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

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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-

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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

drug delivered from the inhaler presented as a percentage of the RD; the fine particle fraction (FPF) was defined as the amount of drug particles deposited in the lower stage (stage two) of the TSI as a percentage of the RD.

2.5. UV analysis of salbutamol sulphate

A UV–vis spectrophotometer (Cary 3 Bio, Varian Instruments, Australia) at a wavelength of 276.5 nm was used for the analysis of the SS content recovered from TSI studies to determine the respirable dose or FPF of SS. Linear regression analysis over the SS concentration range of 50–200 μg/ml using four concentrations and four replicates was performed using Microsoft Excel (Microsoft Corporation, USA). The regression coefficient (r^2) was 1.000 showing good linearity, and there was no significant deviation from the zero intercept ($P > 0.05$). The accuracy ranged from 99.7 to 100.4% and the coefficient of variation (CV) for precision ranged from 1.2 to 2.1% for representative low, medium and high concentrations along the calibration plot. Ultra-violet spectrophotometric analysis was chosen over HPLC as the much higher SS loads in the capsules used in the TSI provided sufficient sensitivity to the assay.

2.6. Determination of particle size–shear pressure profiles

Using a Scirocco cell and Scirocco 2000 dry powder feeder (Mastersizer 2000, Malvern, UK), particle size–shear pressure profiles of the powder mixtures were generated by laser scattering at various shear pressures in order to assess the strengths of agglomerates. Approximately 3 mg of each powder sample was dispersed in air using increasing shear pressures of 50, 100, 200, 300 and 400 kPa. All samples were measured using the default value of the refractive index (1.52), since the real refractive index of the mixtures was impossible to determine due to the unknown concentrations of MgSt and SS. The mean particle size distribution and standard deviation were measured from three replicates of each sample.

2.7. Scanning electron microscopy (SEM)

Powder samples were mounted on adhesive black carbon tabs which were in turn pre-mounted onto aluminium stubs. The samples were then gold coated with a sputter coater (Emitech K550X sputter coater, Edwards Vacuum Pump Model RV3, UK) at 20 nm thickness prior to analysis. The surface morphology of the particles was examined at several magnifications under a Phenom scanning electron microscope (FEI Company, The Netherlands) operated at 5 kV.

2.8. Inverse gas chromatography (IGC)

Inverse gas chromatography (IGC) (IGC 2000, Surface Measurement Systems Ltd, UK) was used to determine the surface energies (dispersive and specific) at infinite dilution, as well as the dispersive surface energy distribution profiles at finite dilution. For the two methods, approximately 1.0 g of each sample (SS, MgSt and SS–MgSt mixture) was packed into a pre-silanized glass column (300 mm × 4 mm internal diameter) by vertical tapping for at least 5 min using a jolting volumeter (Surface Measurement Systems Ltd, UK). Progress was visually monitored and tapping continued until no cracks, hollows or channels in the body of the powder were visible. Both ends of the columns were loosely stoppered with silanized glass wool.

Prior to the measurements, pre-treatment was carried out for 2 h at 303 K to remove impurities adsorbed on the surface. Helium with a gas flow rate of 10 sccm (standard cubic centimeter per minute) was used to carry different probes, and the retention times were detected with a flame ionization detector. Dead volume calculations were based on the elution time of methane which was used at a concentration of 0.1 p/p^0 (where p denotes the partial pressure and p^0 the vapour pressure). The specific conditions of measurement for the two methods are described below.

Surface energy measurement by infinite dilution method: GC grade heptane, octane, nonane and decane were used to determine the dispersive surface energy (γ^D), whereas both dichloromethane and ethyl acetate were used to determine the specific free energies (G^{SP}). The concentrations of all these probes were 0.03 p/p^0. The results were analyzed using SMS-iGC analysis software V1.3 (SMS, UK). Surface energy measurements at infinite dilution were performed in triplicate.

