Beclomethasone Micronization Using Gas Antisolvent Process.

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Gas antisolvent process performances for micronization of beclomethasone dipropionate from ethyl alcohol solutions have been investigated.
The experimental tests have been performed using a new patented nozzle for the injection of the supercritical solvent and the solution into the particle precipitation vessel.
The influence of pressure, temperature, solution flow rate and solution concentration on particle size and powder yield have been investigated.
The experimental tests have been performed in the pressure range 7.0-10.8 MPa and at temperatures of 40 and 50 °C.
The maximum powder yield was 36 % and was obtained at 40 °C and 8.2 MPa. Powder mean size has been evaluated by SEM image analysis. The minimum mean size of powders is of about 1 μm and was obtained at 40 K and 80 bar.

INTRODUCTION

The properties and effectiveness of a pharmaceutical active rely on their chemical properties, but are also strongly influenced by physical properties such as crystal features and surface properties, which can influence the bio availability of drug and, consequently, the requested drug dosage. For those drugs that are delivered by inhalation, particle size and particle size distribution has a great influence on the deposition of particles in the lungs, on the uniformity of dosing and on the bio availability of the drug [1].
The pulmonary delivery of small and large molecules to treat both local and systemic diseases is a quite common practice, one of the major prerequisites for a successful pulmonary drug application is a suitable particle size of the drug which mass median aerodynamic diameter (MMAD) should be in the range of 1–5 μm [2].
To overcome the shortcomings and limitations of traditional processes for the production of fine powders many researchers have explored the potentialities of processes based on the use of supercritical fluids. The main processes for fine powder production are RESS (rapid expansion of supercritical solutions) and GAS (gas anti solvent). Jung and Perrut [3] and Shariati and Peters [4] performed extensive reviews on the different techniques available for particle design using SCF.
Beclomethasone dipropionate is a largely used drug for treating of pulmonary deseases, and it is usually delivered by aerosol inhalation.
Golriz et al. [5] studied the production of fine powders of fenantrene and beclomethasone using RESS and GAS processes. At 30-40 °C and at 8-22,9 MPa, using GAS process, they

obtained beclomethasone powders from methanol solutions with a mean size of 4 μm. The yield of powders is not reported.
Steckel et al. [6] studied the performances of ASES process for the production of fine powders of different steroids, including beclomethasone. They obtained powders with a mean size of about 5 μm from solutions of dichloromethane at 40 °C and 8,5 MPa. No powders were produced from solutions of beclomethasone and betamethasone.
Steckel et al. [7] also studied the production of budesonide powders with the ASES process from 1% (w/w) solution of budesonide in methylenechloride at 40 °C and 8.5 MPa. They obtained particle size distribution characterized by a distribution parameter d50% ranging from 6 to 8 μm and a yield in the range of 50–70%.

I - MATERIALS AND METHODS

Carbon dioxide 99,9 was supplied by Rivoira, 99.8% ethyl alcohol by Fluka.
A PHILIPS SEM 505 electron scanning microscope was used to observe samples of the powders. Particle size distribution was determined by SEM image analysis.
A self built bench scale plant equipped with a patented nozzle was used. The plant has been described in detail elsewhere [8], the volume of the precipitation vessel is about 600 cm^3. The nozzle used for the injection of solution and of supercritical carbon dioxide in the precipitation vessel is described in detail elsewhere [9, 10]. The basic characteristic of the nozzle is that it provides separate inlets for the supercritical fluid and for the solution, which come into contact in the precipitation vessel. The experimental tests reported in this work have been performed using a nozzle with two outer orifices to feed carbon dioxide and a central orifice for the liquid solution inlet. Two different nozzles have been used with outer orifices diameter of 60 and 80 μm and with the central orifice diameter of 30 μm in both cases.
After stopping the feeding of solution, pure carbon dioxide was fed to the precipitation vessel to dry the powders. An amount of carbon dioxide of about four precipitation vessel volumes were enough to obtain dry powders.
In table 2 are reported the experimental conditions and the results of experimental tests. All the tests have been performed using a constant carbon dioxide flow rate of 30 g/min.
The yield has been defined as the amount of powder collected in the precipitation vessel divided by the total amount of beclomethasone fed with the solution, multiplied by 100.
In figure 1 is reported the phase behavior of the system ethyl alcohol-carbon dioxide at 40 and 50 °C, together with the conditions of the experimental tests.
The experimental tests were aimed at evaluating the influence of solution concentration, of solution flow rate, of temperature and of pressure on the yield and size of powders.
The maximum yield was about 36% and was obtained at conditions of test No. 1 (40 °C, 8.2 MPa), the powder mean size is in the range from 1.15 to 1.87 μm, with the exception of test No. 10. These values can be favorably compared with the value of 2.1 μm of untreated beclomethasone.
In figure 2 and in figure 3 are shown the particle size distribution of powder produced in test No. 1 and the particle size distribution on untreated beclomethasone.
In figure 4 and in figure 5 are shown the SEM micrograph of powders produced in test No. 1 and of untreated beclomethasone, respectively.
The influence of the solution concentration can be evaluated by comparing test No. 1 and 3 (1 %) with test No. 7 and 8 (0.5 %), respectively. Test No. 3 and 8 have been performed at 7.0 MPa, 40 °C, with a solution flow rate of 0.4 ml/min, while test No. 1 and 7 been performed at

