Supercritical Antisolvent Precipitation of Sotalol Hydrochloride: Influence of Solvent and of Apparatus Design

P.Alessi*, I.Kikic, F. Vecchione, T.Gamse[(1)]
Dipartimento di Ingegneria Chimica, dell'Ambiente e delle Materie Prime (DICAMP)
University of Trieste, Piazzale Europa 1, 34127 Trieste, Italy
Email: Paolo.Alessi@dicamp.units.it
[(1)] Department of Chemical Engineering and Environmental Technologies, Graz University of Technology, Inffeldgasse 25/C, A-8010 Graz, Austria
Email: Thomas.Gamse@TUGraz.at

The Supercritical Anti-Solvent precipitation (SAS) technique was invested in order to obtain the precipitation of a beta receptor drug, sotalol hydrochloride, from two different organic solvents (methanol and ethanol). In preliminary studies the solubility of sotalol hydrochloride in CO_2 was determined and with the SAS batch apparatus the precipitation pressure for different drug concentration at a given temperature was tested. The following step was to analyse vapour-liquid equilibria (VLE) modifications induced by the presence of the active principle, sotalol hydrochloride, for the binary system CO_2-ethanol and CO_2-methanol at different solute concentration with a variable volume cell.

The final step was the precipitation of sotalol hydrochloride with two different designs of semi-continuous SAS apparatus. Scanning Electronic Microscopy (SEM) analysis completed the study in order to determine the role of SAS process parameters (pressure, concentration) and the effect of different solvents on the size and morphology of the drug.

INTRODUCTION

In pharmaceutical area, micro and nano particles with a narrow particle size distribution are required to obtain a high surface area to increase the bioavailability of a drug and its absorption from the gastro intestinal tract. In an attempt to find improved methods of pharmaceutical processing great interest has been expressed in the SCFs technology. Carbon dioxide (CO_2) is the most commonly used supercritical fluid. In dependence on the properties of the drug different processes are developed. Substances with good solubilities in SC-CO_2 can be treated by the RESS process (**R**apid **E**xpansion of **S**upercritical **S**olution). For materials, which do not decompose until reaching the melting point, the PGSS-process (**P**articles from **G**as **S**aturated **S**olution) is suitable, where the solid is melted in the presence of a fluid and this gas saturated melt is depressurised causing fine solid particles.

Due to the low solubility of many drugs in CO_2 and to the thermal sensitivity, anti-solvent techniques should be employed. The basic of all these anti-solvent processes is that by the contact of the SCF and the solvent, in most cases organic solvents, the fluid causes a volume expansion of the liquid solvent. This causes a rapidly decrease of the solvent power and the dissolved solids precipitate from the liquid phase. The aim of this study was to investigate Supercritical Anti-Solvent (SAS) precipitation technique in order

to obtain the precipitation of a beta receptor drug, sotalol hydrochloride, from two different organic solvents (methanol and ethanol).

1. MATERIALS AND METHODS

Sotalol is a special type of beta blocker that prevents irregular heart rhythms in addition to slowing the heart rate and lowering the blood pressure. Sotalol Hydrochloride ($C_{12}H_{20}N_2O_3S$*HCl) has a molecular weight of 308.8 g/mol and a melting point of 206-219°C. The chemical structure of sotalol is given in Fig. 1.