Dispersive surface energy distribution profiles at finite dilution: the distribution of dispersive surface energy at finite concentration was determined according to the method detailed by Pirre et al. (2008). Adsorption isotherms were constructed using the peak maximum method (Conder and Young, 1979; Thielmann and Pearse, 2002). Each of the four alkane probes (hexane, heptane, octane and nonane) was run at different concentrations of 0.03, 0.10, 0.25, 0.35, 0.55, 0.70, 0.80, 0.90 and 0.95 p/p^0. BET surface area and adsorption isotherms were calculated using SMS-iGC analysis software V1.2.1 (SMS, UK). The γ^D was calculated according to the Dorris and Gray (1980) method.

2.9. Statistical analysis

Comparison between different groups of FPF was performed using One-Way Analysis of Variance (ANOVA) (SPSS, USA), with probability values (P) of less than 0.05 considered as statistically significant.

3. Results and discussion

3.1. Effect of magnesium stearate concentration, particle size and mixing time on the dispersion of salbutamol sulphate from mixtures

Micronized SS was mixed with different concentrations of MgSt (MS1) (1, 5, 10% w/w) for periods of 0.5 and 3.5 h in the Turbula mixer and the FPF of SS determined. In general, the FPF of SS increased with increasing percentage of MgSt and with increased mixing time (Fig. 1A). For example, using a mixing time of 0.5 h, the addition of 10% MgSt significantly increased the FPF from 1.4 ± 1.1% for SS alone to 7.8 ± 0.7% ($P < 0.001$) and increasing the mixing time to 3.5 h significantly increased the FPF to 12.6 ± 3.3% ($P < 0.05$).

The influence of loading dose using 5 and 20 mg loading doses was studied but not reported in this paper. The loading dose did not have an effect on the aerosolization efficiency of SS, except for one mixture containing 5% MgSt prepared after 3.5 h of mixing where the FPF of SS was significantly greater for the 20 mg loading dose. The reason for the difference observed with the mixture containing 5% MgSt at 3.5 h of mixing was unknown and was not pursued as the influence of dose was not the major focus of the research plan. All studies reported in this paper have used a loading dose of 20 mg of powder.

When micronized SS was mixed with a fraction of MgSt that consisted of a smaller particle size, MS2 (10%, w/w), the extent of dispersion of SS of this mixture was significantly greater than that of pure SS ($P < 0.01$), but was significantly less than that of the mixture containing MS1 ($P < 0.005$) (Fig. 1B). For example, with a mixing time of 0.5 h, the FPF of SS in the MS2 mixtures was 4.2 ± 1.2% which was less than that of the MS1 mixtures (7.8 ± 0.7%).

In these mixtures, the forces generated within the mixture were likely to have two effects. Mixing would cause de-agglomeration

