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Note

Characterisation of excipient-free nanoporous microparticles (NPMPs) of bendroflumethiazide

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Abstract

The purpose of this study was to prepare excipient-free porous microparticles of bendroflumethiazide by spray drying and to characterise the physicochemical properties of the particles produced. Solutions of bendroflumethiazide in ethanol/water, ethanol/water/ammonium carbonate or methanol/water/ammonium carbonate were spray dried using a laboratory spray dryer. Spray dried products were characterised by scanning electron microscopy, X-ray powder diffraction, differential scanning calorimetry, FTIR, laser diffraction particle sizing and density measurement. Nanoporous microparticles (NPMPs) were prepared from the alcoholic solutions containing ammonium carbonate. NPMPs were amorphous in nature, had median particles sizes less than 3 μm and densities that were significantly reduced compared to non-porous spray dried bendroflumethiazide powder. The novel process may be used to produce excipient-free amorphous microparticles with desirable physical properties such as amorphous solid state, porosity and low bulk density. This new engineering technology has applications in the design of other therapeutic agents such as those used in pulmonary delivery.

Keywords: Spray drying; Porous microparticles; Amorphous; Excipient-free; Nanopores

1. Introduction

Spray drying involves the conversion of a liquid, solution or suspension into a powder in a one step process. Micromeritic properties of the spray dried material, such as particle size, shape and density, can be controlled by altering spray drying parameters such as the temperature of the inlet air, the rate of liquid feed entry, the atomizer, or the viscosity, surface tension and the concentration of the liquid feed. The solid-state nature of the spray dried material is largely dictated by the physicochemical properties of the system to be processed. The rapid drying that occurs during spray drying can lead to the production of amorphous materials.

Micronised amorphous materials, such as those produced by spray drying are often desirable for particular formulations and may be critical to the biopharmaceutical performance of the formulation. The high surface area associated with microparticulate materials and increased solubility associated with the high energy amorphous form can often result in an improved dissolution rate and bioavailability for poorly soluble drugs [1]. However, such materials often pose problems in handling and flow due to their cohesive nature, as a result of high surface energy and surface cohesive forces [2].

Particle engineering techniques may be used to optimise the micromeritic properties of particles to try to overcome problems of cohesiveness and poor flowability/dispersion associated with microparticles. Porous microparticles, in particular, have potential advantages over non-porous materials. Such particles are known to be beneficial for drug delivery to the respiratory tract by oral inhalation as they have reduced interparticulate attractive forces and improved flow characteristics relative to micronised drug

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materials [3]. They have low bulk densities and exhibit smaller aerodynamic diameters than their geometric diameters, facilitating greater deposition in the lower pulmonary region. They have potential for improved efficiency of administration to the lungs in the dry form (dry powder inhaler formulations) and also a potential for improved suspension stability in liquid inhaler formulations (metered dose inhalers), with a reduced tendency to sediment in the liquefied propellant.

The increased porosity associated with porous microparticles will be reflected in an increased powder surface area which in turn is likely to result in an increased dissolution rate. If the drug is also present in a high energy amorphous form, this may result in an improved solubility, dissolution rate and potentially improved bioavailability for orally administered drugs. The stability of suspensions for oral administration may also be improved by the use of microparticles with a porous morphology, which will settle slowly in suspension due to their small particle size and low bulk density. This in turn will ensure improved and accurate dosing.

Porous microparticles in the form of Pulmospheres™ have been produced by spray drying an emulsion formulation consisting of a bioactive agent, surfactant, and a blowing agent, such as fluoroalkane [3]. In the spray drying process, it has been postulated that the blowing agent is vaporised and forced through the thin surface wall to form pores in the particles [4]. The stabilising surfactant remains in the spray dried product.

In the present paper, we describe a spray drying process for producing nanoporous microparticles (NPMPs) of the model drug, bendroflumethiazide. The process involves spray drying an active from a solution containing ammonium carbonate as a pore forming agent or process enhancer, to produce excipient-free porous particles. We have previously reported the production and characterisation of non-porous amorphous microparticles of bendroflumethiazide using conventional spray drying techniques [5,6]. Characterisation studies of the micromeritic properties of the NPMPs of bendroflumethiazide prepared are presented. The process involves spray drying a single phase feed liquid to produce surfactant-free particles. If successful in altering the micromeritic properties of the model drug so as to improve flow and handling properties, the process may then be applicable to more therapeutically relevant actives, such as those used in pharmaceutical inhalers.

