COMPRESSED CO_2 ANTI-SOLVENT PRECIPITATION OF DRUG-POLYMER MICROPARTICLES FOR ENHANCED DISSOLUTION.

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The possibility of enhancing the dissolution of the slightly soluble anticonvulsant drug phenytoin by using compressed CO_2 as antisolvent has been assessed. In a first step, the Gas Antisolvent (GAS) and Precipitation with Compressed Antisolvent (PCA) processes were adopted and the effect of the major operating parameters on the particle size and morphology were investigated. In the case of the GAS process, the average size of the particles varied between 200 and 150 μm. In the case of the PCA technique, needle like crystals in the 10-100 μm range were obtained in the initial solution concentration, temperature and flow rate ranges tested. In a second step, the PCA technique was adopted to produce co-formulations of phenytoin and the biodegradable polymer polyvinylpyrrolidone K30 (PVP) and the effect of temperature, pressure and drug to polymer content ratio in the initial solution was studied. At operating conditions below the mixture's critical point submicron spherical particles were obtained and combined analysis using Raman spectroscopy, XRD and DSC showed that phenytoin is not present in the crystalline state, but is molecularly dispersed in the polymer matrix. Results from "in vitro" dissolution rates measurements showed a substantially higher performance of the co-formulations if compared to unprocessed phenytoin. Finally the dissolution rate performance of composites obtained by PCA and spray drying is compared. The formulation of phenytoin in PVP by the PCA technique seems to be a valuable strategy to increase the dissolution rate of this slightly soluble drug.

INTRODUCTRION

The enhancement of the oral bioavailability of slightly soluble drugs is a particularly challenging aspect for the pharmaceutical industry – an aspect that will become even more crucial in future.
An alternative to the conventional ways to enhance the dissolution behavior, hence the bioavailability of drugs, is represented by the method denominated "solid solution (or dispersion)". This involves the embedding of the drug into a water soluble polymeric carrier. However problems concerning the current methods of preparation of the solid dispersions, e.g. poor reproducibility and chemical instability, among others, have hindered their widespread commercial application so far.
This paper explores the possibility of preparing solid dispersions by precipitation from solution with sc-CO_2 as antisolvent using the PCA (Precipitation with a Compressed Antisolvent) technique.

RESULTS AND DISCUSSION

In a first step phenytoin alone was precipitated from acetone/ethanol solutions using the GAS (Gas Anti Solvent) and the PCA (Precipitation with Compressed Antisolvent) processes. The effect of the major operating parameters on the particle size and morphology was investigated. In the case of the GAS process, depending on the CO_2 addition rate and on the acetone/ethanol ratio, crystal shape varied from a prismatic to a more elongated one. Thereby the average size of the particles varied between 150 and 200 µm. In the case of the PCA technique, needle like crystals in the 10-100 µm range were obtained for the values of the initial solution concentration, temperature and flow rate investigated [1].

In a second step, the PCA technique was adopted to produce co-formulations of phenytoin and the biodegradable polymer PVP K30. In the temperature (25 – 33 °C) and pressure (80-100 bar) range and initial drug to polymer ratio (1:4 – 1:2) studied, submicron spherical particles were obtained (see Figure 1). Combined analysis using Raman spectroscopy, XRD and DSC showed that phenytoin is not present in the crystalline state, but is molecularly dispersed in the polymer matrix. Very high drug loadings were determined, but the encapsulation efficiency decreased as the relative amount of drug in the starting solution was increased. When the drug to polymer content ratio was increased to 1:1, needle-like phenytoin crystals were observed in the SEM photomicrographs beside spherical microparticles; this is confirmed by the observation of characteristic phenytoin peaks in the X-ray spectra of this sample [1].

Intrinsic dissolution rate (IDR) measurements showed a ten times higher performance of the PCA co-formulations if compared to unprocessed phenytoin. Better dissolution rate performance of the PCA precipitate was also observed if compared to co-formulations produced with the spray drying technique [1]. Thus, the formulation of phenytoin in PVP by the PCA technique seems to be a valuable strategy to increase the dissolution rate of this poorly water soluble drug.

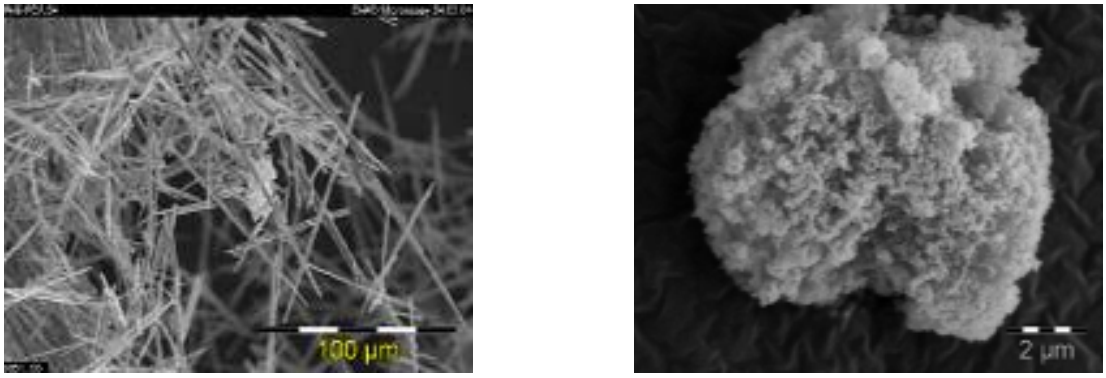

Figure 1: Neat phenytoin (left) and phenytoin-PVP co-formulation (right) precipitated with PCA.

REFERENCES:

[1] MUHRER, G. et al., International Journal of Pharmaceutics, in press.