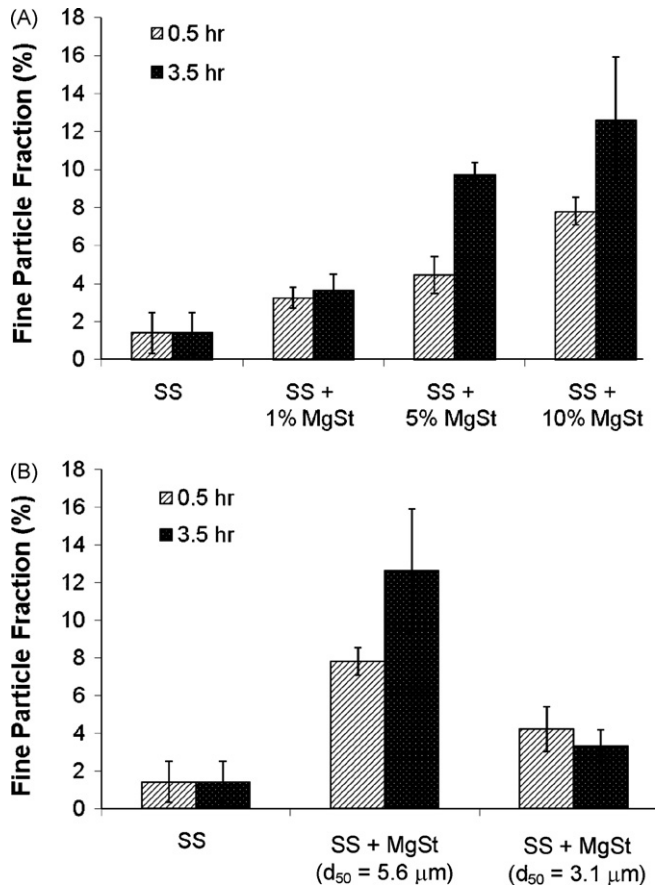

Fig. 1. Effect of (A) magnesium stearate (MgSt) (d_{50} = 5.6 μm) concentration (1, 5, 10% w/w) and mixing time (0.5 and 3.5 h), and (B) MgSt size fraction (d_{50} = 5.6 and 3.1 μm) using a concentration of 10% w/w each with mixing times of 0.5 and 3.5 h, on the dispersion of salbutamol sulphate (SS) from mixtures for inhalation.

of the micronized SS powder. Such effects have been seen previously in the mixing of indomethacin with spray-dried lactose. Increased extent of dissolution of indomethacin and the decrease in agglomerate concentration were observed with greater mixing energy, i.e. increased rotational speed and time of mixing (Kale et al., 2009). The mixing will also cause the MgSt to undergo delamination. These effects are often seen during mixing of MgSt with tablet granulations to facilitate lubrication (Bolhuis et al., 1975; Shah and Mlodozeniec, 1977; Chowhan and Chi, 1985a,b, 1986a,b).

SEMs of SS, MgSt and the SS-MgSt mixture are shown in Fig. 2. Interpretation of SEMs is difficult because of sampling and methodological factors and comments made in this paper are cognizant of this. However, in looking at many SEMs of the powder mixtures, a number of observations can be made. The most obvious was that the larger particles of MgSt acted as micro-carriers and were seen as interactive units containing adhered small particles (Fig. 2A). The composition of the adhered particles was not determined chemically but the particle morphology demonstrated that both small particles of SS (Fig. 2B) and MgSt (Fig. 2C) were present. There was also evidence of agglomerates of fine particles and these agglomerates contained both SS and MgSt (Fig. 2D). It was likely that the constitution of the agglomerates varied widely possibly giving rise to a range of agglomerates, this depending on the ability of the cohesive SS and MgSt particles to de-agglomerate and interact to form mixed agglomerates.

An understanding of mixing theory of fine particles, the observations seen in the SEMs and the knowledge of the delamination behaviour of MgSt point to three possible mechanisms for the improved dispersion performance seen with the addition of MgSt to SS as follows:

(1) The formation of micro-interactive units of MgSt containing adhered SS (and MgSt) facilitated the dispersion of SS since the detachment of SS from MgSt micro-interactive units was more favourable than SS de-agglomeration.
(2) Coating of SS particles with nano-laminates of MgSt decreased SS particle interaction, enhanced de-agglomeration and improved dispersion.
(3) The presence of fine particles of MgSt within a SS agglomerate acted as an agglomerate modifier and enhanced de-agglomeration.

In the remainder of this paper, the three mechanisms are explored and evidence to determine if there was a predominant mechanism gathered and discussed.

