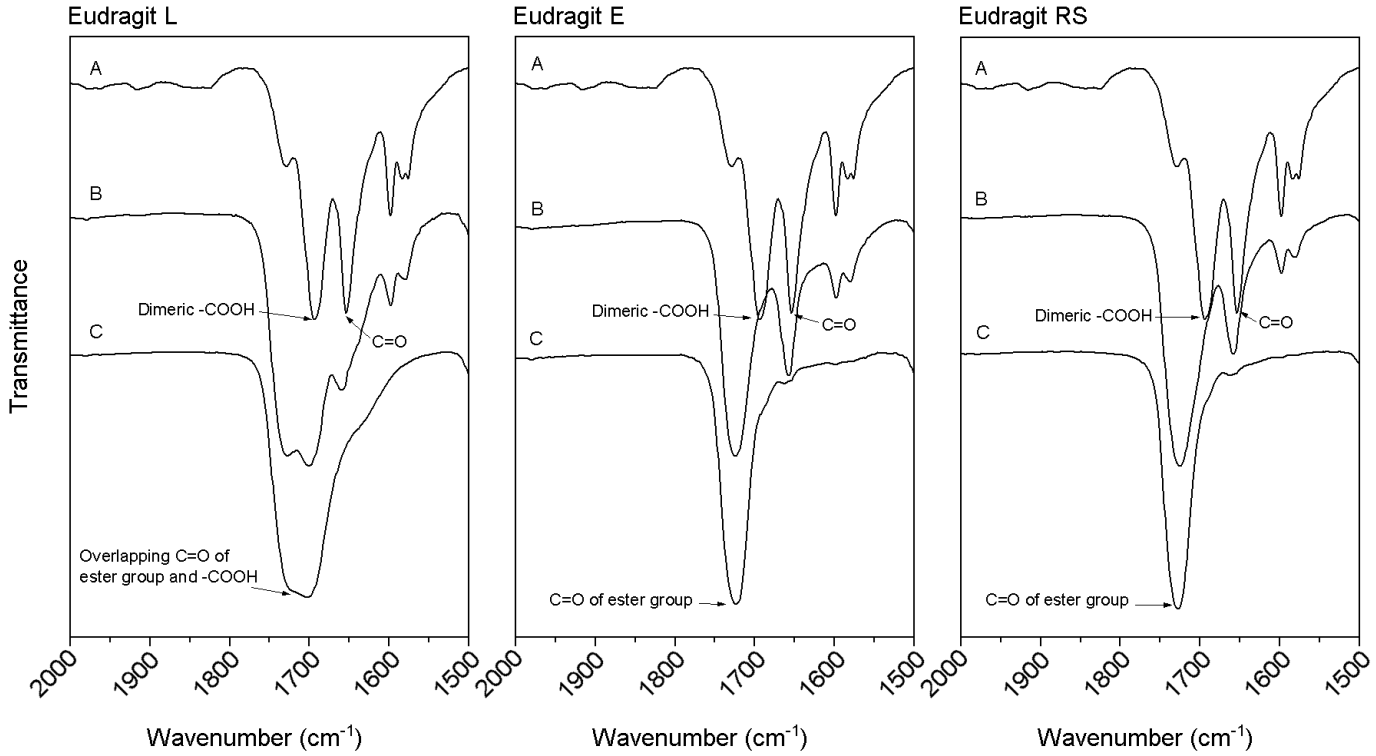


**Figure 7.** Infrared spectra at a wavenumber range of 2000 to 1500 $cm^{-1}$ of the following: A, pure ketoprofen; and nanoparticles containing B, 33% (wt/wt) ketoprofen; and C, 0% (wt/wt) ketoprofen (placebo nanoparticles).

