

SAS MICRONIZATION PROCESS FOR NALMEFENE HYDROCHLORIDE ON A PILOT SCALE

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Optimization studies on the SAS process for micronization of Nalmefene hydrochloride were performed on a laboratory-scale instrumentation, having a 0.5 dm³ precipitation cell using ethanol or DMSO as liquid solvents [1]. This poster presentation shows how the lab-scale process was transferred to an existing pilot-scale instrumentation having a 10 dm³ reaction vessel.

The process conditions were chosen according to the results obtained in the lab-scale study, modifications on various parameters were considered, due to differences in instrumentation and set-up of these different apparatuses. Ethanol was chosen as the liquid solvent. The resulting particles were characterized using scanning electron microscopic and differential scanning calorimetric methods.

INTRODUCTION

The choice of a satisfactory scale-up procedure requires a deep understanding of the controlling steps of the process. Werling and Debenedetti [2] noted that it is difficult to isolate the effect of fundamental aspects responsible for a given trend in process properties. Until now only a very limited number of papers have been published on pilot scale SAS [3,4,5,6]. Since the realization of large scale production of micro and nano-particles for commercially viable fine chemicals is of increasing interest, the study of the SAS precipitation process on a pilot scale plant is important to verify the effect of the scale-up on the process parameters.

The selection of a test compound that has been successfully micronized on a laboratory scale plant for scale up experiments is the way to prove the suitability of a system for the stated purposes.

Nalmefene Hydrochloride is a selective narcotic antagonist, it prevents or reverses the effects of opioids, including respiratory depression, sedation and hypotension. It is used after general anesthesia and in the treatment of overdose and the systemic effects of intrathecal opioids [7]. There is interest of pharmaceutical companies for micronization of this compound; therefore, it is useful to perform SAS precipitation at high production rates.

APPARATUS AND PROCEDURES FOR SAS PRECIPITATION

Apparatus

The pilot plant (Chematur Engineering, Finland) used for SAS experiments (**figure 1**) is located at the MTT Agrifood Research Finland, Jokioinen (Finland).

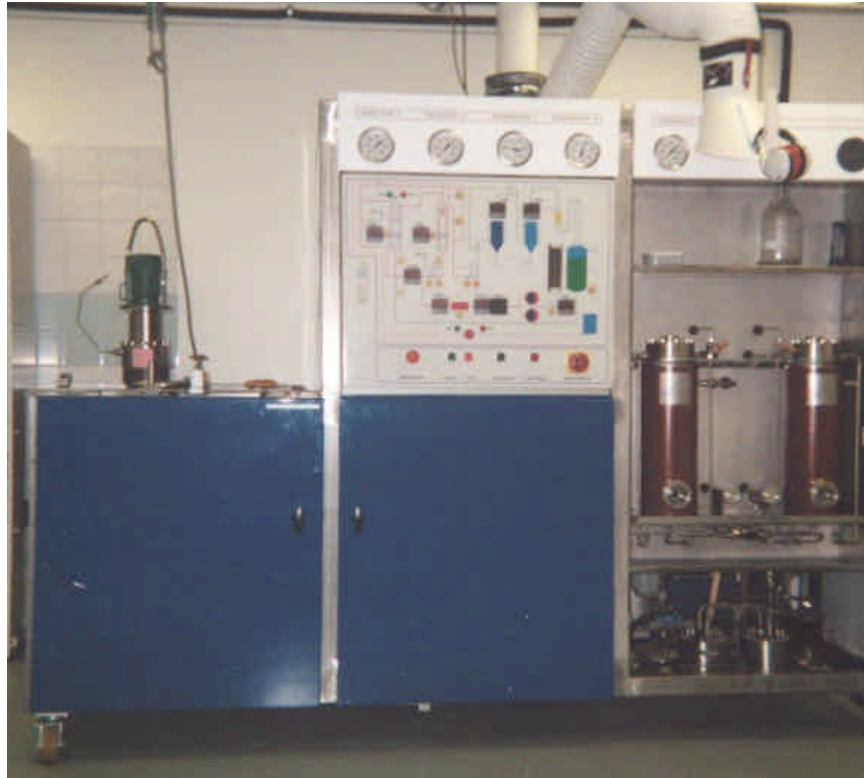


fig. 1. SAS semi-industrial apparatus (MTT Agrifood Research Finland)