2. Materials and methods

2.1. Materials

Crystalline micronised bendroflumethiazide (BFMT) raw material (100.9% purity) was kindly provided by Leo Laboratories, Ireland. Ammonium carbonate was purchased from Sigma–Aldrich, Ireland. Ethanol was obtained from Cooley Distillery (Ireland). Deionised water was produced by a Purite Prestige Analyst HP water purification system. All other reagents were analytical grade.

2.2. Spray drying

2.2.1. Spray drying to produce non-porous microparticles

BFMT was spray dried as previously described [6]. A 2.5% w/v solution of BFMT was prepared in 95% ethanol/5% water and spray dried using a Büchi 290 spray dryer with inlet air temperature 78 °C, outlet temperature 56 °C, pump setting 30%, airflow rate of 670 Nl/h and aspirator rate 100%. Compressed air was used as the drying gas.

2.2.2. Spray drying to produce nanoporous microparticles (NPMPs)

Solutions of BFMT were prepared in ethanol/water (80% v/v ethanol) or methanol/water (80% v/v methanol), to which ammonium carbonate was added. The total solid concentration in solution was 2.5% w/v. The ammonium carbonate was added in a concentration equivalent to 15% of the total weight of solids (such that BFMT concentration in solution was 2.125% w/v).

Ethanol/water/ammonium carbonate/BFMT systems were spray dried with a Büchi 290 spray dryer operating in the open mode with compressed air as the drying gas. Methanol/water/ammonium carbonate/BFMT systems were spray dried with a Büchi 290 spray dryer operating in the closed mode, using the Büchi 295 inert loop and nitrogen as the drying gas. The absence of oxygen prevents the formation of an ignitable mixture when spray drying the organic solvent. In both cases the pump setting was 30%, airflow rate was 670 Nl/h and aspirator rate was 100%. In the case of the ethanolic solution, inlet temperature was set at 78 °C, with a resulting outlet temperature of 53 °C, while for the methanolic solution inlet air temperature was 110 °C and outlet air temperature was 74 °C.

2.3. Characterisation of materials

X-ray powder diffraction measurements (XRD) were made on samples in low background silicon mounts, which consisted of cavities 0.5 mm deep and 9 mm in diameter (Bruker AXS, UK). The Siemens D500 Diffractometer consists of a DACO MP wide-range goniometer with a 1.0° dispersion slit, a 1.0° anti-scatter slit and a 0.15° receiving slit. The Cu anode X-ray tube was operated at 40 kV and 30 mA in combination with a Ni filter to give monochromatic Cu Kα X-rays. Measurements were generally taken from 5° to 40° on the two θ scale at a step size of 0.05 per s.

Differential scanning calorimetry (DSC) was performed using a Mettler Toledo DSC 821^e. Samples (of weights between 6 and 11 mg) were accurately weighed and placed in closed 40 μl aluminium pans with three vent holes. Samples were run at a heating rate of 10 °C/min under nitrogen purge.

Fourier Transform Infrared (FTIR) spectroscopy was carried out using a Nicolet Magna IR 560 E.S.P. spectro-

photometer working under Omnic software version 4.1. A KBr disk method was used with 1% sample loading.

Scanning electron microscopy (SEM) was performed using a Hitachi S-3500N variable pressure scanning electron microscope.

Particle size measurements were performed by laser diffraction using a Malvern Mastersizer 2000 particle sizer (Malvern Instruments Ltd., Worcs., UK) with Scirocco 2000 accessory. The dispersive air pressure used was 2 bars. Samples were generally run at a vibration feed rate of 50%. The particle size reported is the $d(0.5)$, which is the median particle size of the volume distribution. The values presented are the average of at least two determinations. Mastersizer 2000 software (Version 5.22) was used for the analysis of the particle size.