3.2. Is SS detachment from a MgSt carrier more favourable than SS de-agglomeration?

While it can sometimes be difficult to deconvolute the complex effects leading to the potential mechanisms described above, it was clear from the SEMs that some SS had redistributed onto the large micro-carriers of MgSt during the powder mixing process (Fig. 2A). In powder formulations for inhalation, fine drug particles are commonly blended with coarse particles of an inert carrier. This results in a mixture with at least some of the fine drug particles adhered to the surface of the coarse carrier particles, enabling improvements in both the flow and dispersion properties of the highly cohesive drug particles (Lahrib et al., 1999). However, in order for the drug particles to reach their site of action in the lungs, they must detach from the surface of the carrier particles by the energy of the inspired air flow during inhalation. This is the key process that governs the performance of such formulations, and is dependent upon the balance of the adhesive and detachment forces between drug and carrier present in the powder mixture. The interactive behaviour of pharmaceutical powders can be affected by the surface energy of the constituent particles (Buckton, 1995). Surface energy is defined as the energy required to form (or increase the surface by) a unit area of surface under reversible conditions. Knowledge of the surface energies between pure SS particles and between SS and MgSt particles would allow an objective decision to be made about the extent of interaction. If the redistributed SS particles on the surface of the MgSt carrier particles allowed the SS particles to be more easily detached from the micro-carrier surface than from an agglomerate of SS, then the presence of larger MgSt micro-carrier particles could facilitate dispersion. The extent of the interaction between SS particles (cohesion) and between SS particles and MgSt (adhesion) could be quantified by the work of cohesion and adhesion, which in turn can be determined by the atomic force microscope (AFM) colloidal probe approach (Bunker et al., 2005) or inverse gas chromatography (IGC) (Swaminathan et al., 2006). Because of the difficulty in measuring interactive forces of non-symmetrical particles by AFM due to their variable geometries and thus contact surfaces, the work of cohesion of the SS and MgSt particles and the work of adhesion between the SS and MgSt particles were determined by IGC.

The total surface energy (γ) of a material is the additive effect of both the dispersive (γ^D) and polar (γ^P) components (Fowkes, 1964). The dispersive surface energy (γ^D) (surface energy of materials for non-polar interaction sites) and specific free energies (G^{SP}) (surface energy for polar interaction sites) for interaction with dichloromethane and ethyl acetate were directly determined by IGC according to the principles and methods which have been widely described by other scientists (Schultz et al., 1987; Schultz and Lavielle, 1989). Polar energy (γ^P) was calculated from the