examples, even though nanoparticle collection was not successful for all these. Considering first the nanoparticles containing no drug but only polymer (Figure 7, Eudragit L curve C), the Eudragit L polymer contains both carboxylic acid and ester groups. Therefore, the IR spectra showed overlapping carbonyl vibrations of the ester group at 1724 $cm^{-1}$ and the carboxylic acid at 1710 $cm^{-1}$.[27] However, when ketoprofen was included in the nanoparticles, this peak was split into 2 peaks as a function of increasing drug amount (see Figure 7, Eudragit L curve B). The peak at ~1724 $cm^{-1}$ could be attributed to stretching vibrations of the ester group carbonyl, similarly to Eudragit E and Eudragit RS polymers. However, the peak at the lower wavenumber was recorded at 1710 $cm^{-1}$, 1705 $cm^{-1}$, 1703 $cm^{-1}$, 1700 $cm^{-1}$, 1700 $cm^{-1}$, and 1699 $cm^{-1}$ for the nanoparticles containing 0% (wt/wt), 5% (wt/wt), 10% (wt/wt), 25% (wt/wt), 33% (wt/wt), and 50% (wt/wt) ketoprofen, respectively. This peak was interpreted as arising due to the formation of a dimer by the carboxylic acid groups of the polymer and the drug. Due to the formation of the dimer, the vibration of the carboxylic acid carbonyl was shifted to lower wavenumbers.

From Figure 7 it can be seen that the Eudragit RS and Eudragit E materials exhibit quite similar spectra (Figure 7, Eudragit RS curve C and Eudragit E curve C). The strong stretching vibration of the carbonyl moiety of ester groups could be identified for both the materials at ~1724 $cm^{-1}$.[28] For the Eudragit E and Eudragit RS nanoparticles containing ketoprofen, the position of the ester group carbonyl peak at 1724 $cm^{-1}$ was not changed (see Figure 7, Eudragit E curve B and Eudragit RS curve B). However, the peak corresponding to the carboxylic acid group of ketoprofen at 1694 $cm^{-1}$ was not seen in the spectra of the composite nanoparticles, whereas the peak arising from the ketone carbonyl at 1654 $cm^{-1}$ could be identified. The carboxylic acid group of the ketoprofen molecule interacted with the polymers, leading to the disruption of the carboxylic acid dimer of the crystalline ketoprofen. As a result, the carboxylic acid stretching vibration occurred at higher wavenumbers,[25,26] was overlapped by the strong ester vibrations of the polymer, and could not be detected.

Eudragit E is a polymer containing secondary amino groups capable of accepting a proton from an acid molecule. It was initially assumed that at least a fraction of the amino groups of the polymer would be protonated by the acidic drug in the ethanolic solution. The peaks corresponding to the amino groups have been identified previously[29] at 2820 $cm^{-1}$ and 2770 $cm^{-1}$. However, any change in the position of these peaks was not observed when ketoprofen was incorporated in the nanoparticles. Therefore, it was concluded that ketoprofen drug mainly interacted with the ester groups of the Eudragit E polymer, similarly to Eudragit RS.

### *Drug Release*

Drug release was evaluated for the nanoparticles prepared from different polymers, and the results are shown in Figure 8. Nanoparticles prepared from Eudragit L showed an initial,

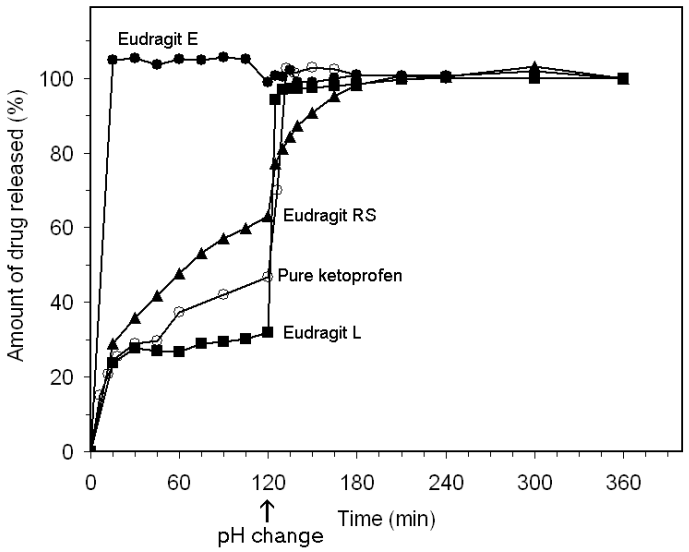


**Figure 8.** Drug release for ketoprofen nanoparticles containing 10% (wt/wt) ketoprofen and 90% (wt/wt) different Eudragits.