8.2 MPa, 40 °C, with a solution flow rate of 1.02 ml/min. Comparison of test No. 1 with test

Test No.	T (°C)	P (MPa)	Conc. (% wt)	Solution flow rate (ml/min)	Outer orifice diameter (μm)	Yield (%)	Powder mean size (μm)	Standard deviation (μm)
1	40	8.2	1.0	1.02	60	36.0	1.15	0.75
2	40	8.2	1.0	0.61	60	20.0	1.27	0.95
3	40	7.0	1.0	0.40	60	18.0	1.38	1.07
4	40	7.0	1.0	0.30	60	14.5	1.51	1.26
5	40	7.0	1.0	0.20	60	12.5	1.61	1.17
6	40	9.0	1.0	1.02	60	16.2	1.69	1.18
7	40	8.2	0.5	1.02	60	15.6	1.47	1.03
8	40	7.0	0.5	0.40	60	15.6	1.87	1.28
9	40	9.0	0.5	1.02	60	\	\	\
10	34	6.0	1.0	0.28	80	10.0	3.32	2.18
11	50	10.8	1.0	3.77	80	8.0	1.69	1.19
12	48	10.8	1.0	3.77	60	14.0	1.84	1.34

Table 1 : Experimental conditions and results of precipitation of beclomethasone from ethyl alcohol solutions. Carbon dioxide flow rate was set to 30 g/min.

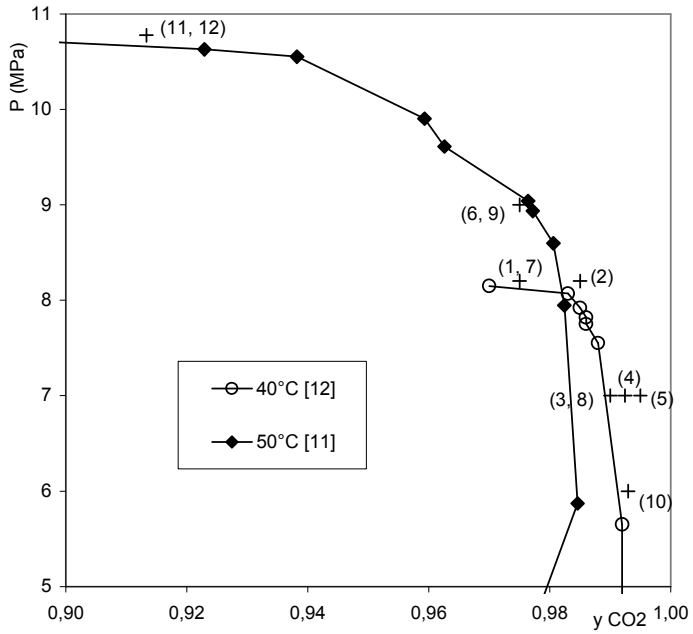

Figure 1: Carbon dioxide-ethyl alcohol phase behavior. +: conditions of experimental tests.

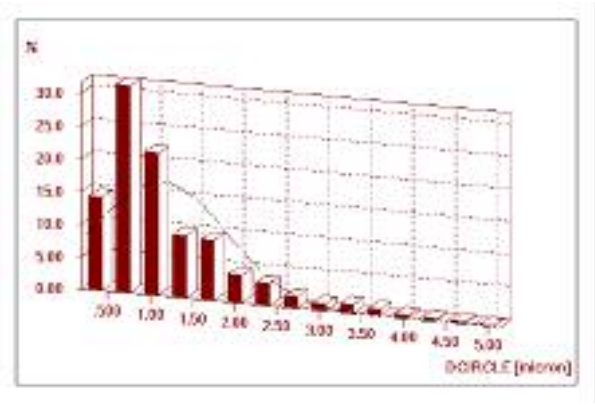

Figure 2. Particle size distribution of powder produced in test No. 1.