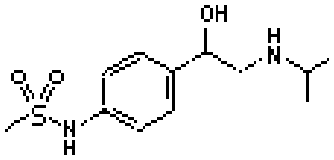

Figure 1: Chemical structure of sotalol

1.1. SOLUBILITY OF SOTALOL HYDROCHLORIDE IN SC-CO_2

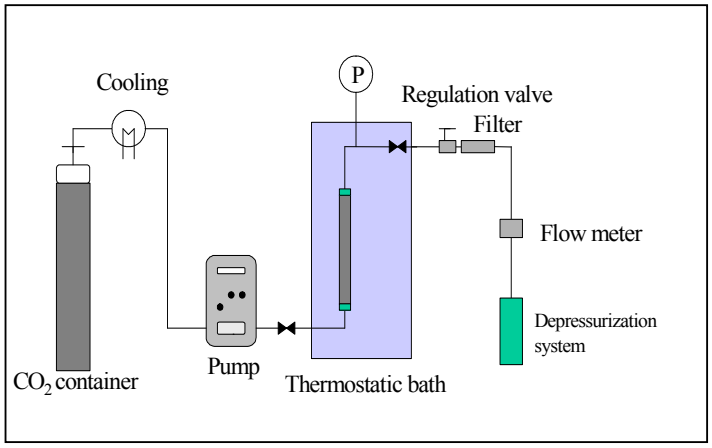

Figure 2: Apparatus for determination of drug solubility in supercritical CO_2

From literature data no solubility data of sotalol in supercritical carbon dioxide were available. For this reason in the first step the experimental apparatus shown in Fig. 2 was used for determination of sotalol solubility in SC-CO_2. The experimental solubility at 100 bar and 60°C resulted in 2 10^{-9} mol/mol. Based on this extremely low solubility the use of a RESS-process is not sufficient for this substance.

1.2. SOLUBILITY OF SOTALOL HYDROCHLORIDE IN METHANOL AND ETHANOL

In the next step a suitable solvent had to be chosen representing a high solubility for sotalol HCl and further a suitable volumetric expansion behavior during contact with SC-CO_2. The best solubilities of sotalol HCl were determined for methanol and ethanol, with saturation concentrations in methanol of 20.1 wt% at 25°C and 24.2 wt% at 40°C and in ethanol of 6.31 wt% at 25°C and 10.1 wt% at 40°C.

1.3. VOLUMETRIC EXPANSION OF METHANOL, ETHANOL AND THEIR MIXTURES WITH SOTALOL HYDROCHLORIDE

The determination of the volumetric expansion of methanol and ethanol but also of sotalol-solvent mixtures was performed in a view cell with an internal volume of 50 cm^3. First the volumetric expansion of the pure solvents depending on pressure and temperature were performed. Based on these data the influence of different sotalol

concentrations on the volumetric expansion behavior of methanol and ethanol was determined.

As shown in Fig. 3 and Fig. 4 both solvents represent a dramatic expansion with increasing pressure. On the other hand no influence of sotalol hydrochloride concentration on the volumetric expansion could be detected, neither for methanol nor for ethanol.

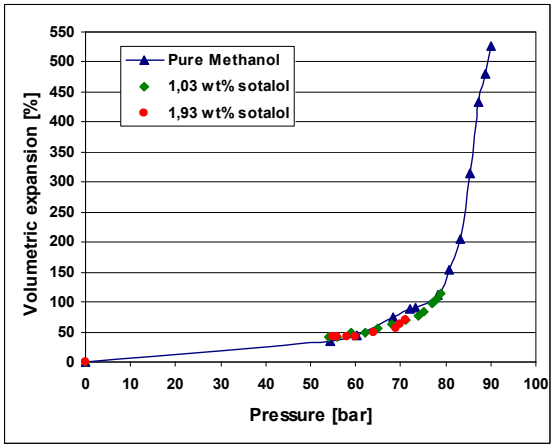

Figure 3: Volumetric expansion curves of methanol and sotalol HCl -methanol mixtures at 40°C

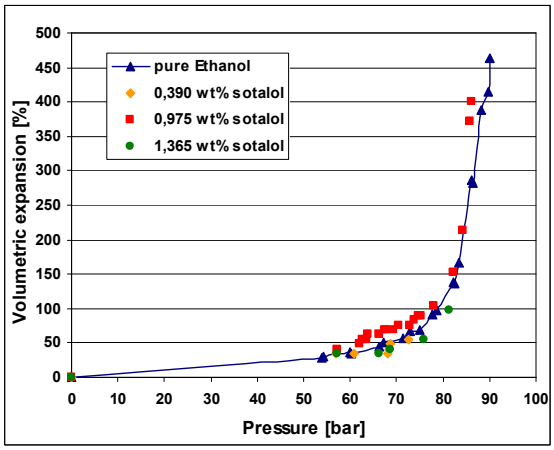

Figure 4: Volumetric expansion curves of ethanol and sotalol HCl -ethanol mixtures at 40°C

1.4. SAS-APPARATUS DESIGN FOR PRECIPITATION OF SOTALOL HYDROCHLORIDE

For choosing convenient operation pressures in the continuous SAS-process first the saturation pressures of the drug were determined in a batch system. From Fig. 5 it is obvious that for methanol as solvent higher concentrations could be achieved compared to ethanol.