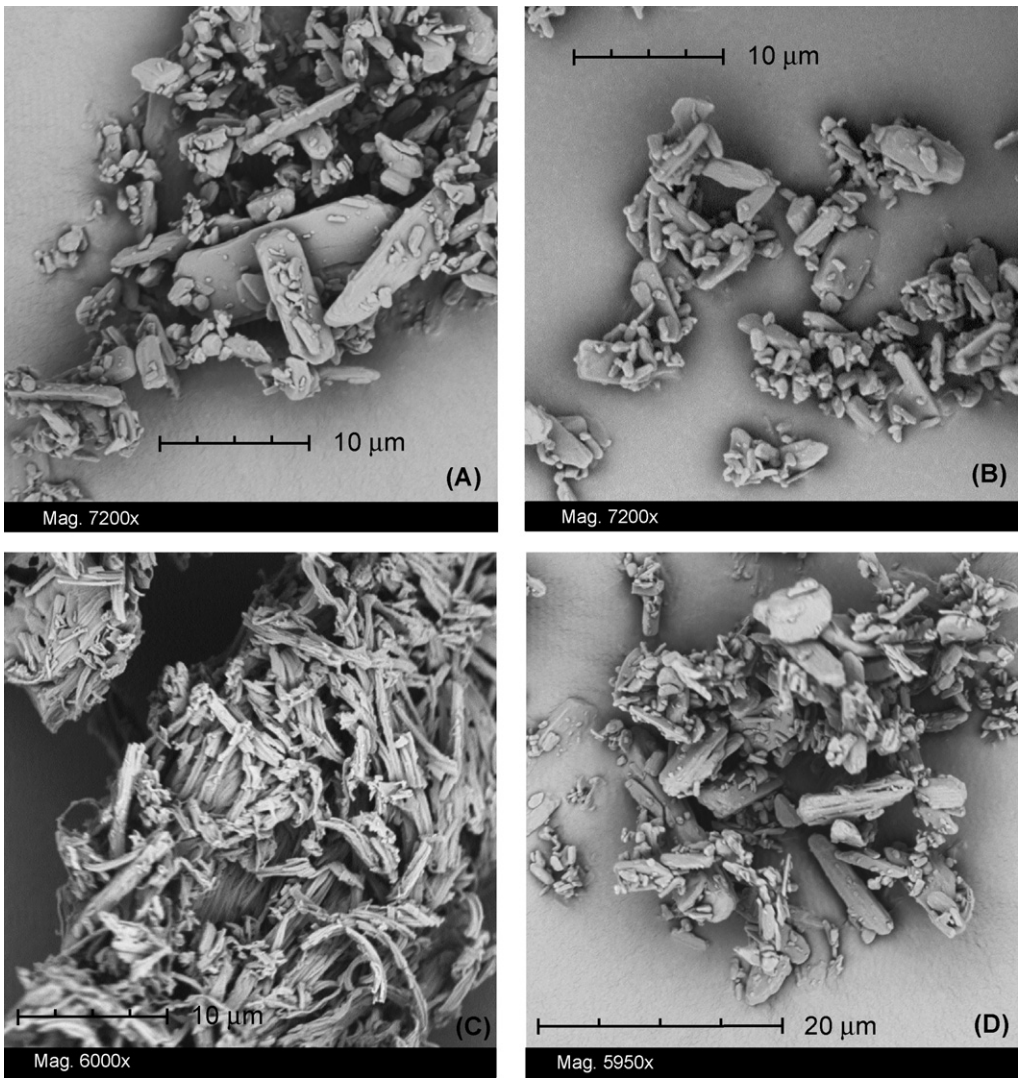

Fig. 2. Scanning electron micrographs of (A) micro-interactive units of magnesium stearate (MgSt) containing smaller adhered particles of both salbutamol sulphate (SS) and MgSt, (B) micronized SS particles, (C) MgSt (d_{50} = 5.6 μm) particles, and (D) agglomerates of fine particles containing both SS and MgSt.

specific free energy values of an acidic probe, dichloromethane, and a basic probe, ethyl acetate according to the method described by Traini et al. (2008), based on the Van Oss' concept (van Oss et al., 1988; van Oss, 1993). Upon determination of the dispersive and polar surface energies, the thermodynamic work of adhesion (W_{ad}) for SS–MgSt interactions and the thermodynamic work of cohesion (W_{co}) for SS–SS interactions can then be calculated using the following equations (van Oss et al., 1988; van Oss, 1993):

$$W_{co} = 2\sqrt{(\gamma_{SS}^{D} \cdot \gamma_{SS}^{D})} + 2\sqrt{(\gamma_{SS}^{P} \cdot \gamma_{SS}^{P})} \quad (1)$$

$$W_{ad} = 2\sqrt{(\gamma_{SS}^{D} \cdot \gamma_{MgSt}^{D})} + 2\sqrt{(\gamma_{MgSt}^{P} \cdot \gamma_{MgSt}^{P})} \quad (2)$$

where γ_{SS}^{D} and γ_{MgSt}^{D} are the dispersive surface energies of SS and MgSt, respectively, and γ_{SS}^{P} and γ_{MgSt}^{P} are the polar surface energies of SS and MgSt, respectively.

The work of cohesion (W_{co}) between SS particles was determined as 407.5 mJ/m^2 and the work of adhesion (W_{ad}) between SS and MgSt was 311.6 mJ/m^2. Thus, the significantly smaller value of W_{ad} between SS and MgSt compared to that of W_{co} between SS particles was consistent with the proposed mechanistic effect of MgSt acting as a micro-carrier in improving the dispersibility of SS powders during aerosolization.

