International Journal of Pharmaceutics 383 (2010) 62–69

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Magnesium stearate increases salbutamol sulphate dispersion: What is the mechanism?

Tracy Tay, Shyamal Das, Peter Stewart*

Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, 381 Royal Parade, Parkville, Victoria 3052, Australia

ARTICLE INFO

Article history:
Received 21 July 2009
Received in revised form 2 September 2009
Accepted 3 September 2009
Available online 11 September 2009

Keywords:
Respiratory delivery
Magnesium stearate
Force control agents
Mechanisms of dispersion
Surface energy

ABSTRACT

The objective was to understand the mechanism of enhancement in salbutamol sulphate (SS) respiratory deposition through addition of magnesium stearate (MgSt). The mixing of MgSt with micronized SS occurred using a Turbula mixer (101 rpm), whilst varying mixing time and MgSt concentration and size. Deposition of SS was determined by a twin-stage impinger. Particle size distributions were obtained using the Malvern Mastersizer 2000. Morphology was examined by scanning electron microscopy and surface energy determined using inverse gas chromatography. Mixing of SS with increasing concentrations of MgSt improved dispersion (FPF of 3.3% using 1% w/w MgSt, 4.5% using 5% w/w MgSt and 7.8% using 10% w/w MgSt compared with 1.4% of pure SS for 20 mg doses) when mixed for 0.5 h; SS dispersion improved further after 3.5 h of mixing. In addition to the action of the MgSt in coating SS particles, a greater understanding of the function of MgSt particles in acting as micro-carriers and in changing the mixture structure through incorporation into agglomerates has been achieved. The mechanistic understanding of improvement in drug deposition using MgSt will allow more directed strategies to be employed in designing powder formulations for inhalation.

1. Introduction

Dry powder inhalers (DPIs) are formulated either as loose agglomerates of micronized drug particles or as carrier-based interactive mixtures (Malcolmson and Embleton, 1998). In order to reach the lower airways where the drug is most efficiently absorbed, the drug particles must de-agglomerate and/or detach from the carrier particles, becoming dispersed in the airflow. Particles <5 μm in aerodynamic diameter are required for penetration into the deep lungs (Newman and Clarke, 1983; Gonda, 1990). However, particles at this fine size are not free flowing due to their cohesive nature thus giving rise to particulate interactions within the DPI formulation. This leads to poor powder dispersion, affecting drug deposition in the lungs and consequently inhalation efficiency. Cohesion and static charge also interfere with drug handling which can reduce uniformity in metering individual doses, and can also cause drug retention within the device. Most commercially available DPI products have been shown to be relatively inefficient, delivering only about 20–30% of the total dose to the lungs (Steckel and Mueller, 1997).

Magnesium stearate (MgSt) has been used for many years in pharmaceutical solid dosage forms as an adhesion modifier and a lubricant (Swaminathan and Kildsig, 2002). In the production of tablets, lubricants are usually added to reduce the intergranular friction and friction between granules and the die wall during the compression and ejection processes; the subsequent formation of a film of low shear strength around the particles has been found to depend upon the amount of MgSt added and the mixing time (Bolhuis et al., 1975). The mechanism by which MgSt exerts its effect has been proposed by several investigators. According to the mechanisms of boundary lubrication put forward by Strickland et al. (1956), solid lubricants such as MgSt are adsorbed on the granule surface and form a uniform surface-adsorbed film in a manner similar to a Langmuir-type adsorption. Other studies showed that during the mixing process, MgSt flakes are mechanically sheared to form film layers which could adhere to the drug–excipient particles and interfere with the inter-particle bonding, resulting in a hydrophobic coating which significantly reduced the drug dissolution rate (Bolhuis et al., 1975; Chowhan and Chi, 1985a,b, 1986a,b; Wang and Chowhan, 1990). Furthermore, Shah and Mlodozeniec (1977) suggested that both the initial surface coverage due to the adsorption of MgSt particles and its delamination induced by the shear effects of continued mixing are responsible for the distribution of the stearate on the surface of particles.

MgSt is also the most frequently used additive to improve the flow properties of powders; it has been proposed to reduce the adhesion due to its effect on long-range van der Waals forces between the particles of a powder bed (Gold et al., 1968). This is sup-

* Corresponding author. Tel.: +61 3 99039517; fax: +61 3 99039583.
E-mail address: peter.stewart@pharm.monash.edu.au (P. Stewart).

0378-5173/$ – see front matter © 2009 Published by Elsevier B.V.
doi:10.1016/j.ijpharm.2009.09.006

ported by the fact that the hydrophobization of materials, achieved with MgSt, is known in the adhesion literature to reduce the force of adhesion significantly (Deryaguin et al., 1978; Zimon, 1982). An optimal MgSt content, i.e. the concentration which improves powder flow the most, can be found when a complete film has been formed to surround each individual particle. Above the optimal concentration, there is a sharp drop in flowability when the film formed increases in thickness or when an overshot of fine particles exists (Jones and Pilpel, 1966).

In the case of DPIs, the addition of a tertiary excipient, in particular MgSt, has shown promise in improving performance by modifying the interaction between the carrier surface and drug particles (Stewart, 1981; Frijlink and de Boer, 2004). The mechanism of increased dispersion was postulated to be due to either dissipation of electrostatic charge of the components of the mixture by MgSt (Staniforth and Rees, 1982; Staniforth et al., 1982), or the formation of easily dispersible mixed drug-excipient agglomerates when a considerable amount of a fine excipient such as MgSt was added (Lucas et al., 1998).

More recently, the engineering of lactose carrier surfaces with the addition of MgSt has been demonstrated to increase the aerosolization efficiencies of such systems by reducing adhesion (Staniforth, 1997; Young et al., 2002; Iida et al., 2004). In these studies, the mechanism of improved dispersion based on particle smoothing was a result of the high affinity of MgSt for the active sites on the surface of lactose particles that would form a layer to cover the depressions and hence facilitate drug separation.