It is a closed loop plant consisting, mainly, of a CO₂ storage vessel (**S**), a CO₂ dryer (**D**), two pressure tanks, an extraction unit (**E**) and a precipitation unit (**P**), two liquid separators (**S1**, **S2**), two pumps and a heat exchanger. The storage vessel has an internal volume of 30 dm³ and is provided with a cooling jacket. CO₂ is carried as liquid from a storage tank, called “maxibottle” (**M**) located next to the plant. Circulating gaseous CO₂ is cooled in a shell and tube heat exchanger, condensed and recirculated to the storage vessel. A CO₂ make up is also provided. Open loop operation is also possible and, in this case, gaseous CO₂ is not recirculated but vented to atmosphere. CO₂ dryer is a filter containing active carbon; it allows the elimination of water traces from CO₂.

The extraction unit is a tank of 10 dm³ and a L/D ratio of 3.6 provided with an oil jacket. The maximum pressure is 530 bar and the maximum temperature of the heating device is 100°C. A stainless steel basket is located inside the extraction unit and at its bottom a filter allows the collection of the extract. The precipitation unit is a tank of 11.5 dm³ with characteristics similar to the extraction unit. There is the possibility of adding a mixing device on the extraction tank.

The liquid solution is delivered to the precipitator by a piston pump (**p1**) (Bran Luebbe, mod. Type N-K31) with a maximum flow rate of 6 L/h (T=10-40°C, P_{max}=550 bar). Liquid CO₂ is delivered using a hydraulic diaphragm pump (**p2**) (Chematur Engineering, Finland) having a maximum flow rate of 1.2 L/min (T=°C, P_{max}=530 bar). The liquid solution and SC-CO₂ are

fed to the chamber through a tube-in tube injection system (inner tube $d=0,75$ mm, outer $d=9,5$ mm). The injector has been designed to produce a fast contact between the two streams at the outlet of the tubes, where a turbulent flow is generated. Similar injection devices have been used for general purpose atomization [8] and by several authors for SAS processing [8]. The liquid separators are 3 dm^3 jacketed vessels having a L/D ratio of 5. The plant has been tested for a pressure up to 530 bar.

During a precipitation test the extraction unit is bypassed and the pressure into the precipitator is regulated by a micrometering valve (or an electronic valve) located before the separator. The pressure in the separator is maintained at about 50 bar. Only one separator is used.

