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Control of the Physical Form of Salmeterol Xinafoate

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Abstract:

Two approaches to the generation of particles of the phenethanolamine, salmeterol xinafoate, are discussed. To produce particles with good flow properties a fast cooling crystallisation process was developed which delivered salmeterol xinafoate as spherical agglomerates of microcrystals which had good powder flow characteristics and could be micronised efficiently in a fluid energy mill. In a radically different approach, salmeterol xinafoate was crystallised using supercritical carbon dioxide in the SEDS (solution enhanced dispersion by supercritical fluids) process. By means of this technique the solid state form, crystal habit, and particle size of salmeterol xinafoate could be effectively controlled.

General Introduction

The development of a successful formulation for a new pharmaceutical agent is highly dependent upon the physical properties[1,2] of the active ingredient, the drug substance. These physical properties affect, for example, bioavailability, powder flow, bulk handling, ease of compression, and physical stability. Hence, control and management of the physical properties of drug substances and the provision of robust processes for their manufacture is an important factor in drug development.

The phenethanolamine, salmeterol xinafoate (Figure 1) is a long-acting beta 2 adrenoreceptor agonist used in the treatment of bronchial asthma. The drug is delivered by inhalation by means of either a metered-dose aerosol inhaler or a dry powder delivery device. In the latter case the drug is formulated as a blend with lactose.

Before salmeterol xinafoate is formulated in the delivery device the drug substance is micronised to a size range of about 2−5 μm to enable a suitable respirable fraction of the drug particles to be delivered to the bronchial region of the lung.[3] Micronisation is achieved using a fluid energy mill[4,5] in which the crystalline powder is driven by air pressure into a cyclone. Impact of the drug particles with each other and with the wall of the cyclone causes fracture and attrition to give particles of the desired size range.

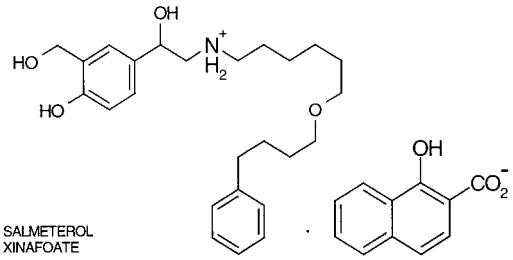

Figure 1. **Structure of salmeterol xinafoate.**

Salmeterol xinafoate drug substance generated by a conventional crystallisation process has very poor powder flow properties, making it unsuitable for size reduction processes such as micronisation.

This paper presents two practical approaches to management of the crystallisation of salmeterol xinafoate. In the first approach (fast cooling crystallisation) the crystallisation process is modified to produce spherical agglomerates of small crystals which flow well and break up readily during micronisation. In the second approach, micronisation may be avoided altogether by a very rapid crystallisation process using supercritical carbon dioxide. This technique, known as SEDS (solution enhanced dispersion by supercritical fluids), can produce particles in a single-stage process in the required size range for delivery to the deep lung air passages.

Fast Cooling Crystallisation

Introduction. Crystallisation of salmeterol xinafoate from organic solvents using the conventional technique of dissolution at elevated temperatures and natural cooling to induce supersaturation provides the drug substance as stable agglomerates of platelike crystals which are readily filtered and washed. A scanning electron micrograph (SEM) of some typical crystals is shown in Figure 2. The preferred solvent for this procedure is 2-propanol and recoveries of >90% of theory from pure salmeterol base and 1-hydroxy-2-naphthoic acid (HNA) have been obtained routinely.

Observation of bulk samples of salmeterol xinafoate prepared in this way shows that the material is highly cohesive; the crystals adhere together and the resultant formation of loose agglomerates inhibits smooth powder flow. Attempted micronisation of this material resulted in blockage of the input venturi of the microniser and failure

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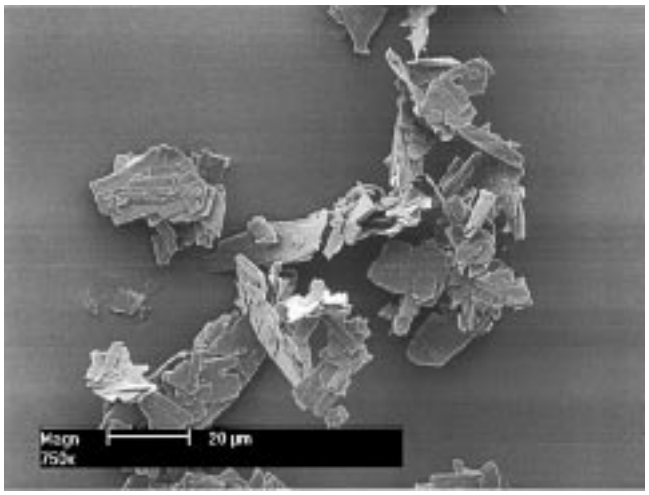

