CHARACTERIZATION OF NALMEFENE HYDROCHLORIDE MICRONIZED BY SUPERCRITICAL ANTISOLVENT TECHNIQUE

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Nalmefene hydrochloride has been micronized using Supercritical AntiSolvent precipitation technique. Experiments have been performed using a laboratory-scale apparatus, and on a pilot-scale plant. Ethyl alcohol (EtOH) has been used as liquid solvent.

The particles produced using the two plants have the same morphology and comparable size (from 0.5 to 2 μm). The micronized product has been characterized using X-ray analysis, to verify the influence of the micronization process on the final product properties. XRD analysis demonstrated that it is possible to obtain amorphous or crystalline precipitates, depending on the process conditions.

INTRODUCTION

SAS technique is largely used to produce micronized pharmaceutical compounds on laboratory scale [1-8]. However, only a few experiments have been performed on pilot scale [9-12] and information on the parameters to be controlled to perform a successful scale-up of the process are still confused.

Moreover, information on SAS produced powders are frequently limited to the particle size and the morphology observed by SEM. A complete characterization of precipitates is missing.

Nalmefene hydrochloride, a selective narcotic antagonist and a promising adjunctive for the treatment of ethanol dependence, has been successfully micronized by SAS and in this work scale-up process and a more detailed characterization of the produced powder will be described.

APPARATUSES AND PROCEDURE FOR SAS PRECIPITATION

Apparatus

The laboratory apparatus used for SAS experiments (**figure 1**) is located at the University of Salerno (Italy) and the pilot plant (10 dm^3 volume) (Chematur Engineering, Finland) is located at the MTT Agrifood Research Finland, Jokioinen (Finland). Descriptions of the two systems and details of the procedure of a SAS experiment have been given elsewhere [13-17].

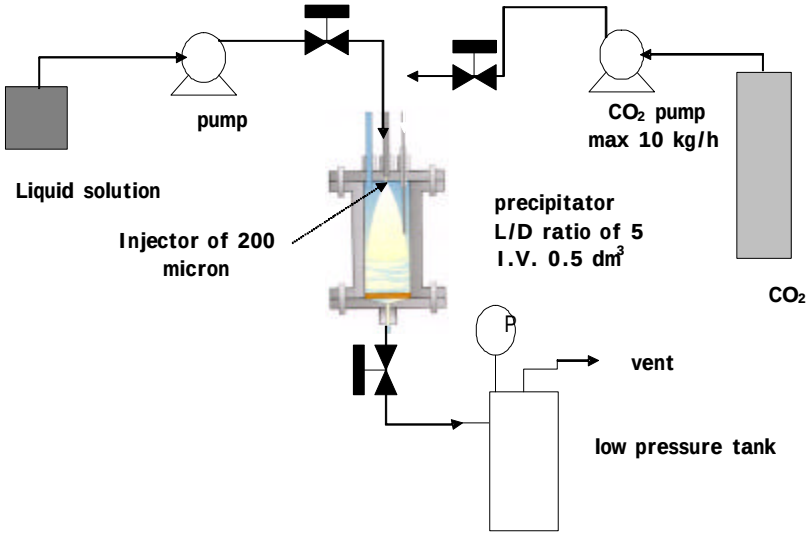

Figure 1 SAS laboratory apparatus

Materials

Nalmefene HCl with a purity of 99.9% (Mw=375.9 MP=203÷206°C) was supplied by Contral Pharma Ltd (Finland). Ethyl alcohol (EtOH) with a purity of 99.9% was supplied by Sigma-Aldrich (Italy) and with a purity of 96% was supplied by Primalco LTD (Finland). CO_2 99.9% was given by SON (Naples, Italy).

The solubility profile of Nalmefene HCl in liquid solvents was obtained from Contral Pharma Ltd. (Finland). The approximate solubility in EtOH is of 26 mg/ml at room temperature. Untreated material was crystalline. All materials were used as received.

Analytical methods

Samples of the powder precipitated on the metallic frit were observed by a Scanning Electron Microscope (SEM) mod. LEO 420. The SEM samples were covered with 250Å of gold using a sputter coater (Agar model 108A). Particle size and particle size distributions (PSD) were measured from SEM images using the Sigma Scan Pro image analysis software (Jandel Scientific); about 800 particle diameters were measured in the elaboration of each PSD.
The X-ray diffractogram of the powder sample was recorded on a BRUCKER D8 ADVANCE diffractometer (BRUKER AXS) operating at 40 kV and 20 mA with Ni-filtered Cu Ka radiation operating at room temperature. The range of 2q diffraction angle examined was 5–35°, the count time for each step was equal to 2 s/step, and the step width was 0.05° (2q).

