FORMATION OF SALBUTAMOL SULPHATE MICROPARTICLES USING SOLUTION ENHANCED DISPERSION BY SUPERCRITICAL CARBON DIOXIDE

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ABSTRACT

Salbutamol sulphate (SS) was precipitated by supercritical carbon dioxide (SC-CO_2) using a homemade system at two different pressures. This process is characterized by spraying a methanolic solution of the drug into the supercritical fluid (SCF), extraction of the solvent by SC-CO_2 and formation of drug particles. The morphology and size distribution of precipitated SS particles were characterized using scanning electron microscope and laser diffraction particle size analyzer respectively. FTIR spectra were used before and after processing to asses crystal modifications. Depending on the processing conditions, needle-like and flake-like particles with different size distributions were observed. The average size of the flake like particles was less than needle-like particles and the span parameter showed a narrower size distribution of the processed in comparison with the unprocessed materials. Analysis by FTIR showed that there was no significant effect on the structure of the drug under these processing conditions.

Keywords: Supercritical fluid, Carbon dioxide, Salbutamol sulphate, Particle formation

INTRODUCTION

The efficacy of pharmaceuticals can be significantly influenced by their physical properties such as particle size distribution and morphology. Fine particles of pharmaceuticals are essential for development of inhalation aerosols, injectable suspensions, controlled release dosage forms, and other specialized modes of drug delivery such as transdermal (1).

Fine pharmaceutical powders are often difficult to produce by currently available micronisation techniques (2). High energy milling techniques such as air jet milling are far from ideal since products of these methods are often cohesive, highly electrostatically charged, and difficult to process downstream. Other alternative methods for preparation of the micronized particles are spray drying, spray freeze drying, solvent evaporation, and emulsion coacervation techniques. Except for the spray drying which is a single step process, all other techniques are of multi stages. With increase in industrial and regulatory concern over residual solvent levels in drugs and excipients which are produced by conventional methods, there is a need for an alternative particle formation process, which would be ideally a single stage operation. The process should be capable to produce a consistent, uniform product with controlled particle properties, preferably with a minimal level of residual solvent (3).

During the last few years, application of supercritical fluids (SCFs) has attracted attention of scientific community to develop new technologies in order to substitute the traditional ones (4).

The supercritical state is achieved, when the temperature and the pressure of a substance is raised over its critical values. In the supercritical state the distinction between the liquid and the gas phase is disappeared and raising the pressure no longer liquefies the fluid and no gas is formed by increase in temperature. The dissolving power of a SCF depends on its density, which is highly adjustable by the change in pressure or temperature. Furthermore, a SCF has a higher diffusion coefficient and lower viscosity and surface tension than a liquid solvent, which makes it favorable for mass transfer (5). Among all the possible SCFs, carbon dioxide is the most widely used, due to its favorable critical parameters (T_c 31.1 ^oC, P_c 73.8 bar), cost and lack of toxicity (6).

While spray crystallization and salting-out are two processes which are frequently used in crystallization, particle formation by SCFs are rapid expansion of supercritical solutions (RESS), and the supercritical antisolvent techniques (7).

RESS consists of solvation of the drug in SCF followed by rapid depressurization of the resulting solution through an appropriate nozzle

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which cause an extremely rapid nucleation of the drug into a highly dispersed material (8).

The anti-solvent process is practically more important for many pharmaceuticals which have low solubility in CO_2. Technical modifications of this method are achieved by mixing techniques (9). The contact between drug solution and supercritical anti-solvent may be accomplished by gradual addition of SCF to the solution which is usually referred to GAS (Gaseous Anti Solvent) or by spraying the solution into the flowing dense gas such as SAS (Supercritical Anti-solvent), ASES (Aerosol Solvent Extraction System) and SEDS (Solution Enhanced Dispersion by Supercritical Fluids).

The GAS process is a batch operation in which the rate of SCF addition may be an important parameter in control of the particle characteristics.

The SAS process is also a batch operation, but the ASES process is a semi continuous process, and in the both methods solutions are introduced into the SCF via a nozzle. In the SEDS process the solution and SCF are introduced in a co-centric nozzle for enhanced mass transfer between SCF and solution (8, 10).

