Preparation of drug nanoparticles by emulsion evaporation method

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Abstract. Polymeric drug nanoparticles were prepared by emulsion solvent evaporation method. In this study, prepared the polymeric drug nanoparticles consist of ketoprofen and Eudragit E 100. The morphology structure was investigated by scanning electron microscopy (SEM). The interactions between the drug and polymer were investigated by Fourier transform infrared spectroscopy (FTIR). The size distribution was measured by means of Dynamic Light Scattering. The nanoparticles have an average size of about 150 nm. The incorporation ability of drugs in the polymeric nanoparticles depended on the integration between polymer and drug as well as the glass transition temperature of the polymer.

Keywords: Nanoparticles, Eudragit, emulsion evaporation method, polymeric nanoparticle, drug.

1. Introduction

Drug nanoparticles can be defined as drug-containing particles having size measured by μm. They have potential applications for tissue targeting in cancer therapy, controlled release, carrier action for the delivery of peptides, and increase of the solubility of drug [1, 2]. Drug nanoparticles consist of the drug material and, usually, a stabilising polymer. First polymer nanoparticles for pharmaceutical application were prepared in the late 1960’s and early 1970’s [3, 4].

Various techniques have been used to manufacture nanosized drug particles with size down to hundreds and even tens of nanometres. One of the popular methods for the encapsulation of drug within water - insoluble polymer is the emulsion solvent evaporation method. The emulsion evaporation techniques were developed at the end of the 1970s and have been used successfully in the preparation of microspheres made from several biocompatible polymers.

Eudragits are biocompatible co-polymers synthesized from acrylic and methacrylic acid esters. These polymers have been widely used in pharmaceutical industry for various coating applications as well as for microencapsulation and nanoparticle synthesis purpose [5]. Eudragit E 100 is a co-polymer consisting of 1:2:1 molar ratio of methol methacrylate, N, N – dimethylaminoethyl methacrylate, and butyl methacrylate monomers.

The aim of the study was to prepare drug nanoparticles using emulsion solvent evaporation method. Eudragit E 100 was used as stabilisation materials in this study. The model drug used was ketoprofen.
2. Experimental

2.1. Materials
The following chemicals were obtained from commercial sources and used as received: Ketoprofen (USP-30) (Röhm Pharma, Darmstadt, Germany), Eudragit E 100, chloroform (Merck, Germany), Lactose (Merck, Germany), Sodium dodecyl sulphat (SDS) (Merck, Germany), Aceton (Merck, German).

2.2. Preparation of the drug nanoparticles
Eudragit E100 was used as stabilisation materials in this study. The model drug used was ketoprofen, which is an example of a poor water soluble corticosteroid. Ketoprofen and Eudragit were prepared by separately dissolving in chloroform at room temperature using a magnetic stirrer. After that, the solution of Eudragit and ketoprofen was combined at respective amounts. Sodium dodecyl sulphat was then added into solution containing ketoprofen and Eudragit to achieve a final solution. The mixture was agitated with a magnetic stirring until the complete evaporation of organic solvent was accomplished. After that, the protective excipients glucose (50 - 400 mg) and lactose (100 - 300 mg), as aqueous solutions, were added to the nanoparticle dispersions. The nanoparticle dispersions were frozen at -32°C for a minimum of 12h and freeze-dried at -55°C and 0.5 kPa for 24 h.

2.3. Characterization of particles
The morphology of the particles was analyzed using a scanning electron microscopy (SEM) (JSM 6480LV-JEOL- JAPAN). The size distribution was measured by means of Dynamic Light Scattering (HORIBA Lb-902-JAPAN).

The interactions between the drug and the polymers were investigated using a Fourier transform spectrometer (FTIR) (TENSOR™ 37-BRUNER-USA) in the wavelength region from 4000 to 400 cm⁻¹.