Figure 2. **Scanning electron micrograph of crystalline salmeterol xinafoate, exhibiting platelike habit.**

Table 1. **Typical physical properties of conventionally crystallised and granular salmeterol xinafoate**

physical property	conventionally crystallized	granular
Bulk density[a] ($g \cdot ml^{-1}$)	0.16	0.30
Compressibility[b] (%)	40	9
Cohesivity[c] (%)	82	1.34
Mean particle size[d] (μm)	26	156
Mean surface area[e] ($m^2 \cdot g^{-1}$)	1.9	9.6

[a] Untapped.[2,6] [b] Calculated from bulk density.[2,6] [c] Determined by sieve analysis. [d] Determined by laser diffraction analysis (Malvern Mastersizer). [e] Determined by BET analysis.

of the size-reduction process. The measurement of bulk density and the calculation of the compressibility[2,6] of the drug substance gave values of >40%, consistent with other poorly flowing materials.[7] More detailed data on the flow properties of salmeterol xinafoate are given in Table 1.

Crystallisation Procedures. To modify the crystallisation process and produce a crystal habit with better flow properties, more aggressive crystallisation conditions were examined. A faster cooling regimen was investigated to produce a high degree of supersaturation and rapid nucleation. This was expected to produce smaller crystals, possibly with a new crystal habit and with the potential to obviate the need for micronisation.

The addition of salmeterol xinafoate in hot 2-propanol to a chilled quench solvent induced crystallisation, but the product was obtained as large spherical agglomerates of microcrystals rather than as a microfine powder. A range of solvents, temperatures, and addition methods was examined to investigate the physical behaviour, yield, quality, and throughput of the product. A delay in nucleation was observed in this fast-cooling approach, even though the solution was highly supersaturated, but once crystallisation had begun the process was rapid. For example, using 2-propanol as both dissolution solvent (9.5 volumes) and quench solvent (14 volumes) an induction period before the appearance of crystals of up to 4 min was observed after complete mixing of the solutions. At the point at which particles became visible in suspension the temperature was below 20 °C, and the concentration was 4.25% w/v (solubility in 2-propanol is 0.17% w/v at 22 °C).

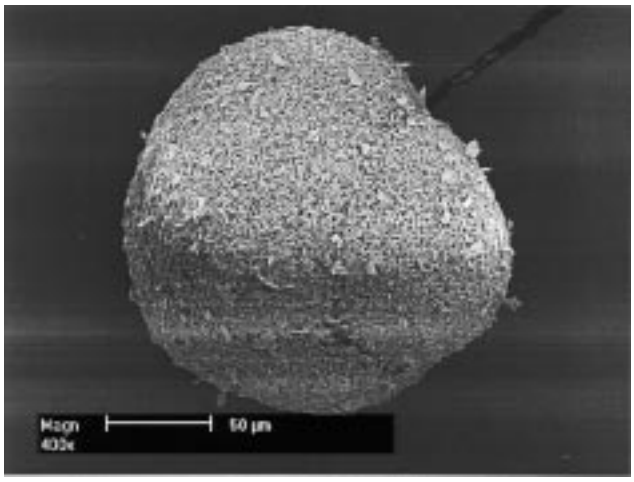

Figure 3. **Scanning electron micrograph of granular salmeterol xinafoate.**

Bulk Physical Properties of "Granular" Salmeterol Xinafoate. The bulk physical properties of granular salmeterol xinafoate were dramatically different from typical crystalline material. The data are summarised in Table 1. Flow and handling were greatly improved, and micronisation was efficient and reproducible from batch to batch. The size of the spherical agglomerates was typically in the range 100−250 μm and amounts of loose irregular crystals were generally small. Residual solvent content was low (typically about 0.1% w/w). A SEM of typical granular material prepared by this method is shown in Figure 3.