RESULTS AND DISCUSSION

Nalmefene HCl was successfully micronized using a SAS laboratory scale apparatus and a semi-industrial scale apparatus. The SAS precipitation process was performed on the laboratory scale plant in a 0.5 dm^3 precipitator having an L/D ratio of 5 [16] and on the pilot scale plant in a 10 dm^3 precipitation vessel [17]. From a design point of view, the most relevant differences between the two apparatuses are the kind of injector and the precipitator volume that has been increased of more than one order of magnitude.

SEM investigations of the powder produced with the laboratory plant showed particles with different morphologies and dimensions depending on the operative conditions of the micronization process. Operating at 40°C and different pressures, particles were submicronic ans slightly coalescent. At 60°C and in the range of pressure between 120 and 150 bar

particles obtained were micronic, spherical and well separated, as demonstrated by SEM images in **figure 2**.

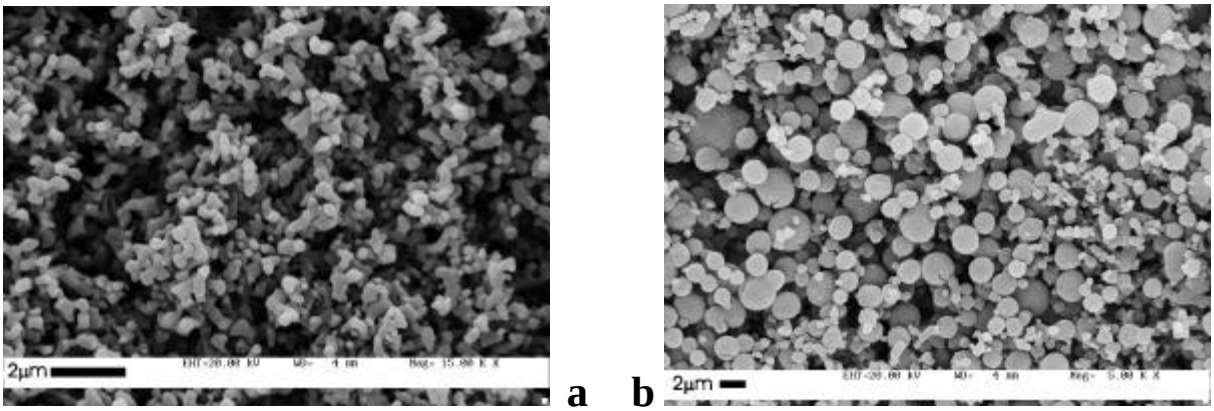

Figure 2 Comparison of SEM image of Nalmefene HCl particles precipitated from EtOH (a) at 150 bar, 40°C and (b) 130 bar, 60°C.

The particles produced using the pilot plant also show different morphologies in changing the micronization temperature: in **figure 3** we can observe that by increasing the temperature there was an increasing of particle size and a variation of morphology from spherical micronic particles to empty balloons several microns in diameter.

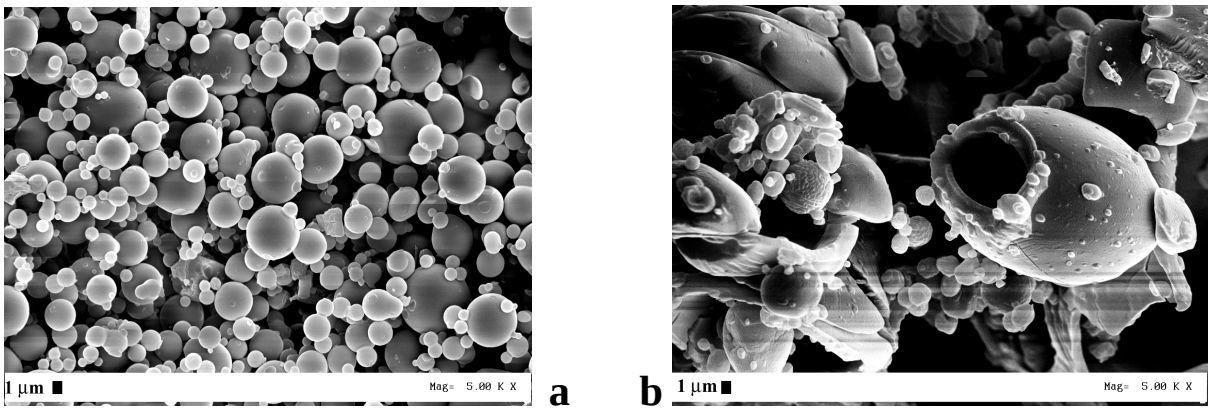

Figure 3 Comparison of SEM image of Nalmefene HCl particles precipitated from EtOH at 130 bar (a) 45°C and (b) 65°C.