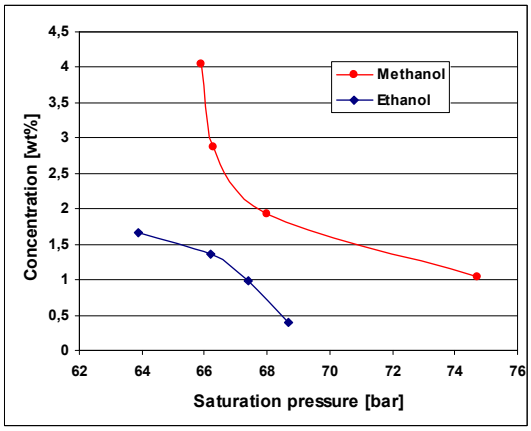

Figure 5: Saturation pressure of sotalol hydrochloride in methanol and ethanol at 40°C

The final step is the precipitation of sotalol hydrochloride with two different designs of semi-continuous SAS apparatus. Fig. 6 shows the flow sheet of the apparatus of DICAMP, University of Trieste. The solution enters separately from the CO_2-stream the precipitation chamber by a nozzle of 100µm inner diameter. At the outlet of the precipitator a filter separates the particles before the separation of solvent and CO_2 takes place.

The SAS-apparatus of Graz University of Technology is shown in Fig. 7. The main difference is that the solution is contacted with the SC-CO_2-flow within a coaxial nozzle. The inner diameter of the CO_2-pipe is 2,23 mm. The pipe of the solution,

which is inside the CO_2-pipe and ends 20 mm before the CO_2-pipe, has an outer diameter of 1,59 mm and an inner diameter of 0,39 mm.

For the semi-continuous SAS experiments the parameters pressure (80 - 120 bar), temperature (40 - 55°C), sotalol concentration (2,0 - 4,0 wt% in methanol, 0,5 - 1,5 wt% in ethanol) and the flow rates of CO_2-and solution were varied.

Scanning electronic microscopy (SEM) analysis of the processed particles were performed to determine the role of the different SAS-process parameters and the effect of different solvents on the size and morphology.

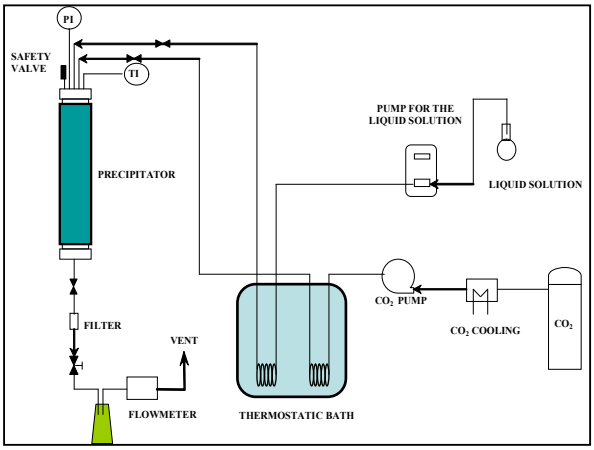

Figure 6: SAS-apparatus of University of Trieste

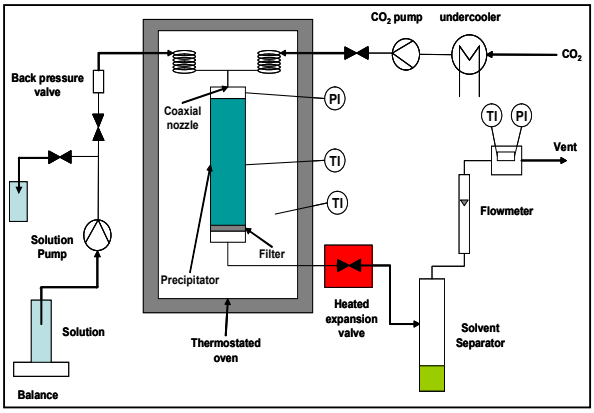

Figure 7: SAS-apparatus of Graz University of Technology

2. RESULTS

The origin sotalol hydrochloride crystals analysed by SEM shows particle sizes of 50 - 100 µm (see Fig. 8).