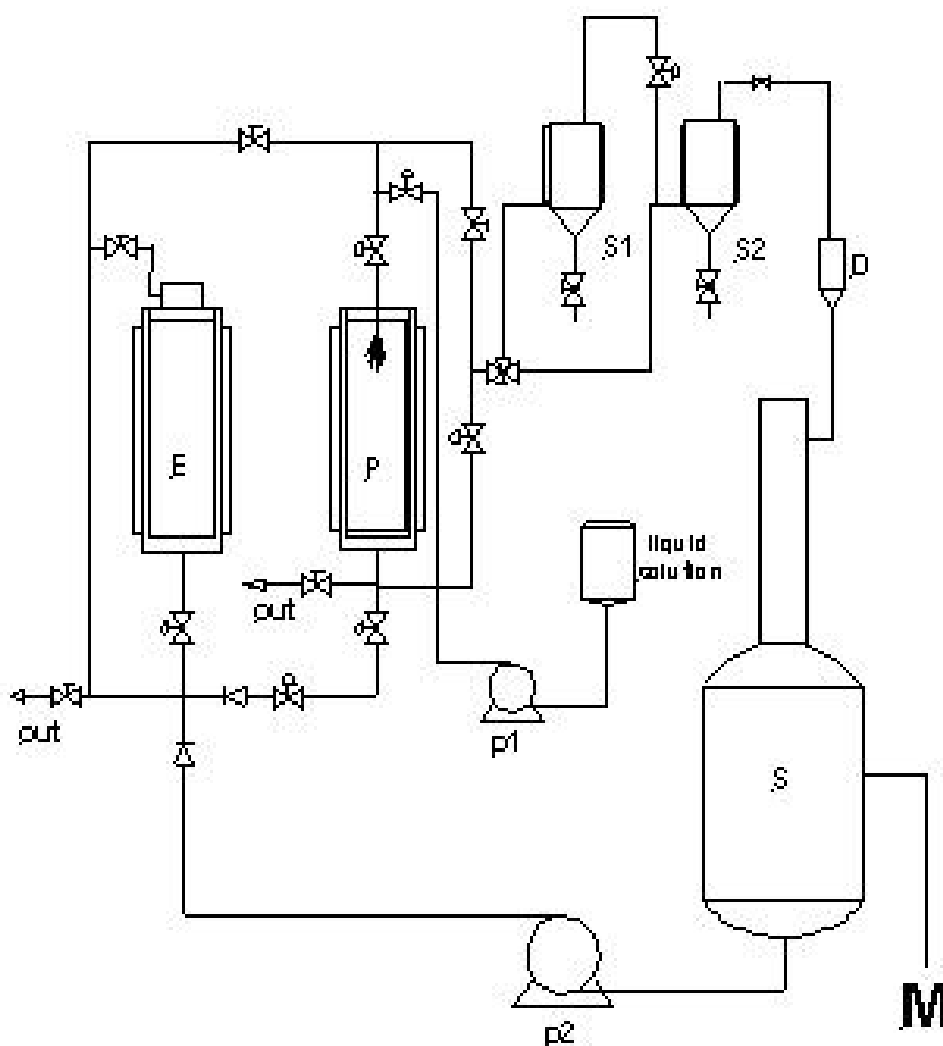


fig. 2. Simplified scheme of SAS semi-industrial apparatus

Materials

Nalmefene HCl with a purity of 99.9% ($M_w=375.9$ MP=203-206°C) was supplied by Contral Pharma Ltd, Finland. Ethanol (EtOH) with a purity of 94% was supplied by Primalco, Finland. CO₂ 99.7% was supplied by AGA, Helsinki, Finland.

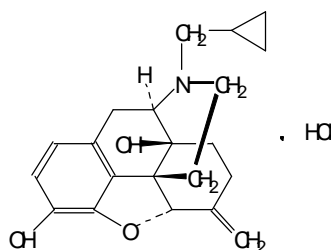


fig. 3. Nalmefene Hydrochloride

The solubility profile of Nalmefene HCl in liquid solvents was obtained from Contral Pharma Ltd. (Finland). At VTT Processes (Espoo, Finland) phase separation studies were performed using a static Variable Volume View-cell. The approximate solubility in EtOH was measured by our research group and was 26 mg/ml at room temperature. Untreated material was crystalline.

Procedures

The SAS precipitation process has been described in many works, referred to laboratory scale processes[10-14] and to pilot scale [3,4,6]. The pilot plant operation has been carried out in the continuous mode, recirculating CO₂ exiting from the precipitation chamber; whereas the liquid solvent, after the expansion in the liquid separator, has been purged and stored.

A SAS precipitation experiment starts by pumping CO₂ at a constant flow rate into the precipitator. Before entering the precipitator, CO₂ passes through the preheater reaching supercritical conditions. CO₂ flow rate is regulated by the micrometering valve. When operative conditions have been reached, pure liquid solvent is fed to the chamber through the injector until steady state conditions are reached. The solvent flow is then stopped and the liquid solution of the compound to be precipitated is fed to the chamber at the same flow rate as the pure solvent. When a prefixed amount of solution has been delivered the liquid pump is stopped, and only CO₂ continues to flow through the chamber. Operating in this manner the solvent is totally washed out from the precipitator. The washing time has been established by assuming a CSTR behavior of the precipitation tank and calculating it as the 99% of the time required for the complete elimination of the solvent. At the end of the washing step, CO₂ flow is stopped, the precipitator is depressurized down to the atmospheric pressure and finally the chamber is opened and the internal basket of the precipitator is removed. During the experiment the liquid solvent is continuously discharged out from the separator using an regulating valve.

Analytical methods

Samples of the powder precipitated on the metallic frit were observed by a Scanning Electron Microscope (SEM) mod. LEO 420. SEM samples were covered with 250Å of gold using a sputter coater (Agar model 108A).