Bulk density ($b\rho$) was measured by filling the dry powder in a 1 ml graduated syringe with a funnel. The weight of the powder required to fill the 1 ml graduated syringe was recorded to calculate $b\rho$. The tap density ($t\rho$) of the powder was then evaluated by tapping the syringe onto a level surface at a height of one inch, 100 times. The resultant volume was recorded to calculate $t\rho$. Each measurement was performed in triplicate.

Bendroflumethiazide was assayed by the potentiometric titration method outlined in the European Pharmacopeia (5.7) [7], using a 702 SM Titrino titrator (Metrohm AG, Switzerland). Results are the average of three determinations.

Elemental analysis was performed using an Exeter Analytical CE-440 elemental analyser (Exeter Analytical, MA, USA), on samples weighing between 1.6 and 1.8 mg. Analysis was performed in duplicate on two samples for each system tested.

3. Results and discussion

SEM micrographs of the systems spray dried from ethanol/water/ammonium carbonate and methanol/water/ammonium carbonate are shown in Fig. 1(c) and (d), respectively, alongside the micronised crystalline raw material (Fig. 1(a)) and the sample spray dried from ethanol/water solution (Fig. 1(b)). The SEMs indicate that roughly spherical nanoporous microparticles, approximately 1 to 5 μm in diameter, were prepared from the alcohol/water/ammonium carbonate systems, in comparison to the non-porous microparticles prepared by spray drying without ammonium carbonate. Particles spray dried from methanol/water ammonium carbonate appear to be more uniform in size and shape than those spray dried from the equivalent ethanol-based solution.

The absence of crystallinity in the NPMP spray dried systems was evident from the lack of peaks in the XRD (Fig. 2(c) and (d)). The amorphous halo in the XRD pattern contrasts with the distinctive peaked pattern obtained for the crystalline raw material but is indistinguishable from that of the BFMT system spray dried

