PRODUCTION OF POLYMORPHS OF IBUPROFEN SODIUM BY SUPERCRITICAL ANTISOLVENT (SAS) PRECIPITATION

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Ibuprofen sodium has been successfully micronized using the Supercritical Anti Solvent (SAS) process. The influence of different process and operating parameters such as pressure, temperature, concentration, flow ratios, mixer design and precipitator size on product characteristics (purity, particle size and morphology, and polymorphism) has been analyzed. Product analyses indicate that SAS processing does not cause any contamination or degradation of the product. Moreover, it has been shown that with an adequate selection of the supersaturation and precipitation rate during the precipitation, which can be controlled by manipulation of parameters such as temperature and CO_2:solution ratio, it is possible to selectively produce either crystalline particles with rod crystal habit and particle sizes of 1-5 μm, or amorphous spherical particles with particle sizes of about 500 nm.

INTRODUCTION

Ibuprofen is a non-steroidal ani-inflamatory drug (NSAID), used to reduce fever and to treat pain or inflammation. Although the ibuprofen free acid is the most frequently used form of ibuprofen in pharmaceutical formulations, the low solubility of this acid in aqueous media can limit the dissolution and absorption rates into the organism [1]. Formulations based on ibuprofen sodium have been developed by Bayer Consumer Care [2].

It is well known that polymorphism is important in the development of pharmaceutical ingredients, as various polymorphic forms of a chemical compound can present different physical properties affecting many characteristics such as bioavailability [3]. In the case of racemic ibuprofen sodium, three different polymorphs have been described by Zhang et al. [4].

Supercritical fluid technologies for precipitating pharmaceuticals and natural substances, and particularly the Supercritical Anti Solvent (SAS) process, can be a good alternative to conventional processes [5]. Since the solubility of ibuprofen in supercritical carbon dioxide is relatively high [6], several researchers have successfully micronized it using the Rapid Expansion of a Supercritical Solution (RESS) process [7,8]. However, preliminary tests demonstrated that, as it could be expected, the solubility of ibuprofen sodium in supercritical carbon dioxide is very low, therefore making impossible the application of RESS techniques. For this reason, a precipitation process using Supercritical carbon dioxide as Anti Solvent (SAS) has been applied in this work.

MATERIALS AND METHODS

Ibuprofen sodium salt with a minimum purity of 99.8% was purchased from Sigma-Aldrich. Absolute ethanol with a minimum purity of 98%, purchased from PANREAC Química (Spain) was used to prepare the ibuprofen sodium solutions sprayed into the precipitator. Carbon dioxide at 99.95% was delivered by Carburos Metálicos S.A. (Spain).

A laboratory SAS precipitation plant was used. The main elements of this plant are one diaphragm pump for the CO_2, capable of delivering a maximum CO_2 flow rate of 0.75 kg/h; one chromatographic pump for the solution, which has a variable workspace between 1-10 mL/min; a stainless steel precipitator with an internal volume of 75 mL; a back pressure regulation valve and a separation flask used to achieve the separation of solvent and CO_2 after

pressure release. The precipitator and the separation flask are submerged in a thermal bath to control temperature. More details about the experimental procedure can be found in ref [9].

RESULTS AND DISCUSSION

SEM pictures of particles obtained are shown in Figures 1-3. With the conditions used for producing the particles presented in Figure 1 (10 MPa, 313 K, CO_2/solution mass ratio 10:1), needle-like particles showing high agglomeration were produced. A change in process conditions in order to achieve a faster precipitation (10 MPa, 323 K, CO_2/solution mass ratio 10:1) allowed to produce 5 μm rod-like particles that were less agglomerated, as shown in Figure 2. A further increase in precipitation rate (12 MPa, 323 K, CO_2/solution mass ratio 15:1) produced spherical particles of about 500 nm, as presented in Figure 3.

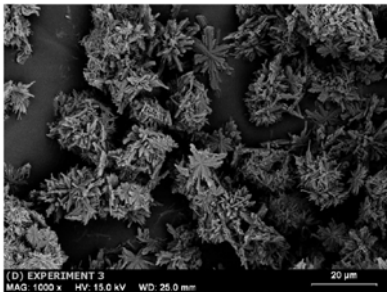

Fig 1 : Particles produced with 10 MPa,313 K, 10 kg CO2/kg sol

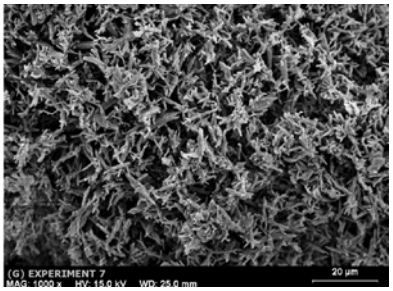

Fig 2 : Particles produced with 10 MPa,323 K, 10 kg CO2/kg sol

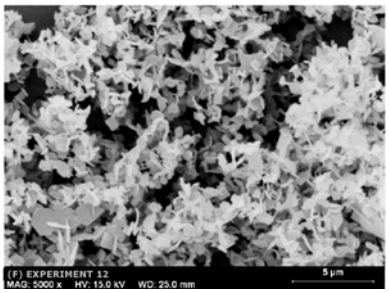

Fig 3: Particles produced with 12 MPa,323 K, 15 kg CO2/kg sol

These changes in size and morphology where accompanied by a change in crystalline structure. Diferential Scanning Calorimetry of the raw material showed an endothermik peak at 195ºC. In particles shown in Figures 1 and 2, the endothermic peak was displaced to 150ºC, and in particles shown in Fig 3, to 100ºC. Powder X-Ray Diffraction (PXRD) analysis were coherent with this result : the PXRD analysis of the raw material showed the characteristic crystalline peaks of the γ polymorph, but the PXRD analysis of particles shown in Fig 1 and 2 showed different crystalline peaks, and the PXRD pattern of particles shown in Fig.3 was nearly flat, indicating an amorphous structure. Therefore different crystalline polymorphs or amorphous particles were produced depending on the precipitation conditions.

CONCLUSIONS

Ibuprofen sodium was successfully precipitated from ethanol solutions using the Supercritical Anti Solvent process. Different particle sizes, in the range 5 μm – 500 nm, with different morphologies (rod-like or spherical) were produced. It was also possible to produce different crystalline or amorphous polymorphs by changing the rate of the precipitation.

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