We have calculated the particle size distribution of the powders obtained and presented it in terms of percentages calculated on particle number. All the distributions are approximately log-normal, as shown in **figure 4**. The mode of the particles size distributions ranges between 1 and 1.5 µm for the particles obtained with the laboratory scale plant and from 1.8 to 5 µm for the semi-industrial plant. The difference might be related to the different precipitation temperature. We observed that increasing the operative pressure in the both apparatuses the particles obtained had an increasing mean particles size and an enlargment of size distributions.

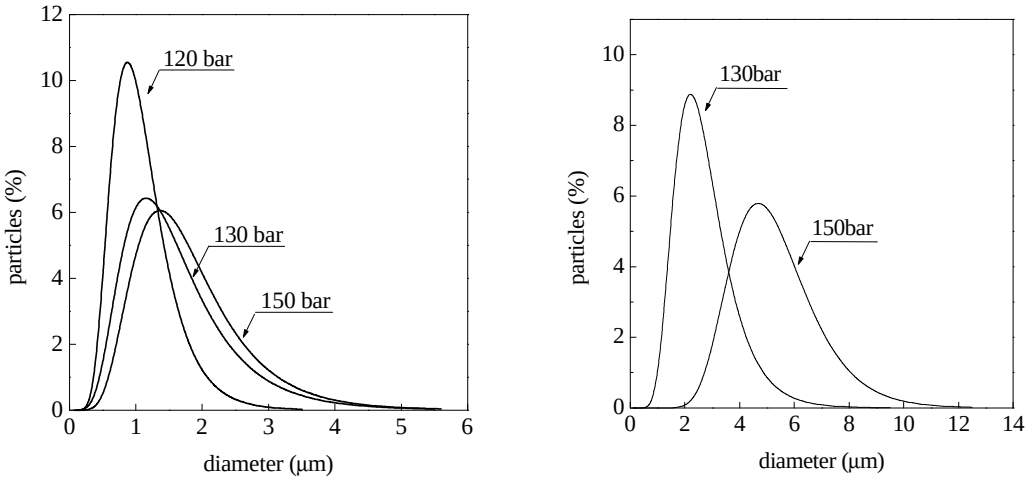

Figure 4 PSDs of Nalmefene HCl powders from EtOH produced using the laboratory plant at 60°C (left side) and the pilot plant at 45°C (right side).

X-ray analysis has been performed on the micronized powder. Untreated nalmefene HCl shows as expected a crystalline structure (**figure 5**).

The powder obtained on laboratory scale at 150 bar 40°C showed a XRD trace typical of amorphous compounds, the same results were obained varying the SC-CO_2/solvent flow ratio. Increasing the process temperature to 60°C a XRD trace of a crystalline product has been obtained as shown in **figure 6**.

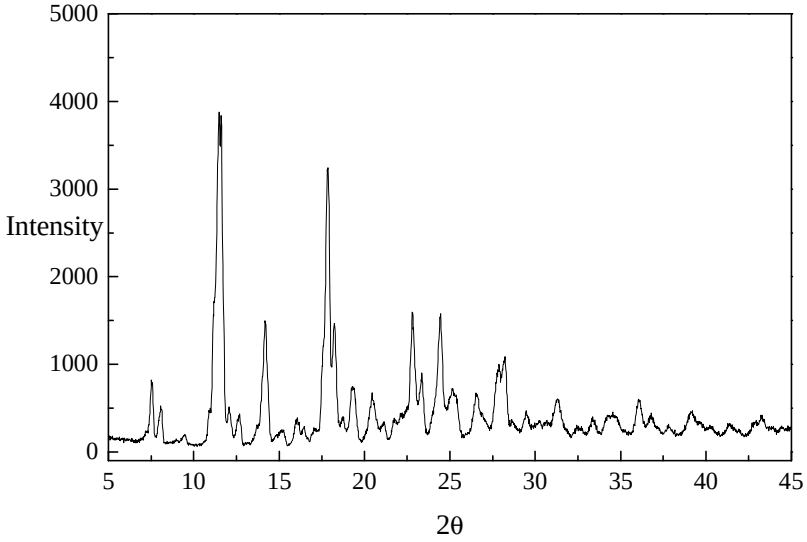

Figure 5 X-ray of untreated nalmefene HCl

The powder produced using the semi-industrial plant at similar operative conditions showed also a crystalline structure (**figure 6**).