The use of MgSt as a force control agent (FCA) has also been studied to improve dispersion in dry powder formulations for inhalation. As FCAs exhibit anti-adherent and/or anti-friction properties, their primary role is to modify the interfacial properties of the excipient particles to decrease drug–excipient adhesion. With the use of a novel solid coating technique termed mechanofusion, Begat et al. (2005) demonstrated the potential value of MgSt in optimizing the efficiency of a carrier-based formulation. The generation of a nanometer-thick coating onto the host particles through this highly intensive co-processing system reduced the adhesive interactions between drug and excipient, thus assisting the detachment of drug particles from the carrier upon aerosolization.

Most of the studies have focused on the use of MgSt as a force control agent modifying specific particle interactions between drug and lactose within the powder mixture. During preliminary research within our laboratories, observations of the structure of cohesive mixtures containing MgSt pointed to other possible mechanisms for improved dispersion. The purpose of this study was to understand the dispersion behaviour of a model drug, salbutamol sulphate (SS) when mixed with MgSt and to define specific mechanisms by which MgSt acts to improve powder dispersion. In this work, the influence of MgSt on SS dispersion for respiratory delivery was studied by varying mixing times and MgSt particle size and concentration.

2. Materials and methods

2.1. Materials

Micronized SS of inhalation grade (Cambrex Profarmaco Milano S.r.l., Italy) was employed as the model drug (d_{10} = 0.8 μm, d_{50} = 2.3 μm, d_{90} = 5.3 μm). Two different size fractions of the same batch of MgSt (Sigma–Aldrich, Germany) were investigated as the FCA, the first referred to as MS1 (d_{10} = 0.7 μm, d_{50} = 5.6 μm, d_{90} = 26.1 μm) and the second as MS2 (d_{10} = 1.0 μm, d_{50} = 3.1 μm, d_{90} = 7.9 μm). Hydrochloric acid (Univar Ajax Finechem, Australia) and Milli-Q grade water (Millipore Corporation, USA) were used for the preparation of solvents.

2.2. Particle size analysis of powders

Volume-weighted particle size distributions of both pure SS and MgSt powders were determined by laser scattering using a Scirocco cell and Scirocco 2000 dry powder feeder (Mastersizer 2000, Malvern, UK). Approximately 3 mg of each powder sample was dispersed in air at a shear pressure of 400 kPa. Particle size distributions were characterized by the d_{10}, d_{50} and d_{90} cumulative particle undersize values. All measurements were performed in triplicate and a default value of the refractive index (1.52) was used during analysis.

2.3. Preparation of powder mixtures

Carrier-free formulations consisting of SS only were mixed with MgSt of different size fractions and concentrations using a Turbula mixer (Model T2F, Klausen Engineering, Australia). All samples were prepared in 2 g batches weighed out in 25 ml glass jars and placed in a plastic container secured into the Turbula. Samples were then mixed for time periods of up to 3.5 h at the instrument's maximum rotational speed of 101 rpm. Powders of SS alone were not agitated in the Turbula. After mixing, all powder mixtures were stored in the air-tight glass jars. Using a validated UV assay (Section 2.5), the homogeneity of the powder mixtures was assessed with ten 20 mg samples and the coefficient of variation was less than 3.5% indicating satisfactory homogeneity.

In order to prepare mixtures of SS with immobilized MgSt, double-sided tape and superglue were used as adherents to immobilize MgSt (MS1) onto the inside walls of the 25 ml glass jars. Two separate jars were used for each of the different adherents. Following application of the adherent onto the walls of the jar, approximately 1 g of MgSt was lightly tapped against the adherent and the excess MgSt removed; 2 g of SS was then accurately weighed out and placed into the jar, and mixed in the Turbula for 0.5 h at 101 rpm.

2.4. In vitro aerosol deposition studies

The *in vitro* aerosol deposition of pure SS and the powder formulations produced after mixing were determined using a twin-stage impinger (TSI, Apparatus A; British Pharmacopoeia, 2000) (Copley, UK). A Rotahaler was used as a model inhaler (Glaxo Wellcome, UK) and a solvent of 0.1 M hydrochloric acid (analytical reagent grade) was used as the impinging liquid with 7 and 30 ml placed into stage one and stage two of the TSI, respectively. The air flow was drawn through the TSI using a vacuum pump (Model OD5/2, Dynavac Engineering, Australia) and the air flow rate was adjusted to 60 l/min at the mouthpiece prior to each measurement (Fisher and Porter, Model 10A3567SAX, UK), giving a corresponding aerodynamic cut-off diameter of 6.4 μm. The powder formulations were loaded (20 mg doses) into hard gelatin capsules (size 3, Fawns and McAllan Pty Ltd., Australia). The filled capsule was inserted into the Rotahaler, which was then twisted to release the powder into the body of the device. The Rotahaler was placed into a moulded mouthpiece attached to the TSI and an air volume of 4 l (four s at 60 l/min) was drawn for each measurement. Each of the three sections of the TSI apparatus (inhaler, stage one and stage two) was rinsed with 0.1 M hydrochloric acid, the liquid was then collected and the volume adjusted to 100 ml. Five replicates of each mixture were performed for TSI measurement. Each sample was then centrifuged (Model GS-6R centrifuge, Beckman-Coulter, USA) at 3500 rpm at 25 °C for 20 min in order to remove the insoluble MgSt before determination of the SS content by ultra-violet spectrophotometry. The recovered dose (RD) was defined as the total amount of drug collected from the inhaler device, stage one and stage two; the emitted dose (ED) was defined as the amount of