Polymorphism of Salmeterol Xinafoate. Examination of differential scanning calorimetry (DSC) scans of salmeterol xinafoate (see Figure 4 for a typical example) showed two major endothermic phase changes at about 125 and 139 °C, respectively. These events were assigned as the melting points of two polymorphs in an enantiotropic system.[8] The higher melting form (form **II**) was produced by heating solid samples of the lower melting form (form **I**) at about 100 °C for prolonged periods. Comparison of X-ray powder diffraction, infrared, and DSC data established clear differences between the two polymorphs. The thermodynamic transition temperature between the two forms was established by infrared experiments to be about 80 °C. Nujol mulls containing equal amounts of the two polymorphs were aged at different temperatures, and the polymorphic ratio was measured by infrared spectroscopy. A sample aged at 80 °C for 20 h showed negligible change in polymorphic ratio, whilst samples aged at 70 and 90 °C converted into forms **I** and **II**, respectively.[8]

Although form **II** has the higher melting point, it is metastable with respect to form **I** at room temperature. Form **II** is more soluble (e.g., 0.28% w/v in 2-propanol vs 0.17%

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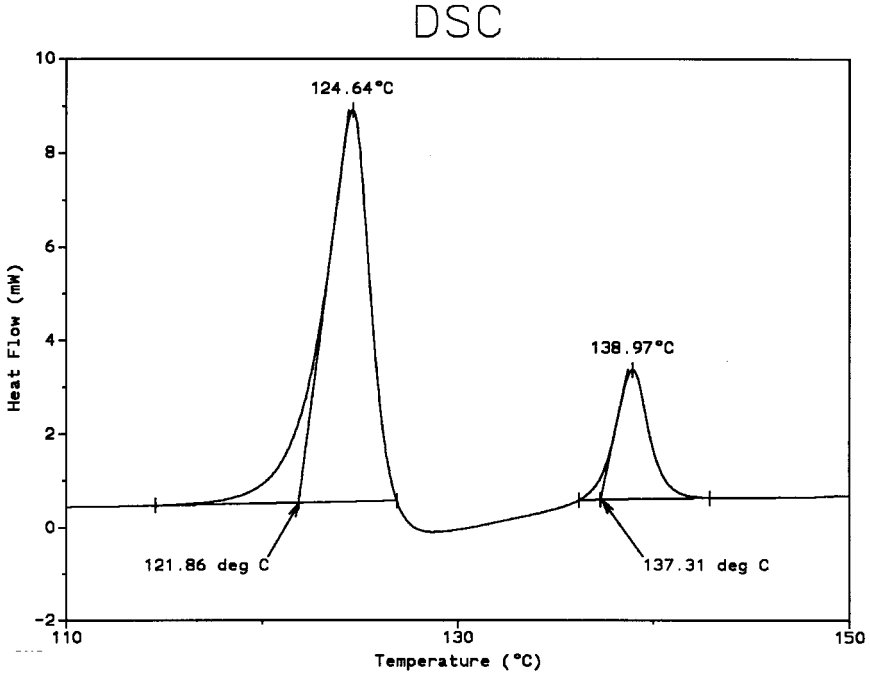

Figure 4. **DSC profile of conventionally crystallised salmeterol xinafoate.**

for form **I** at 22 °C) and crystallisation of salmeterol xinafoate from a range of organic solvents and adding seeds of forms **I** or **II** to the solution, always delivered form **I**. In all cases the product crystallised at temperatures below 80 °C. The fast-cooling crystallisation process described above gave, as expected, exclusively form **I** of salmeterol xinafoate.

Crystallisation of Salmeterol Xinafoate using Supercritical Carbon Dioxide

Introduction. Over recent years, increasing attention has been directed to alternative approaches to particle formation in an attempt to bypass and even eliminate the constraints imposed by, as well as problems arising from, conventional crystallisation and precipitation processes. The difficulties of controlling final crystal/particle physical properties in conventional processes, as well as the potential for batch-to-batch variation, have to be overcome to minimise inefficiency in downstream processing and potential product malfunction. With increasing regulatory and environmental demands on the preparation and specifications of pharmaceuticals and the desire for crystal engineering of materials with preferred chemical and physical properties, new approaches which address these issues offer timely benefits. This is especially the case for compounds delivered by inhalation such as salmeterol xinafoate, where the direct preparation of dry, 2−5 micrometer-sized particles for drug delivery would avoid further size reduction operations following particle generation and harvesting.

A particularly attractive technique for particle formation which has been considered for the past decade has been the use of supercritical fluids (SCFs) both as solvents and antisolvents.[9−12] Whilst the benefits of this technology have been recognised for some time in extraction procedures and in chromatography, only recently has research demonstrated the potential for SCF techniques in particle formation. A supercritical fluid can be defined as a substance existing as a single fluid phase above its critical temperature (T_c) and pressure (P_c). At temperatures and pressures above the critical conditions the single-phase domain defines the supercritical region.