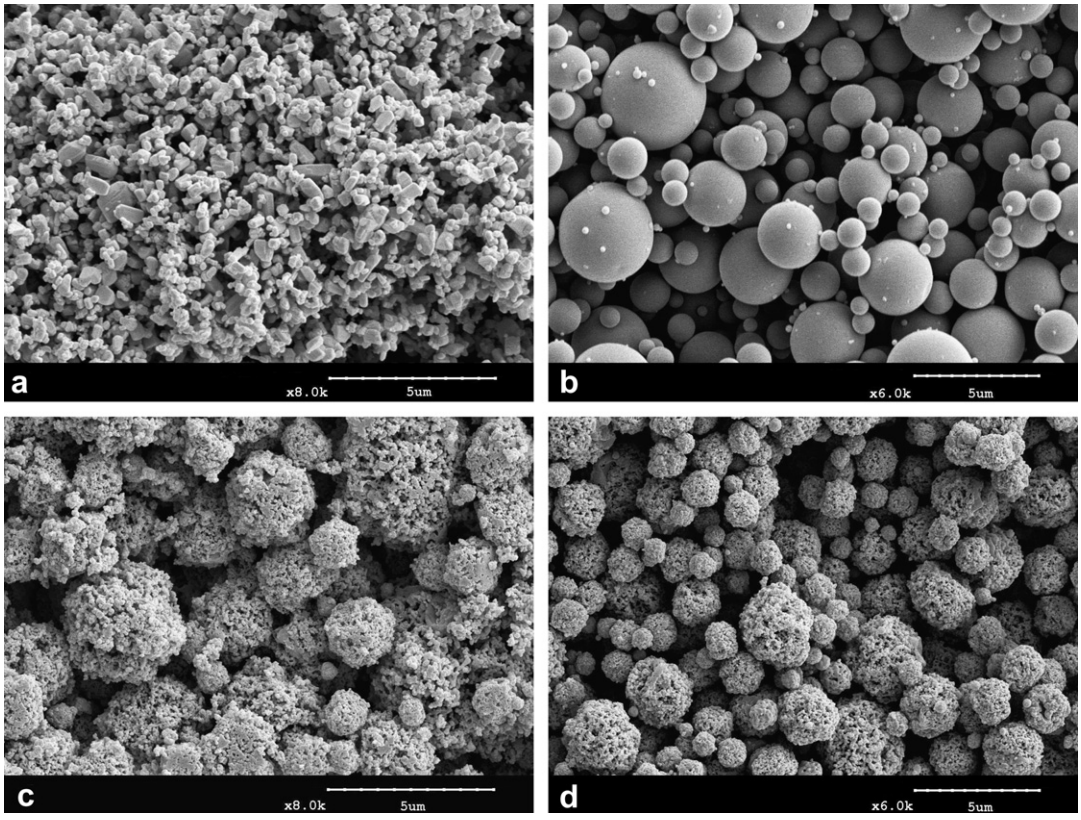

Fig. 1. SEM micrograph of (a) BFMT starting material, (b) BFMT spray dried from 95% ethanol, (c) BFMT/ammonium carbonate 85:15 system spray dried from 80% v/v ethanol and (d) BFMT/ammonium carbonate 85:15 system spray dried from 80% v/v methanol.

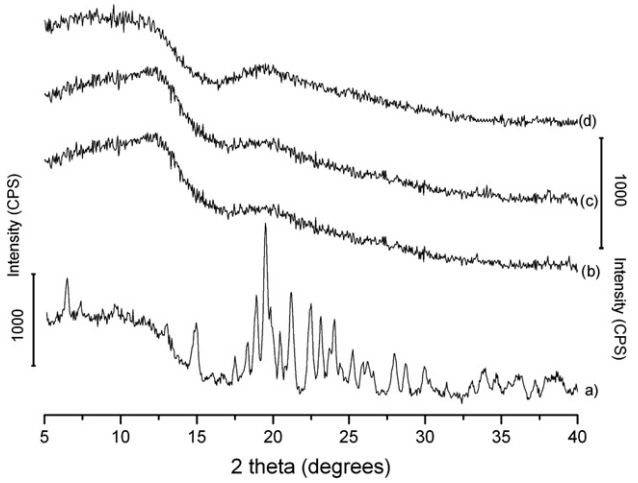

Fig. 2. XRD of (a) BFMT raw material (b) BFMT spray dried from ethanol/water solution, (c) BFMT/ammonium carbonate 85:15 system spray dried from 80% v/v ethanol and (d) BFMT/ammonium carbonate 85:15 system spray dried from 80% v/v methanol.

from ethanol/water alone (without ammonium carbonate) (Fig. 2(b)).

DSC data, shown in Fig. 3, support the amorphous nature of the NPMPs. A change in the baseline of the DSC trace, with an onset temperature of approximately 120 °C, was indicative of glass transition and was followed by an exotherm (recrystallisation of the amorphous phase) with an onset temperature of approximately 155 °C (ethanol system) or 151 °C (methanol system). This was then followed by the melting endotherm, which had an onset temperature at approximately 224 °C (ethanol system) or 209 °C (methanol system). The DSC scans are similar to that obtained for BFMT spray dried alone from 95% v/v ethanol, for which an exotherm with onset at 155 °C and a melting endotherm with onset at 217 °C was observed (Fig. 3(b)).

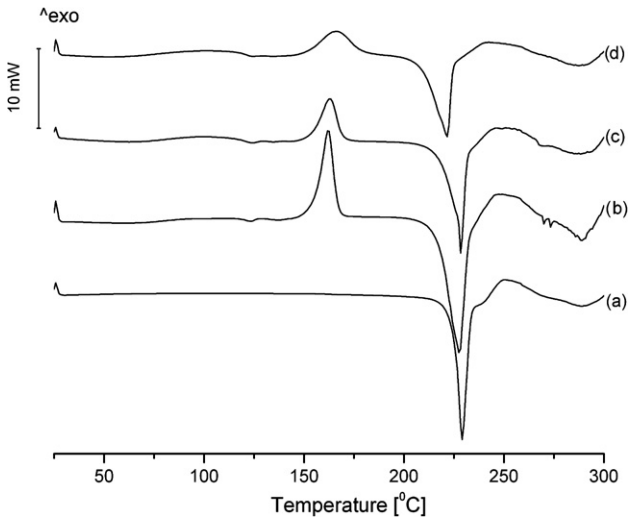

Fig. 3. DSC of (a) BFMT raw material (b) BFMT spray dried from ethanol/water solution, (c) BFMT/ammonium carbonate 85:15 system spray dried from 80% v/v ethanol and (d) BFMT/ammonium carbonate 85:15 system spray dried from 80% v/v methanol.