In order to complete the review of SCFs based processes, one may cite the PGSS (Particles from Gas Saturated Solutions) route, which consists of dissolvation of SCF into a liquid substrate, or a solution or suspension of the substrate(s) followed by a rapid depressurization of this mixture through a nozzle (11).

Salbutamol sulphate (SS) is a well known drug in treatment of asthma, and the aim of this study was to investigate the applicability of methanol as a feasible solvent for precipitation of SS particles using a homemade apparatus which was designed on the basis of SEDS technique.

MATERIALS AND METHODS

Salbutamol sulphate BP, was gifted by Daru Paksh Ltd., Iran. Methanol and chloroform of analytical grades were purchased from Merck, Germany. CO_2 of high purity (>99.9%) was purchased from Daga Co., Iran. All chemicals were used without further purification.

Particle formation apparatus

A schematic diagram of the apparatus, which was used in this study, is shown in Fig. 1. Carbon dioxide is drawn from the source cylinder (A) by a deep tube and after passing through a dryer (B), is condensed by a cooling device (C). The CO_2 is then fed through a conduit to a particular double syringe pump (D) which is designed for high-pressure operation. From there, two lines conduct CO_2 into high-pressure precipitator (E). The line L_1 which is controlled by valve V_1, is a line for direct passage and the line L_2 which is controlled by valve V_2 is connected to the co-centric nozzle (F) in the upper side of the precipitator. The precipitator is a vessel of 0.4 liter internal volume, and is placed in an equipped oven (G) for exact temperature regulation. Applying the co-centric nozzle with internal passage diameter of 0.3 mm, allows co-introduction of SCF and drug solution into the precipitator and improves dispersion of droplets. The solution of the drug in a suitable organic solvent is conducted to the internal passage of nozzle by a Jasco high pressure pump (H). The supercritical CO_2 leaves the precipitator via a needle valve (V_3) which controls the pressure discharge in the system.

Experimental

The experiment began by delivering CO_2 to the precipitation chamber via line L_1, until the desired pressure was reached. Then, line L_1 was closed by valve V_1 and CO_2 was conducted to vessel via line L_2. After that, pure methanol was delivered through the nozzle to the chamber in order to obtain steady state conditions during the solute precipitation. Pure methanol was fed to the chamber for 10 min. At this point, the drug solution containing SS in methanol (5mg/ml) was delivered through the nozzle at 0.5 ml/min flow rate while CO_2 flow rate was maintained at 20 ml/min. During this process particles were precipitated on a filter which was located on the walls of the bottom of the chamber. A typical duration of this stage of the process for collection of adequate solid particles was about 60 min or higher. The experiment used to be over whenever the delivery of the drug solution to the chamber was interrupted. However, supercritical CO_2 continued to flow for 15 min to wash the chamber from residual methanol which was solubilized into the supercritical antisolvent. When the washing process was completed, the CO_2 flow was stopped and the chamber depressurized down to atmospheric pressure. All the experiments in this work were performed at the precipitator temperature of 40 ^oC, where the pressure was set at 140 or 180 bar.

Scanning electron microscopy (SEM)

The morphology of unprocessed and precipitated particles was examined by SEM (CamScan MV 2300, England). Particles of the representative samples were coated with gold-palladium at room temperature before examination. The accelerator voltage for scanning was 25.0 kV.

Particle size measurement

A small amount (about 5 mg) of each SS sample was dispersed in 5 ml chloroform by the aid of water bath sonication (Starsonic 60, Liarre, Italy)