The use of MS2 (d_{50} = 3.1 μm) in the mixture led to lower SS dispersibility than MS1 (d_{50} = 5.6 μm) (Fig. 1B), due to a reduction in the content of MgSt large enough to act as carriers. Thus, the capacity to form interactive units because of the decreased number of potential carriers has been reduced. In addition, the mixture containing MS2 appeared more cohesive and was likely to have decreased flow properties. This is evident in the influence that MS2 showed on capsule emptying during aerosolization of the SS in the TSI. The emitted dose (ED) data showed that the mixing of MS2 with SS compromised the flowability of the resultant powder mixture and decreased capsule emptying; for example, following mixing for 0.5 h, the ED for the mixture containing MS2 (67.3 ± 4.2%) was significantly lower than when MS1 was used (79.1 ± 3.3%) (P < 0.05). The FPF shown in Fig. 1 were calculated on the basis of recovered dose. When these are recalculated on the basis of emitted dose, the FPF of SS–MS1 was 9.9 ± 1.2% while that of SS–MS2 was 6.3 ± 1.5%. If the mixtures behaved in a homogeneous manner during capsule empting then there is clear evidence that the larger MgSt particles are facilitating SS dispersion; however, non-homogeneous capsule emptying with selective retention of SS remains a possibility and, if this were the case, then the evidence to support the IGC derived works of cohesion and adhesion is not as strong.

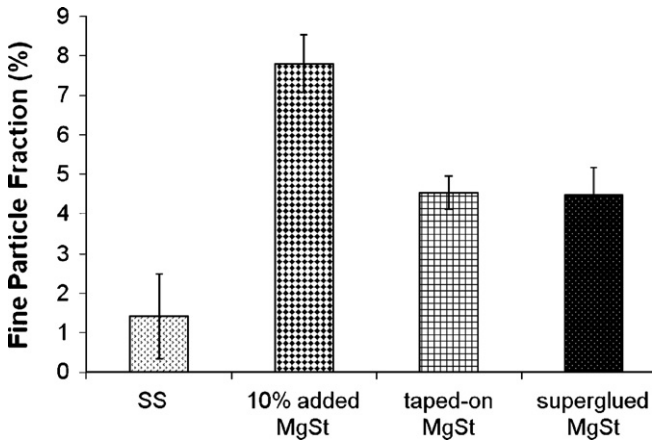

Fig. 3. Effect of immobilized magnesium stearate (MgSt) (taped-on and superglued) on the fine particle fraction (FPF) of salbutamol sulphate (SS) when mixed for 0.5 h.

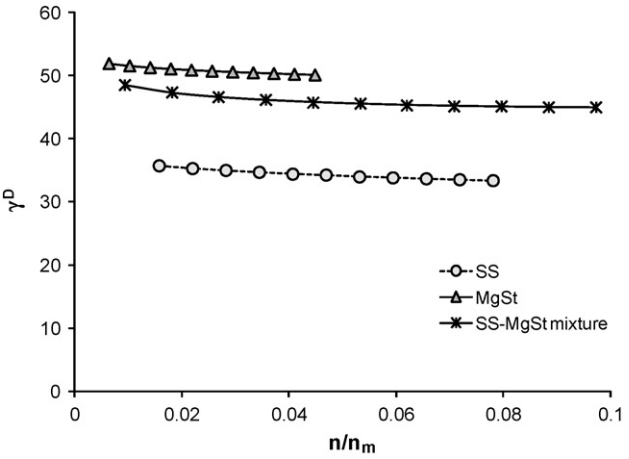

Fig. 4. Dispersive surface energy profiles of salbutamol sulphate (SS), magnesium stearate (MgSt) and SS–MgSt mixture determined by IGC at finite concentration.

3.3. Are the SS particles coated by MgSt?

Magnesium stearate can form continuous hydrophobic films around particles especially after prolonged mixing times (Wells and Rubinstein, 1993). The improvement in drug dispersibility therefore may have been due to the formation of a hydrophobic coating of MgSt on the surface of SS particles with resultant changes in particle interaction (Deryaguin et al., 1978; Zimon, 1982). As high-speed mixing proceeds, the delamination of MgSt particles occurs resulting in a greater surface coverage of SS particles by MgSt nanostructures. The thin film layer formed on the surface of SS particles would not fill all gaps and crevices but nonetheless would result in easier separation of drug particles from each other and potentially increased dispersion. The increased FPF seen in Fig. 1 could result from either the micro-carrier effect described above or the coating of SS by MgSt or both effects.