instant release of ~30% of the drug in the acidic stage of the test. However, the drug release was slightly slower than of pure ketoprofen. After the pH change, complete dissolution of the nanoparticles took place rapidly. At the buffer conditions (pH 6.8), the Eudragit L copolymer was ionized and soluble in the medium, thereby releasing the drug immediately. Eudragit E polymer, however, is soluble at the acidic conditions. Complete release of the drug was obtained for Eudragit E nanoparticles in the acidic medium in less than 15 minutes as a result of polymer dissolution. As the polymer dissolved, also the drug contained in the nanoparticles was forced into the solution. Drug release from the nanoparticles was much faster than of pure ketoprofen (see Figure 8). Eudragit RS nanoparticles showed sustained release of the drug at the acidic conditions, and the drug release was found to be approximately linear. Similar to Eudragit L nanoparticles, ~30% of the drug was released initially. Further drug release from the nanoparticle matrix was controlled by the polymer. When the pH was changed, the amount of the released drug changed rapidly from ~60% to almost 80%. At the buffer conditions, release of the drug was faster as the ketoprofen molecules were ionized. Most likely, the ketoprofen molecules at or close to the surface of the nanoparticles could deprotonate at these conditions, and had a greater tendency to dissolve.

Two possible mechanisms are proposed for the initial 30% drug release from Eudragit L and Eudragit RS nanoparticles. First, the nanoparticles can contain a larger a proportion of drug at the surface of the particles in comparison to the interior of the particles. Such an uneven distribution could arise from diffusion of the small molecules to the particle surface during the particle preparation and drying process. When such particles are immersed in dissolution medium, the drug at the surface is immediately released, and only further control of drug release is due to the polymers. Second, if the dissolution medium can penetrate to some extent to the polymer matrix, the drug molecules at and close to the surface will dissolve.[30,31] Theoretically calculated for a 100-nm nanoparticle, which has a uniform distribution of drug (10% [wt/wt]) and polymer (90% [wt/wt]), medium should be able to initially penetrate to a 5-nm depth to allow 30% drug release. As in the previous case, further control of drug release is controlled by the properties of the polymer.

## CONCLUSION

In this study, it was observed that 2 factors affect the stability of nanoparticles during collection in the aerosol flow reactor method. First, the interactions between the drug and the polymer had an effect on the drug loading of the nanoparticles. For Eudragit L nanoparticles, the solubility of drug in the polymer matrix was the limiting factor for drug incorporation. When the amount of drug in the polymer matrix was higher than the solubility limit of drug in the polymer, crystallization of drug was observed. Second, the thermal properties of the drug-polymer composite nanoparticles affected the stability of the nanoparticles. For the nanoparticles containing Eudragit RS and Eudragit E, the thermal properties of the nanoparticles did not allow collection of dry powders. The drug acted as a plasticizer to the polymers, and the glass transition temperature of the nanoparticles was lowered close to room temperature. Consequently, the mechanical strength of the nanoparticles was lost, which led to coalescence of the nanoparticles.

## ACKNOWLEDGMENTS

The authors are grateful to Mr Marc Donsmark (Donsmark Process Technology, Fredriksberg, Denmark) for donating the Eudragit materials. The authors wish to thank Mr Raoul Järvinen for his assistance in building the experimental setup. Prof Heikki Tenhu (University of Helsinki, Department of Chemistry) is acknowledged for DSC and IR analysis equipment time.

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