FTIR analysis showed no differences between the spray dried BFMT/ammonium carbonate 85:15 systems and the BFMT starting material.

Particle size analysis of the NPMPs spray dried from ethanolic solution was performed and compared with the particle size of both BFMT crystalline raw material and BFMT spray dried alone from 95% v/v ethanol, i.e. the non-porous spray dried sample (Table 1). The median particle size of the volume distribution, $d(0.5)$, for the NPMPs was 2.36 μm. The particle size distribution was monomodal in contrast to that of the raw material micronised drug, which was bimodal and had a $d(0.5)$ of 1.43 μm. The $d(0.5)$ of the non-porous spray dried BFMT was 2.82 μm. For the BFMT NPMPs spray dried from methanol/water/ammonium carbonate solution, the $d(0.5)$ was 2.24 μm which is very similar to the $d(0.5)$ for the same system spray dried from ethanol water/ammonium carbonate.

The bulk (bρ) and tap (tρ) densities of the BFMT systems also showed variation in accordance with the morphological differences apparent in the SEMs (Table 1). The densities for the raw material were higher than those determined for the BFMT non-porous spray dried system, which suggests that particles of the latter system might be hollow. The bρ and tρ values for both NPMPs systems were much lower than those measured for both crystalline BFMT raw material and non-porous spray dried BFMT. The bulk and tap densities of the NPMPs spray dried from methanolic solution were higher than the equivalent values for NPMPs spray dried from ethanolic solution.

Assay results shown in Table 1 indicate the purity of the spray dried NPMPs to be equivalent to that of the spray dried non-porous material (from ammonium carbonate-free solvent), demonstrating the removal of ammonium carbonate during the spray drying process.

Elemental analysis was performed on the BFMT raw material and BFMT NPMPs spray dried from methanol/water/ammonium carbonate solution. There was no significant difference ($p < 0.05$) in the percentage carbon, hydrogen or nitrogen between the two materials (BFMT raw material: $C = 42.75 \pm 0.02\%$, $H = 3.29 \pm 0.08\%$, $N = 9.83 \pm 0.04\%$; BFMT NPMPs: $C = 42.77 \pm 0.16\%$, $H = 3.39 \pm 0.01\%$, $N = 9.65 \pm 0.11\%$). This confirms the removal of the ammonium carbonate during the spray drying process.

Since the volatilisation temperature of ammonium carbonate is 60 °C, it is postulated that the ammonium carbonate undergoes decomposition with volatilisation (forming ammonia and carbon dioxide) and that the volatilisation process enhances pore formation in the particles.

4. Conclusions

In the present study, porous microparticles of BFMT were obtained by a novel spray drying process which involved spray drying ethanolic/water or methanolic/water solutions of the drug, the solutions also contained ammonium carbonate as a pore forming agent/process enhancer.

Table 1
Median particle size, bulk and tap densities and BFMT assay results for BFMT raw material and spray dried systems

	Volume median diameter (μm)	Bulk density (g/cm^3)	Tap density (g/cm^3)	Assay results for BFMT (%)*
Raw material	1.43	0.288	0.575	
Non-porous spray dried BFMT	2.82	0.206	0.411	98.4 ± 0.4
NPMPs of BFMT (1) (spray dried from ammonium carbonate/ethanol/water)	2.36	0.131	0.239	99.0 ± 0.3
NPMPs of BFMT (2) (spray dried from ammonium carbonate/methanol/water)	2.24	0.161	0.323	98.5 ± 0.1

* Normalised to the raw material (100%).

Since the process involves spray drying of solutions rather than surfactant-stabilised emulsions, the novel process provides for the production of excipient-free microparticles with desirable physical properties such as amorphous solid state, porosity and low bulk density.

In their assessment of Exubera™, a spray dried dry powder inhalable form of insulin, a FDA advisory committee expressed concern about excipients in Exubera's formulation, which the members feared could irritate the lungs [8]. The opportunity exists to apply this particle engineering technology, which results in excipient-free particles, to therapeutically relevant actives such as those that are candidates for drug delivery by oral inhalation.

Further studies will explore the applicability of the technology to such therapeutic agents.

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