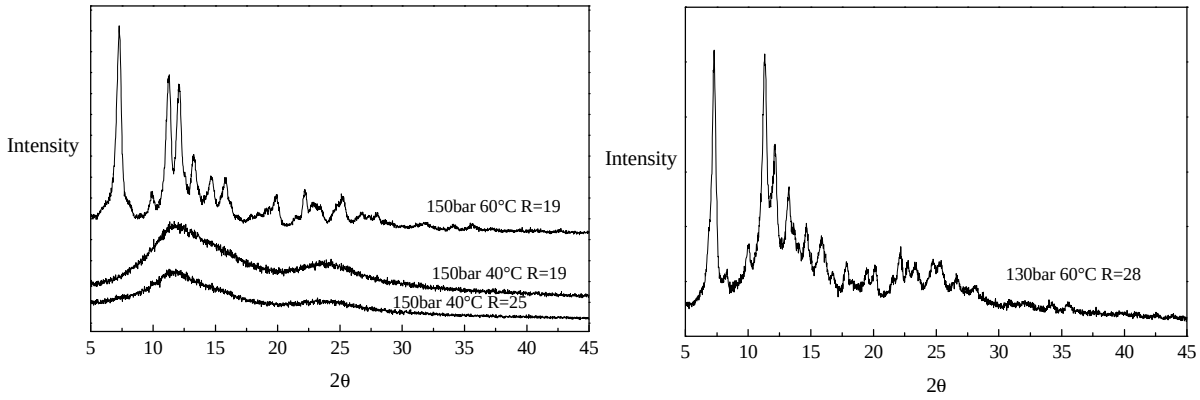

Figure 6 X-ray of nalmefene HCl micronized with SAS laboratory apparatus (left side) and semi-industrial apparatus (right side)

If we compare X-ray results with SEM images we can observe that the submicrometric particles produced using the laboratory plant are amorphous; whereas, the spherical micronic particles produced with both apparatuses are crystalline. It means that not only the particle size can be varied changing the SAS operative conditions but it is also possible to control the switch from amorphous to crystalline particles that is particularly relevant in pharmaceutical applications.

Moreover, the combination of the analyses performed proved that the scale-up of the SAS micronization process of nalmefene HCl can be reliable, thus, larger particles have been obtained using the larger plant.

Further investigations are necessary to trace a complete framework of results and to give an interpretation of changes in particle size, morphology and crystallinity.

Acknowledgments

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REFERENCES

[1] WERLING, J. O., DEBENEDETTI, P. G., J. Supercrit. Fluids, Vol. 18, **2000**, p. 11.
[2] JUNG J., PERRUT M., J. Supercritical Fluids, Vol. 20, **2001**
[3] REVERCHON, E., J. Supercrit. Fluids, Vol. 15, **1999**, p. 1.
[4] REVERCHON, E., DELLA PORTA, G., Powder Technology, Vol. 106 (1-2), **1999,** p. 23.
[5] REVERCHON, E., DE MARCO, I., DELLA PORTA, G., Int. J. Pharm., Vol. 243 (1-2), **2002**, p. 83.
[6] REVERCHON, E., DE MARCO, I., DELLA PORTA, G., International Journal of Pharmaceutics, Vol. 243, **2002**, p. 83.
[7] REVERCHON, E., DE MARCO, I., J. Supercrit. Fluids, **2004**, in press
[8] DEHGHANI, F., FOSTER, N.R., Current Opinion in Solid State and Materials Science, **2004**, in press.
[9] WEBER, A., TSCHERNJAEW, J., BERBER, Th., BORK, M, Proceedings of the 5th Meeting on Supercritical Fluids, Nice, **1998**, pp. 281-285.
[10] YORK, P., PSST 2 (11), **1999**, p.430.

[11] KORNER, J.P., BORK, M, Proceedings og the 5th Meeting on Supercritical Fluids, Nice, **1998**, pp. 287-290.
[12] REVERCHON, E., DE MARCO, I., CAPUTO, G., DELLA PORTA, G., J. Supercrit. Fluids, Vol. 26, **2003**, p. 1.
[13] REVERCHON, E., DELLA PORTA, G., PACE, S., DI TROLIO, A., Ind. Eng. Chem. Res., Vol. 37, **1998**, p. 952.
[14] REVERCHON, E.; DELLA PORTA, G.; CELANO, C.; PACE, S. DI TROLIO; A; J. of Material Res., Vol. 13 (2), **1998**, p. 284.
[15] DIXON, D.J., JOHNSTON, K.P., BODMEIER, R.A., AIChE J., Vol. 39 (1), **1993**, p. 127.
[16] ADAMI, R., REVERCHON, E., AALTONEN, O., JARVENPAA, E., HUOPALAHTI, R., Proceedings of 6th International Symposium on Supercritical Fluids, Versailles, **2003**, pp. 1623.
[17] ADAMI, R., REVERCHON, E., AALTONEN, O., JARVENPAA, E., HUOPALAHTI, R., Proceedings of 6th International Symposium on Supercritical Fluids, Versailles, **2003**, pp. 1753.