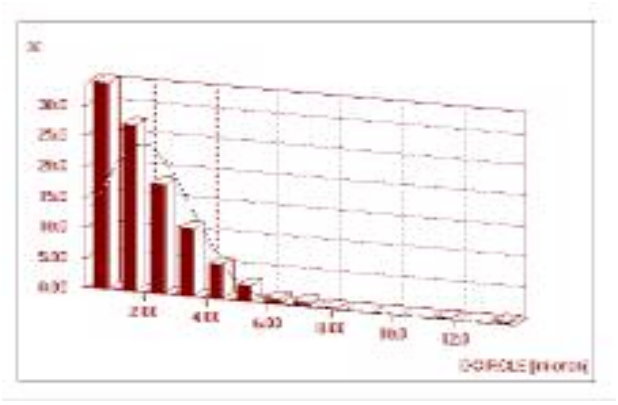

Figure 3. Particle size distribution of untreated powder.

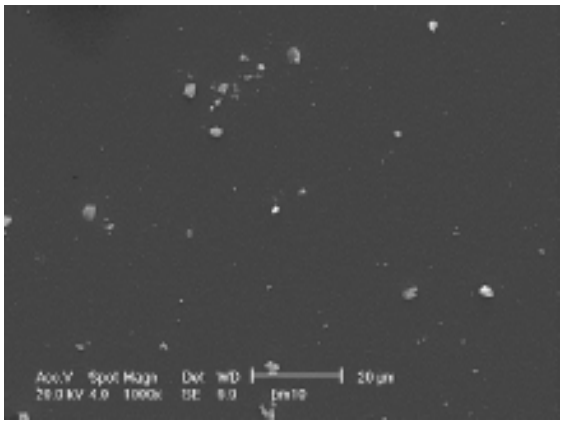

Figure 4. SEM micrograph of beclomethasone powders produced in test No. 1.

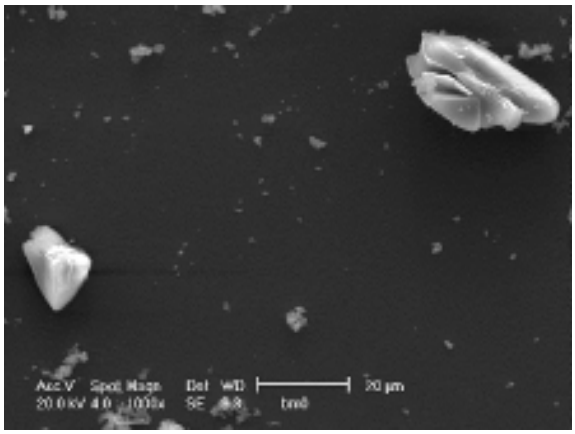

Figure 5. SEM micrograph of untreated beclomethasone powders.

No. 7 and test No. 3 with test No. 8 show that in both cases, increasing solution concentration, yield of powders increases while the average diameter of powder decreases.

Test No. 6 and 9 have been performed at 9.0 MPa, 40 °C, with a solution flow rate of 1.02 ml/min, solution concentration 1 and 0.5%, respectively. The powder yield for test No. 6 was 16.2%, while no powder was produced during test No. 9, confirming the influence of concentration on yield.

The influence of solution flow rate can be evaluated comparing tests No. 3, 4 and 5, performed at 40 °C and 7.0 MPa, with solution flow rate of 0.2, 0.3 and 0.4 ml/min, respectively. It can be observed that increasing solution flow rate, yield of powders increases, while the average diameter of powders decreases. The same conclusions can be drawn by comparison of tests No. 1 and 2, (40 °C, 8.2 MPa, solution flow rate 0,61 and 1.02 ml/min, respectively), again the experimental results show that increasing solution flow rate, an increase of powder yield and a decrease of average diameter is observed.

The influence of pressure can be estimated comparing the results of tests No. 2, 3 and 10, performed at 40 °C and at 6.0, 7.0 and 8.2 MPa, respectively. With increasing pressure, an increase of powder yield and a decrease of powder mean diameter is observed. The highest

values of yield and the lowest values of powder mean diameter are obtained at pressures around the upper critical point of the system, as it is shown by the results of test No. 1.
The influence of temperature can be estimated comparing the results of tests No. 1 and 7 with tests No. 11 and 12, respectively. The results show that with increasing temperature an decrease of powder yield and an increase of average diameter is observed.

CONCLUSION

The influence of solution concentration, process temperature, pressure and solution flow rate have been investigated for the production of beclomethasone powders with Gas antisolvent process. The best results were obtained at 40°C, 8.2 MPa, 1% wt solution concentration, 1.02 ml/min solution flow rate. In these conditions a yield of 36.0 % was obtained and the powder mean size was 1.15 μm.

Work is in progress to improve the yield of powders.
The results can be favourably compared with literature data of Golriz et al. [5]
Experimental results show that increasing solution concentration, solution flow rate and pressure, powder yield increases and powders mean size decreases.

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