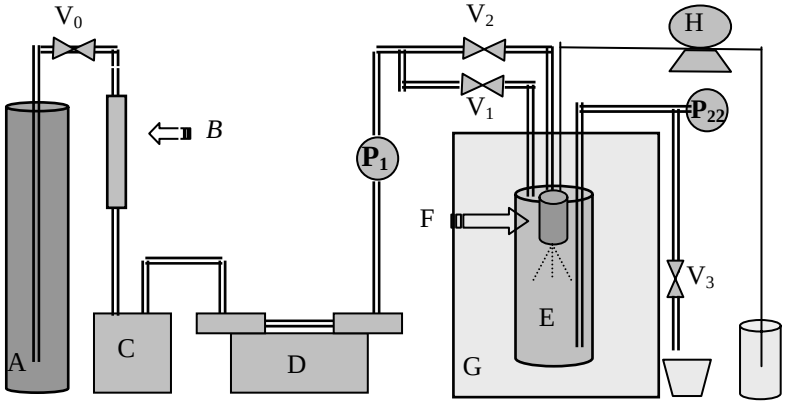

Figure 1. Schematic diagram of apparatus; A: Carbon dioxide cylinder, B: Dryer, C: Cooling device, D: CO_2 pump, E: High-pressure precipitator, F: Co-centric nozzle, G: Oven, H: Solution pump.

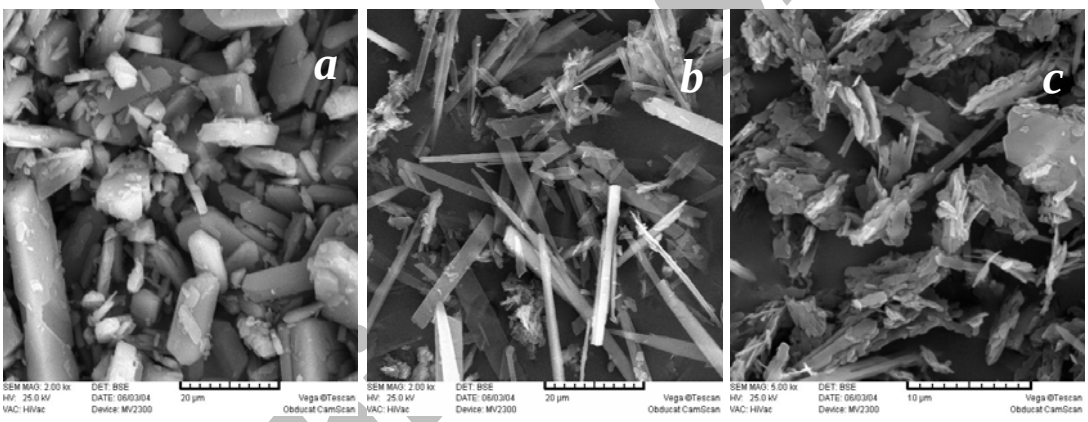

Figure 2. Scanning electron micrographs of salbutamol sulphate (SS); a) unprocessed, b) processed at 140 bar, c) processed at 180 bar.

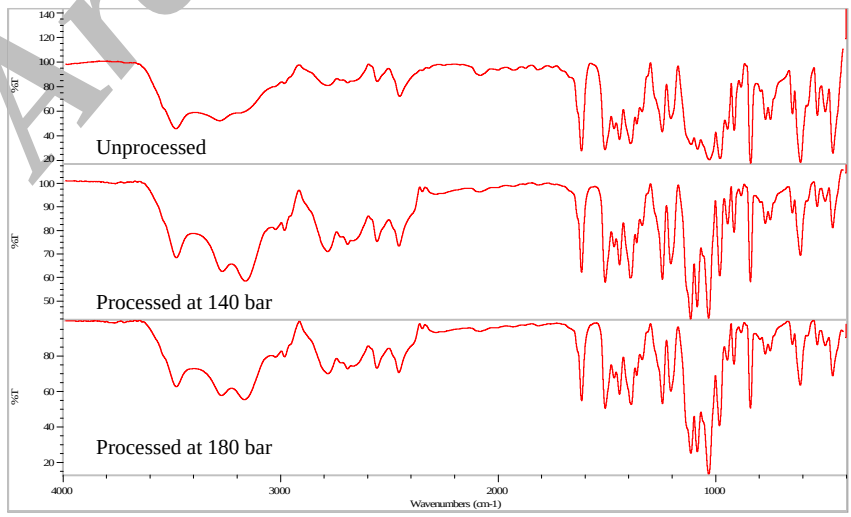

Figure 3. FT-IR spectra of salbutamol sulphate before and after precipitation.