RESULTS AND DISCUSSION

Nalmefene HCl has been successfully micronized using a SAS laboratory scale apparatus located at University of Salerno (Italy). The SAS precipitation process was performed in a 0.5 dm³ precipitator having an L/D ratio of 5 [1]. CO₂ and the liquid solution were fed in the precipitator from two different inlet points: the liquid solution was sprayed through an injection nozzle with a diameter of 200 µm. We have repeated the experiments

using a semi-industrial scale apparatus in order to find the operative conditions that gave the same results of the smaller scale.

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. This represents the main difficulty for the reproducibility of the experiments in a larger scale because it has increased the residence times of the process.

We have chosen a pressure of 130 bar, a temperature of 60°C and a ratio CO₂/solution 26.35 reproducing the laboratory scale experiments. The yield of Nalmefene particles production has been evaluated in all the pilot scale experiments. About the 89% of the amount of compound injected has been recovered after the micronization process. The remaining powder was partly lost on the wall of the precipitator, partly blocked in the filter meshes and traces were found into the solvent recovered into the separator.

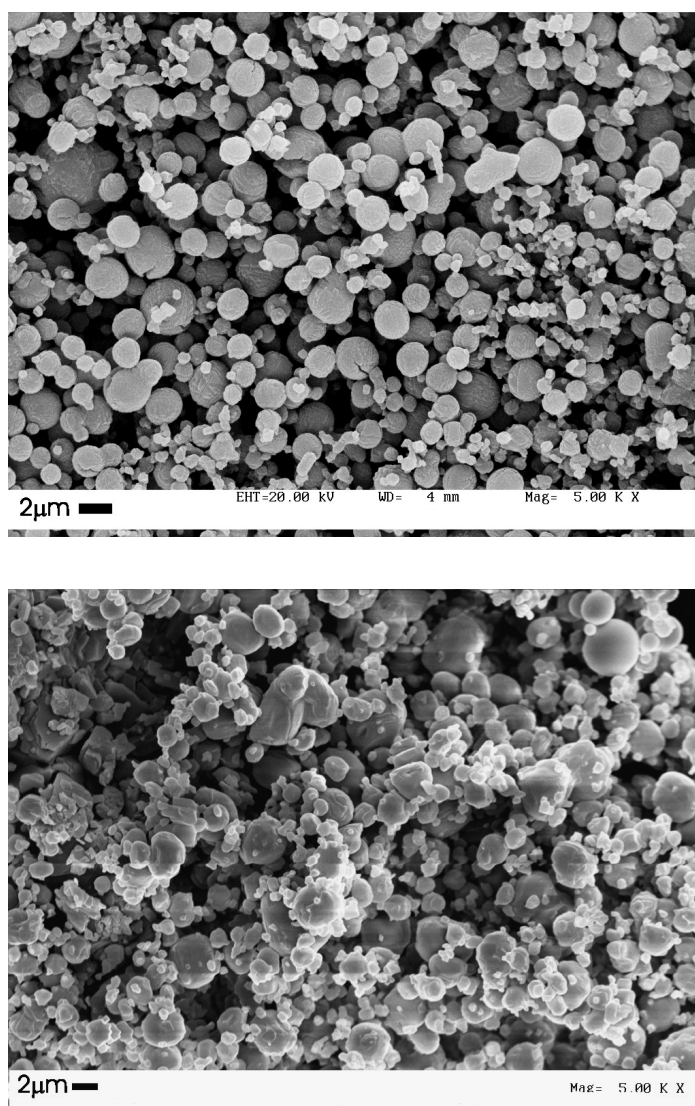


fig. 4. SEM image of Nalmefene HCl particles precipitated from EtOH at 150 bar, 60°C, 15 mg/mL, with the laboratory scale plant (upper) and pilot scale plant (lower).

The product obtained was successfully micronized and had the same morphology of that processed with the laboratory scale plant. From **figure 4** it appears that there are only slight differences between the samples and particle size distributions are comparable. The mean particle size is around 2 μm .

More experiments, at different operative conditions will test the flexibility of the plant for SFE and micronization with SAS process.

Acknowledgments

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