SCFs exhibit interesting physical and chemical properties which can vary between liquidlike and gaslike characteristics. Such features include large compressibility, high diffusivity, lower surface tensions and viscosities than liquid solvents, densities which can be varied between gaslike and liquidlike values in a controlled manner by changing the temperature and pressure conditions, and enhanced solvation power and mass transfer rates compared with those of liquids. Carbon dioxide, the most commonly used SCF (T_c = 31.1 °C, P_c = 73.8 bar), provides the additional benefits of being relatively inert, nonoxidising, and nondegrading, useful features when handling sensitive compounds.

The processes which have previously been developed where SCFs are used as a solvent or antisolvent in particle formation are respectively termed rapid expansion of supercritical fluid solutions (RESS) and gas antisolvent (GAS) processes. In RESS the material of interest is packed into an extraction vessel, and an SCF is passed through the vessel under pressure. The SCF extracts (dissolves) some solid, and the resultant supercritical solution is sprayed via a nozzle into a particle formation vessel generally at ambient conditions. The pressure reduction on spraying causes a rapid expansion (10^{-6} secs) causing high supersaturation, fast nucleation, and the formation of fine particles. In the GAS process, a solid, which is insoluble in the selected SCF, is

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dissolved in a solvent which is miscible with the SCF. The SCF is added to the solution, and as it dissolves in the solvent, a rapid increase in volume occurs with a corresponding drop in solvation power, an increase in supersaturation, and the consequent nucleation of the solid. The precipitated solid requires harvesting and isolation by conventional filtration and drying. Modifications of the GAS process, involving spraying the material or material:adjuvant solution into a continuum of supercritical fluid, have also been reported.

The GAS process requires the compound of interest to be poorly soluble, or practically insoluble, in the SCF, which is generally the case for pharmaceuticals with carbon dioxide. RESS is restricted to the relatively few pharmaceutical materials which are appreciably soluble in SCFs. However for GAS recrystallisation, problems can occur with product and solvent recovery when the system is depressurised and, for both processes, the resultant size and morphology of formed particles are not controlled or predictable.[13]

Solution Enhanced Dispersion by Supercritical fluids (SEDS). The SEDS process, developed in Pharmaceutical Technology at Bradford University, builds on the benefits of the RESS and GAS particle formation processes and provides the major benefit of directed control over particle properties such as particle size.[14] A schematic diagram of the SEDS equipment is illustrated in Figure 5.

In the SEDS process a solution of the material of interest in an organic solvent and SCF carbon dioxide are fed into a specially designed coaxial nozzle. The jet of drug solution is broken by the high velocity jet of SCF carbon dioxide and mixed with the SCF carbon dioxide, and the organic solvent is immediately extracted and dissolved in the SCF carbon dioxide. These mechanical, physical, and chemical processes occur virtually instantaneously, leading to very high supersaturation conditions and the rapid formation of particles which are retained in the particle formation vessel. The oven and back-pressure regulator control the selected temperature and pressure of the experiment, respectively, in the particle formation vessel. These factors, together with the precise metering of the flow rates of the solution of material and SCF carbon dioxide through the nozzle, provide constant and uniform conditions and thereby control over nucleation and particle generation.

The supercritical solution formed (i.e., SCF plus extracted solvent) flows through the back-pressure regulator and expands in a controlled manner so that the solvent and carbon dioxide gas can be recovered and, if required, recirculated.

Advantages of Particle Formation by the SEDS Process. Whilst the RESS and GAS processes offer benefits over conventional precipitation and crystallisation methods, both techniques are limited in achieving the goal of particle design and crystal engineering due to the lack of control over the size, size distribution, and morphology of the resulting particles. In RESS, nozzle blockage is also frequently encountered, whilst in GAS processes recrystallisation occurs