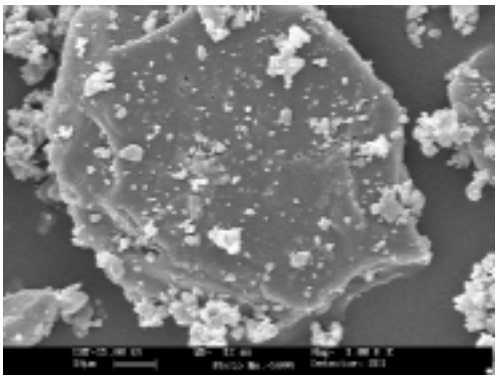

Figure 8: Orginal sotalol hydrochloride

2.1. INFLUENCE OF SOLVENT

For all experiments the particles processes with ethanol as solvent represent a much better and uniform morphology and of better size distribution (see Fig. 9). In contrary the particles processed with methanol produce in many cases thin films with large surfaces. So for SAS-processing ethanol gives the better results, with the disadvantage that the solubility of sotalol hydrochloride is much lower than in methanol.

2.2. INFLUENCE OF PRESSURE

An increase of pressure up to 120 bar results for all methanol and ethanol solutions with different concentrations of sotalol hydrochloride in smaller and more uniform particles (see Fig. 10).

2.3. INFLUENCE OF TEMPERATURE

At temperatures of 40°C smaller and more uniform particles were produced for all ethanol solutions with different concentrations and for all

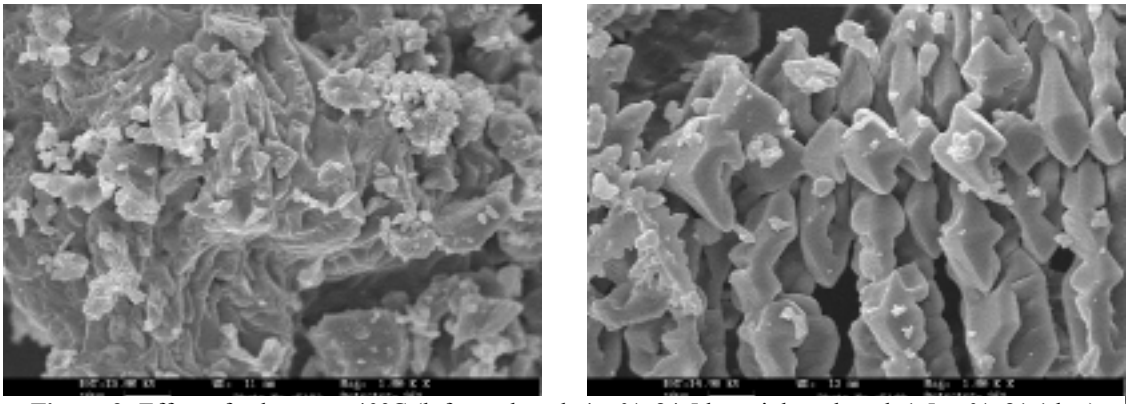

Figure 9: Effect of solvents at 40°C (left: methanol, 4wt%, 84,5 bar, right: ethanol, 1,5 wt%, 81,1 bar)