Table 1. Particle size distribution of processed and unprocessed salbutamol sulphate

Material	Cumulative percent (undersize)[a]			Span[b]
	$d_{10\%}$ (μm)	$d_{50\%}$ (μm)	$d_{90\%}$ (μm)	
Unprocessed	3.14	13.73	39.60	2.65
Processed at 140 bar	2.83	9.74	21.66	1.93
Processed at 180 bar	2.46	7.48	17.30	1.98

[a] Equivalent volume diameters at 10 ($d_{10\%}$), 50 ($d_{50\%}$) and 90% ($d_{90\%}$) cumulative volume; [b] ($d_{90\%}$ - $d_{10\%}$) / ($d_{50\%}$)

for 3 min. The particle size of the powders were measured by laser diffraction (Mastersizer X, Malvern Instruments, Malvern, UK) at obscuration between 0.18 and 0.20. Each sample was measured in triplicate. The size distribution was expressed by equivalent volume diameters at 10 ($d_{10\%}$), 50 ($d_{50\%}$) and 90% ($d_{90\%}$) cumulative volume.

Fourier transform infrared spectroscopy (FT-IR)

FT-IR spectra were recorded with a spectrophotometer (Mega-IR, 550, Nicolet, USA) in the range of 400-4000 cm^{-1}, using a resolution of 4.000 cm^{-1} and 4 scans. Samples were diluted with KBr at concentration of 1% and pressed to obtain self-supporting disks.

RESULTS AND DISCUSSION

A homemade apparatus was applied to investigate the feasibility of particle production from SS by supercritical carbon dioxide (SC-CO_2).

Methanolic solutions of SS were sprayed into SC-CO_2 and the effect of pressure on morphology and particle size was studied.

A similar study in which supercritical antisolvent system was employed for formation of SS particles from methanol and DMSO (Dimethylsulfoxide) solutions has been reported (12). While spraying SS-methanol mixture in SC-CO_2, resulted in production of powders without appropriate particle characteristics (12), by using DMSO solutions, particles with well defined shapes such as needles and expanded droplets (balloons) were observed.

In the present study, the immediate macroscopic observation showed that the precipitated particles were uniformly distributed on the wall of the bottom of the precipitation vessel, and the occupied volume by the processed drug was larger than unprocessed material.

The SEM photographs of SS particles are shown in the Figure 2. The processed particles presented completely different morphology depending on the operation pressure. The SS sample precipitated at 140 bar showed needle-like particles, whereas precipitation at 180 bar resulted in the production of flake-like particles. For both samples there was no network between particles.

Similar observation on effect of different pressures on particle morphology has been reported for hydrocortisone which has been attributed to increased solubility of the drug in SC-CO_2 at higher pressures which results in decreased nuclei density, thereby formation of the elongated needles (13).

In comparison with results of the previous report (12), our success in obtaining separated particles may be related to the application of co-centric nozzle in the system, in which the external passage serves to carry a flow of SC-CO_2 and the internal one serves passage of drug solution. Therefore in the tip of nozzle, better dispersion of droplets are attained and mass transfer between solvent and SC-CO_2 is possible and particles will be formed and dried without agglomeration.

The results of the particle size analysis which are presented in Table 1, indicate a reduction in particle size of SS after precipitation by SC-CO_2. The $d_{50\%}$ of flake-like particles (7.48μm) is less than needle-like particles (9.74μm). The span parameters showed a narrower size distribution for both processed materials in comparison to unprocessed samples.

FTIR spectra of SS before and after process have been compared in Figure 3. A brief overview of all spectra showed a characteristic multi-peak transmittance pattern of the SS between 1650 and 400 cm^{-1} which suggest that there is no remarkable alteration in the structure of SS.

CONCLUSION

The present study showed that our homemade apparatus for particle formation by SCF was successful in precipitation of SS from methanolic solutions, and further studies to modify the particle characteristics of SS are possible by using methanol as solvent. Indeed, in future studies the effect of process parameters such as pressure, temperature, flow rate of drug solution, flow rate of SCF, nozzle diameter should be investigated in order to obtain appropriate SS microparticles for pharmaceutical purposes particularly for pulmonary drug delivery.

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