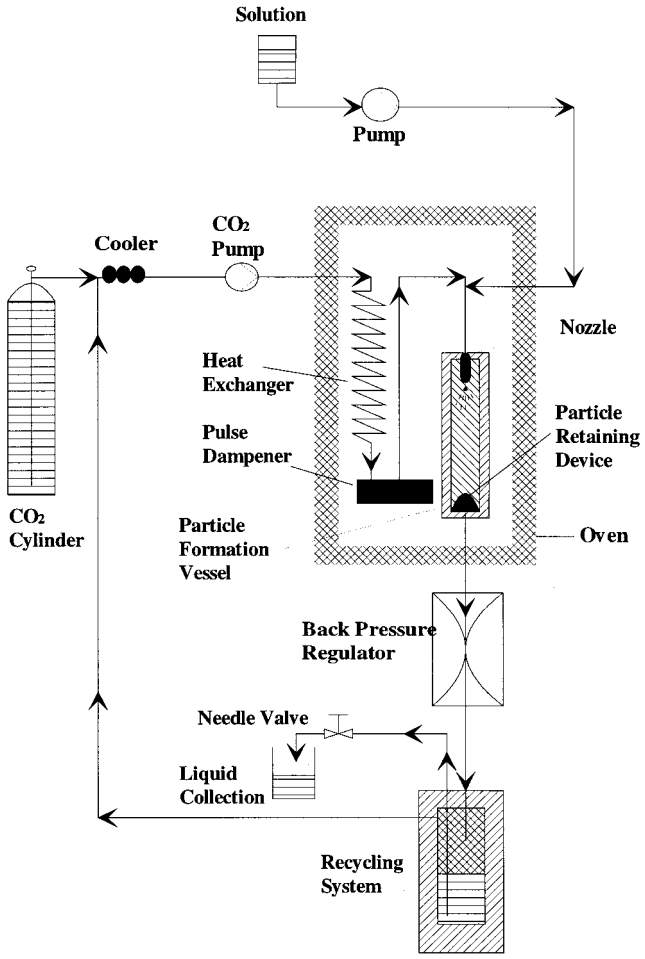

Figure 5. **Schematic diagram of the solution enhanced dispersion by supercritical fluids (SEDS) process.**

in bulk solution either by rapid (<1 min) or slow (>20 min) introduction of SCF. In the former conditions, fine particles are produced,[9] while in the latter large particles are formed[10] with similar features to those associated with conventional crystallisation from solution.

In SEDS, these aspects are avoided as the SCF is introduced in a way which not only dissolves and extracts the solvent rapidly, but also controls the dispersion of the solution. By modification of the carefully controlled working conditions it is possible to manipulate the characteristics of the particles, including particles in the micrometer-sized range.

It is also clear that in achieving this level of control of the variables at the point of nucleation, a high level of consistency and reproducibility is possible between batches. Powders prepared by this process will also be (virtually) free of retained solvent due to solvent transformation to the supercritical state and removal in the SCF stream. These features are coupled with the direct production of dry, uncharged materials directly from a solution stream. Regulatory and environmental issues are addressed as the system is a clean and closed process, avoiding atmospheric release of impurities, solvents, and particulates and in-process contamination. In addition, given the range of advantageous properties provided by SCFs, it is likely that by probing the supercritical domain, operating conditions which achieve

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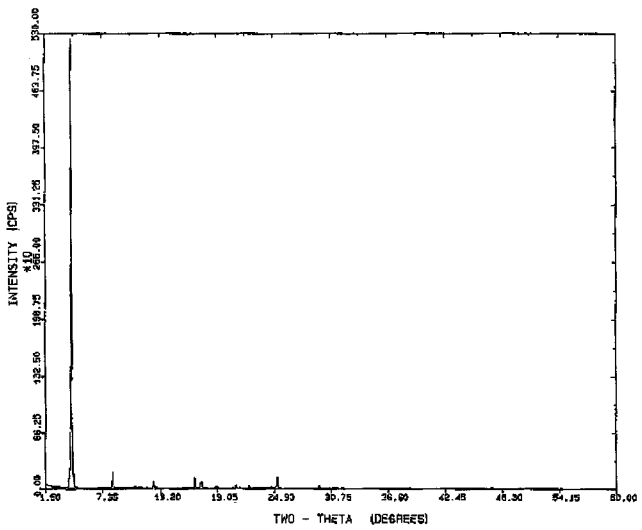

Figure 6. **XRPD pattern of SEDS prepared salmeterol xinafoate at 60 °C and 350 bar.**

Table 2. **Particle size distribution data for two samples of salmeterol xinafoate prepared by the SEDS process[a]**

	mean spherical diameter (μm)	% <5 μm	% <10 μm
sample 1	7.2	31.6	67.8
sample 2	7.7	28.3	64.5

[a] Determined by laser diffraction analysis (Malvern Mastersizer). Working conditions: 35 °C; 300 bar.