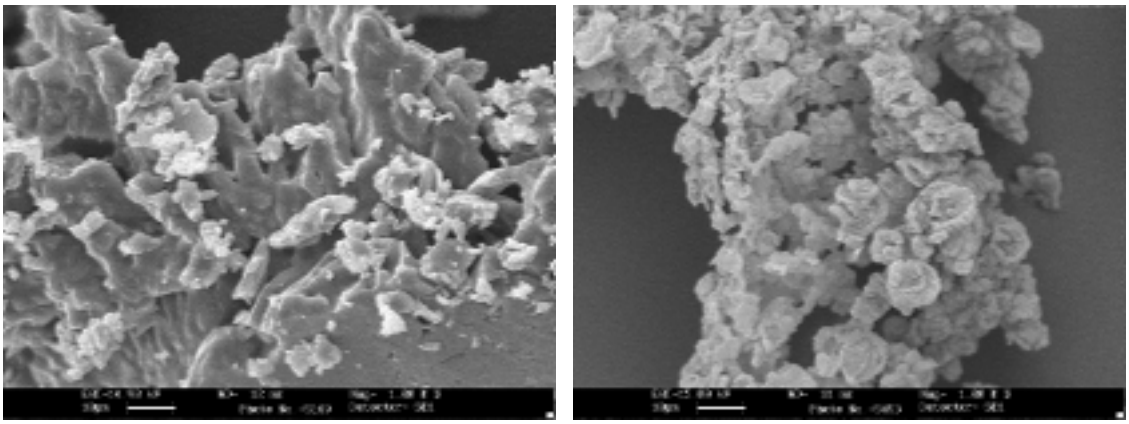

Figure 10: Effect of pressure ((left: 83 bar, right: 120 bar)
40°C, 1 wt% sotalol hydrochloride in ethanol, 5ml/min solution flow rate

pressure levels.

2.4. INFLUENCE OF FLOW RATIOS

For both SAS-apparatus the flow ratios of SC-CO_2 to solution were varied. For both SAS-apparatus the CO_2-flow was kept constant and by changing the solution flow different flow rates were adjusted. For all experiments lower solvent flow rates at constant CO_2-flow resulted in better particles (see Fig. 11). This is based on the phase equilibria because an excess of the supercritical fluid guarantees that the whole solvent is completely dissolved in the fluid phase and by this a rapid and uniform particle precipitation occurs.

2.5. INFLUENCE OF APPARATUS DESIGN

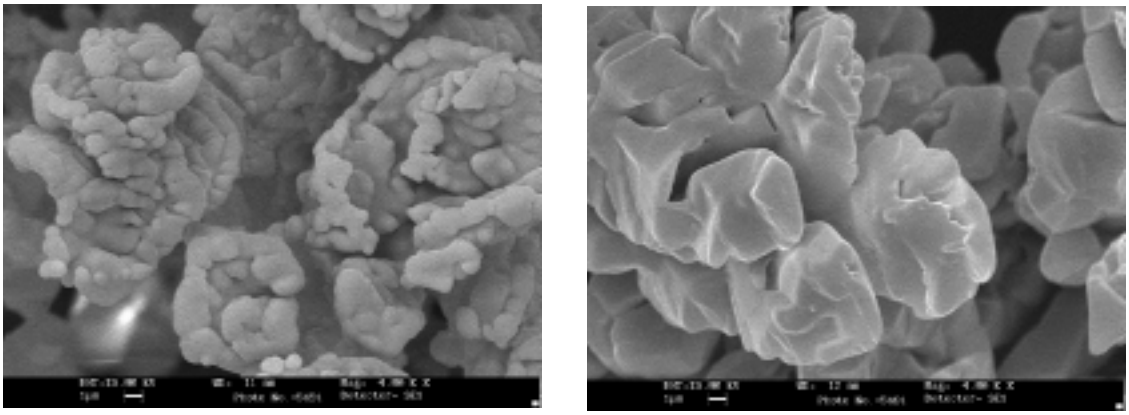

Figure 11: Effect of ethanol flow rate at 120 bar, 40°C and 1 wt% sotalol hydrochloride concentration (left: 5 ml/min solution flow rate, right: 10 ml/min solution flow rate)

Two different SAS-apparatus were tested as shown in Fig. 6 and Fig.7and no difference in the produced particle could be detected. This means that the kind of contact of the supercritical fluid with the solution has no influence on the final product. This has the advantage that the results achieved by this project can easily scaled-up to larger plant sizes.

CONCLUSION

Sotalol hydrochloride was successfully precipitated by SAS-technique in very fine crystalline form with uniform particle size distribution. The optimized process parameters are using the solvent ethanol with low concentrations of sotalol hydrochloride. The process should be operated at temperatures of 40°C and pressures of 120 bar. With high CO_2 flow rates and relatively low ethanol flow rates very uniform particles in the low µm range are produced. For these products at the moment dissolution tests are performed to determine the difference of dissolution velocity in the human body in comparison with the original product.

ACKNOWLEDGEMENT

We would like to thank MIUR for the Grant COFIN. Further this work was supported by the Italian Foreign Affair Ministry and the Austrian ÖAD in the frame of Scientific and Technological Collaboration between the Republic of Italy and Austria, project number 3/2004, "Production of Nanoparticles for Pharmaceutical Purposes by Supercritical Fluid Techniques".