The crystal phase identification of the studied samples was carried out using X-ray diffraction (XRD) (Philips PW 1710 diffractometer, Eindhoven and Almelo, The Netherlands) with Cu-Kα radiation at 40 kV and 100 mA, the scan range (2θ) was from 5° to 40°.

3. Results and discussion
Figure 1 shows scanning electron microscopic photographs of ketoprofen (a) and nanoparticle containing ketoprofen and Eudragit E100 (b and c). In figure 1c, the morphology of particles was spherical and not aggregated. The spheres have mean diameters around 150 nm. The nanoparticles dry powder consists of individual nanoparticles, which touch each other, but retain their original size and shape.

![Figure 1](image1.jpg)

**Figure 1.** SEM images of Ketoprofen (a) nanoparticles containing ketoprofen and Eudragit E 100; (b) magnification 500 x; and (c) magnification 15000 x.

Infrared spectroscopy was used to study the interactions between the drug and the polymers. Figure 2 shows IR spectra at a wavenumber range of 4000 - 400 cm⁻¹. In figure 2a, the IR spectra of the pure Eudragit E 100 shows the strong stretching vibration of the carbonyl moiety of ester groups at 1732

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**Figure 2.** IR spectra of Ketoprofen and nanoparticles containing ketoprofen and Eudragit E 100.
cm$^{-1}$. The peak corresponding to the amino groups of the Eudragit E 100 have been identified at 2958.35 and 2773.87 cm$^{-1}$. However, any change in the position of these peaks was not observed when ketoprofen was incorporated in the nanoparticles (figure 2c). It can be concluded that ketoprofen drug does not protonate the amino groups, but mainly interacts with the ester groups of the Eudragit E 100. Figure 2b shows the IR spectra of ketoprofen. The peak corresponding to the carboxylic acid group of ketoprofen at 1697.03 cm$^{-1}$ was observed in the spectra. However, this peak was not observed in the spectra of the nanoparticle (figure 2c). The carboxylic group of the ketoprofen molecule interacts with the polymers, leading to disruption of the carboxylic acid.

![Infrared spectra](image)

**Figure 2.** Infrared spectra at a wavenumber range of 4000 to 400 cm$^{-1}$ of the following: (a) pure Eudragit E 100; (b) pure ketoprofen; (c) nanoparticles containing Eudragit E 100 and ketoprofen.

Figure 3 shows the particle size distribution of nanoparticles containing ketoprofen and Eudragit E 100. Size distributions were determined by Dynamic Light Scattering in aqueous solution, the size of the particles was in the range from 50 to 200 nm, the mean diameter was 150 nm.
Figure 3. Particle size distributions of nanoparticle containing ketoprofen and Eudragit E 100.

Figure 4 shows X-ray diffraction patterns of (a) ketoprofen and (b) nanoparticles containing ketoprofen and Eudragit. In figure 4b, XRD shows diffraction pattern of the amorphous structure and no crystallinity. The strongest diffraction peaks of crystalline ketoprofen at $6.5^\circ$ ($2\theta$) could not see in the diffraction curve of the nanoparticles containing ketoprofen and Eudragit E 100. We can conclude that the nanoparticles powder as-prepared was amorphous, as peaks corresponding to diffraction from drug crystal lattice were not detected.

Figure 4. X-ray diffraction patterns: (a) Ketoprofen; (b) nanoparticle containing ketoprofen and Eudragit E 100.

4. Conclusion
Polymeric drug nanoparticles were prepared by emulsion solvent evaporation method. By using a mixture of protective excipients glucose and lactose as the dispersed organic phase, the more stable particles could be prepared. The SEM observations give the surface morphological features, morphology of particles was spherical and homogeneous. The size distribution of the nanoparticles prepared was found in the range from 50 to 200 nm, the mean diameter was 150 nm. The interaction between the drug and the polymer was determined by FTIR. The carboxylic group of the ketoprofen molecule interacts with the Eudragit.

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