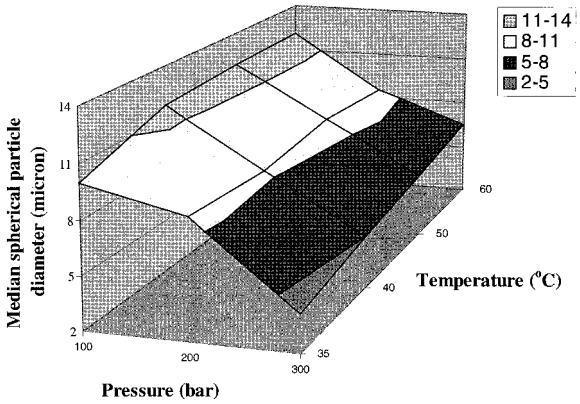

Figure 7. **Effects of pressure and temperature on particle size of SEDS prepared salmeterol xinafoate, at constant solution and SCF CO_2 flow rates.**

purity enhancement and even polymorphic separation may be located.

In view of these factors, and in particular the opportunity to obtain 2−5 micrometer-sized particles directly, the single-step SEDS process is an alternative for the preparation of salmeterol xinafoate particles for drug delivery by the respiratory route.

Characterisation of Salmeterol Xinafoate Products Prepared by the SEDS Process. Solutions of salmeterol xinafoate, in ethanol and acetone, were introduced into the SEDS apparatus under a range of working conditions (i.e., temperature, pressure, drug solution concentration, and solution and supercritical carbon dioxide flow rates). The particulate products were examined for residual solvent and

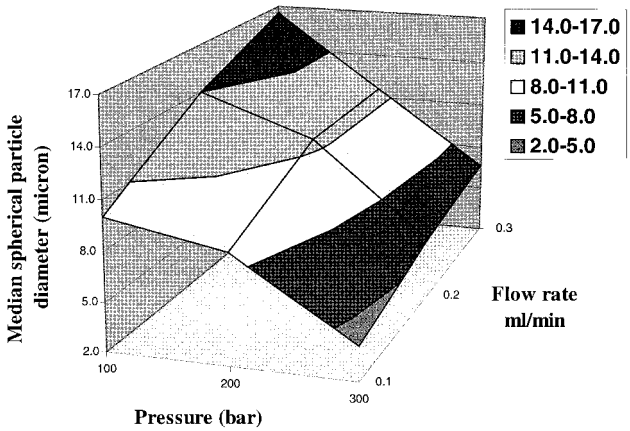

Figure 8. **Effects of pressure and solution flow rate on particle size of SEDS prepared salmeterol xinafoate, at 35 °C.**

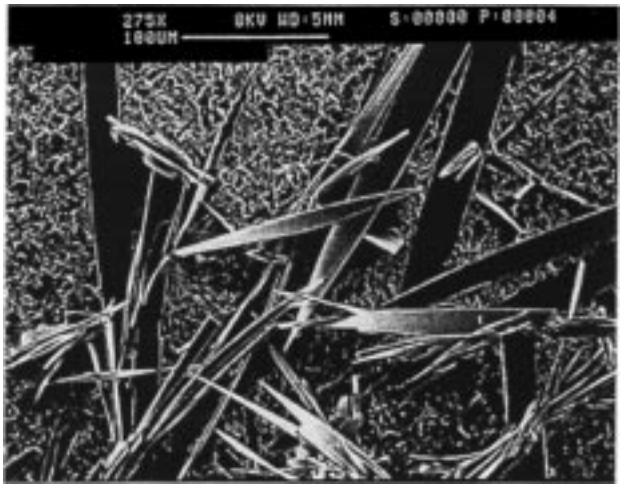

Figure 9. **Scanning electron micrograph of SEDS prepared salmeterol xinafoate from ethanol solution at 60 °C and 300 bar.**

by HPLC, DSC, X-ray powder diffraction (XRPD), and particle size analysis.

All salmeterol xinafoate products recovered from the particle formation vessel were dry, uncharged, and easy flowing. Samples were of high chemical purity and crystallinity when examined by HPLC and XRPD (see Figure 6), respectively.

Control of Particle Size. Consistency of particle size and particle size distribution in the 1−10 μm range between batches prepared under the same working conditions is impressive (see Table 2). Manipulation of the working conditions provided controlled change in mean particle size (see Figures 7 and 8). Clearly within the range of working conditions employed in this study, it is possible to control the mean particle size between 3 and 17 μm, with all of the samples exhibiting a narrow particle-size distribution. As expected, increased pressure and/or reduced solution flow rate led to smaller mean particle sizes.

It is interesting to note that particle morphology was modified by changing the solvent used to prepare the salmeterol xinafoate solution. When prepared from ethanol solutions, salmeterol xinafoate particles exhibited a thin, bladelike habit (see Figure 9), whilst those from acetone showed accretion forms (Figure 10).

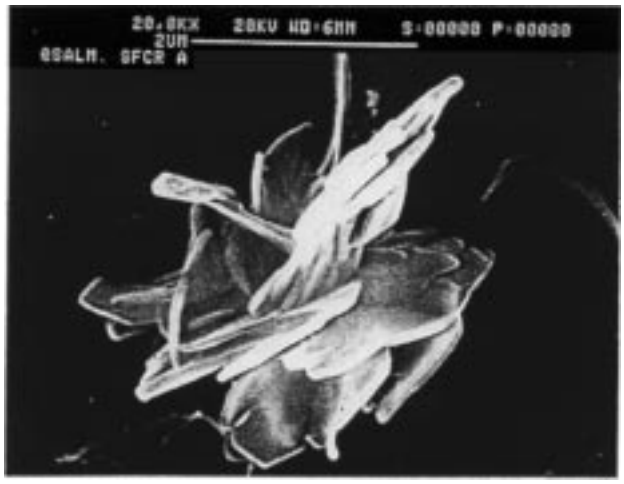

Figure 10. **Scanning electron micrograph of SEDS prepared salmeterol xinafoate from acetone solution at 50 °C and 200 bar.**

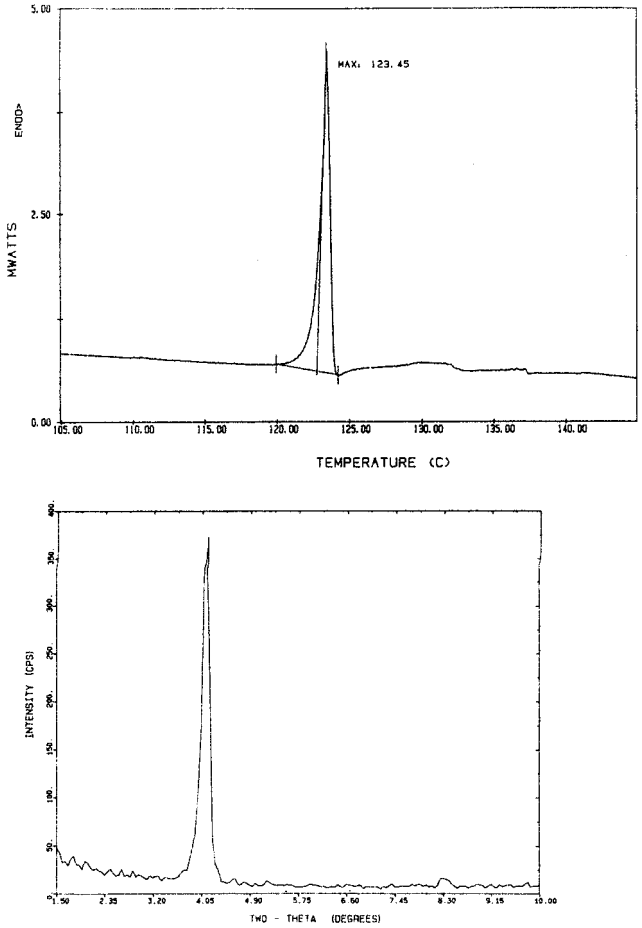

Figure 11. **SEDS prepared salmeterol xinafoate form I: (a) DSC profile; (b) XRPD pattern.**

Control of Polymorphs. As discussed above, two polymorphic forms (**I** and **II**) of salmeterol xinafoate have been identified, with melting points of about 125 and 139 °C, respectively. Because of the potential for controlling the particle formation process using SEDS, it was of interest to carry out a study to explore different regions of the supercritical domain which might provide "pure" polymorphs **I** and **II**. Figures 11 and 12 show combined DSC and XRPD

Table 3. **Residual solvent content in SEDS prepared salmeterol xinafoatesamples[a]**

sample	pressure (bar)	temperature (°C)	residual solvent (ppm)
Samples Prepared from Acetone Solutions			
1	300	45	8[b]
2	300	45	9[b]
3	200	60	5[b]
Samples Prepared from Ethanol Solutions			
1	100	50	ND[c]
2	200	60	ND
3	300	60	ND

[a] Typical solvent content in granular salmeterol xinafoate (methanol/2-propanol) about 1000 ppm. [b] Acetone content. [c] ND = ethanol not detected.

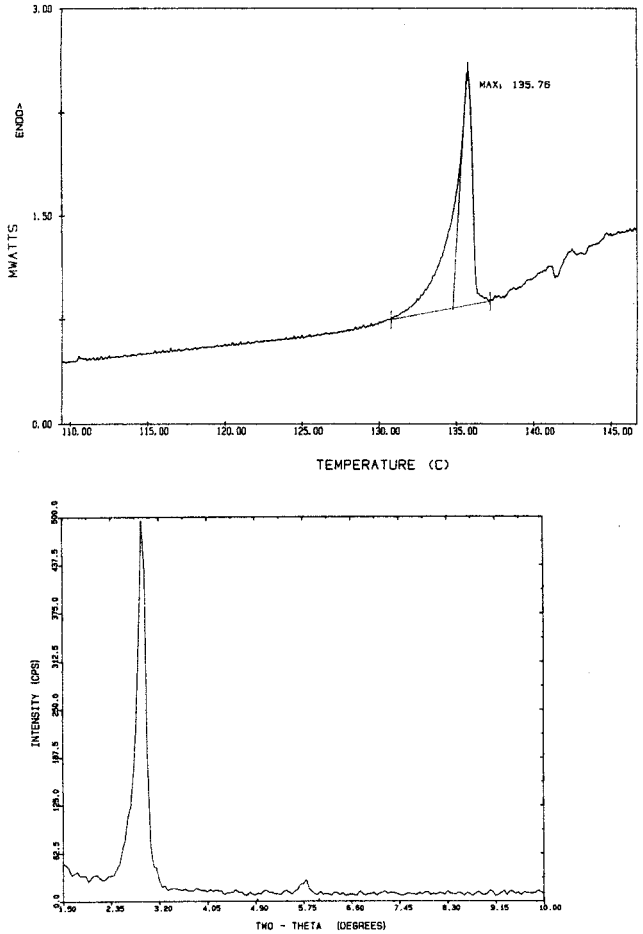

Figure 12. **SEDS prepared salmeterol xinafoate form II: (a) DSC profile; (b) XRPD pattern.**

(expanded) profiles for samples obtained from different regions of the supercritical domain, both prepared from an acetone solution of salmeterol xinafoate. Identified pressure and temperature conditions for form **I** preparation with acetone as the drug solvent were 100−250 bar and 35−60 °C and above 250 bar and 70−100 °C for form **II**. Figure 11 shows characteristics of salmeterol xinafoate form **I** and Figure 12 for form **II**. Interestingly, no interconversion between the two forms is seen on the DSC trace for form **I** (Figure 11a) which suggests a high purity sample of polymorph **I**. Also no conversion of form **I** into form **II** was seen when operating the DSC at heating rates up to 50

°C·min^{-1}. Thus, the SEDS process appears to offer a means for the production of pure polymorphic forms **I** and **II** of salmeterol xinafoate. The absence of interconversion by DSC and stability of the samples on storage is attributed to the high degree of chemical and crystallographic purity achieved using SEDS.

Solvent Removal. SEDS products of salmeterol xinafoate prepared from acetone and ethanol solutions were examined for residual solvent by a gas chromatographic method. Table 3 lists the results and data demonstrate the virtual absence of acetone and nondetectable levels of ethanol in examined samples. This factor provides considerable benefit over conventionally crystallised material where retained solvent levels were typically in the range of 500 to 1000 ppm. The extremely low levels or absence of retained solvent in SEDS prepared products is generally found and is thought to be a contributing factor in the observed enhanced stability of such materials with high chemical and crystallographic purity.

General Comments

The formulation requirement of microfine 2−5 μm particles of salmeterol xinafoate for respiratory drug delivery has presented opportunities for direct control of the physical form of prepared particles. Two different approaches to crystallisation control have been successfully employed. Given the poor flow and microniser mill feeding characteristics of conventionally crystallised drug, a fast-cooling crystallisation from a selected optimal solvent system was developed to provide a granular form of salmeterol xinafoate. This spherical, crystalline agglomerated form exhibited good flow properties from which a milling process providing 2−5 μm-sized particles was possible.

An alternative and novel process, relying on using SCF technologies and the SEDS process with SCF carbon dioxide as an antisolvent, was studied. This process was able to provide, directly without an extra milling operation, microfine crystalline 2−5 μm-sized particles of salmeterol xinafoate which were virtually free from retained solvent and easy flowing. Of particular interest for preparing the polymorphic forms of salmeterol xinafoate the SEDS process, unlike conventional or modified conventional crystallisation procedures, was able to produce pure forms of the two polymorphs, forms **I** and **II** and controlled mean particle sizes between 2 and 17 μm by varying the working conditions.

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