In order to distinguish between the micro-carrier and the MgSt coating effects on the improved dispersion performance, further experiments were undertaken involving the immobilization of MgSt within the mixer by adhering MgSt onto the sides of a glass jar using double-sided tape and superglue. This ensured that MgSt particles were able to contact the SS during mixing but not be incorporated into the mixture with SS. SS particles were mixed with immobilized MgSt in the Turbula for 0.5 h using the same conditions as described previously; mixing times longer than 0.5 h could not be used as the high-speed mixing resulted in SS being completely adhered onto the immobilized MgSt on the walls of the glass jar.

When MgSt was immobilized by double-sided tape and superglue, the FPF of SS significantly increased from $1.4 \pm 1.1\%$ for pure SS to $4.5 \pm 0.4\%$ and $4.5 \pm 0.7\%$, respectively (Fig. 3). These values were significantly different from SS alone ($P < 0.005$) but not significantly different from each other ($P = 0.89$). These results show clearly that MgSt contributed to the improvement in dispersibility under the conditions of the experiment. The increases in SS dispersion resulting when MgSt was immobilized were significantly lower than when MgSt was added into the mixture ($7.8 \pm 0.7\%$) ($P < 0.001$ each). The results indicate that more than one mechanism of dispersion improvement is occurring when MgSt is mixed with SS.

This mechanism was explored further by IGC to determine whether changes in surface properties through particle coating could be identified by examining the dispersive surface energy distributions profiles. As the infinite dilution conditions used to determine surface energies was limited to the interaction of the probe with only high energy sites, the surface coverage of these sites was a mere 0.1% (Pirre et al., 2008). Therefore, surface energy distribution (γ^D) profiles were constructed using the finite dilution technique (Thielmann et al., 2007; Pirre et al., 2008) and these are shown in Fig. 4. Four alkanes (hexane, heptane, octane and nonane) were initially run through pure SS, MgSt and the mixture containing SS with the immobilized MgSt. As highly diffuse peaks were obtained with nonane for all the three samples, only the peaks from the remaining three probes (hexane, heptane and octane) were used in the final γ^D calculation according to the Dorris–Gray equation (Dorris and Gray, 1980) in order to construct the γ^D profile. The y-axis in the γ^D profile represents the dispersive surface energy at a particular surface coverage on the x-axis (n/n_m), the latter of which was calculated from the sorbed amount (n) of a particular alkane divided by its monolayer capacity (n_m). The profile in this study represented an approximate surface coverage of 10% (Fig. 4). The γ^D profile for SS–MgSt mixture is situated between those of both SS (below) and the hydrophobic MgSt (above). In fact, the γ^D profile of the SS–MgSt mixture is within a 5% range of the MgSt γ^D profile. This therefore provides a strong indication of the surface of SS being coated with the immobilized MgSt during the mixing process.

3.4. Does the magnesium stearate act as an agglomerate modifier?

The SEM in Fig. 2D shows that agglomerates of SS and fine MgSt are formed during mixing. The addition of ternary cohesive materials to interactive mixtures has been demonstrated to influence the strength of agglomerates in the mixture. For example, the addition of micronized lactose to drug–lactose interactive mixtures has been shown to facilitate increased dispersion of salmeterol xinafoate in air (Adi et al., 2006) as well as indomethacin in a dissolution medium (Allahham and Stewart, 2007); these improvements in drug dispersion were proposed to occur by modification of the packing fraction or work of adhesion within the agglomerate in some way.

To test if the above effects had occurred with the SS–MgSt mixtures used in this study, particle size–shear pressure profiles of the mixtures were generated using a dry powder feeder and subjected to increasing shear pressures ranging from 50 to 400 kPa. From the particle size distributions determined at each shear pressure, the mode was determined and plotted against shear pressure. These plots give an indication of the propensity of the agglomerates to break up under increasing shear pressures; agglomerate strength was not measured but these plots give an indication of agglomerate strength. Subsequently, the influence of MgSt concentration and mixing time on the ability of the mixture to disperse was determined (Fig. 5).

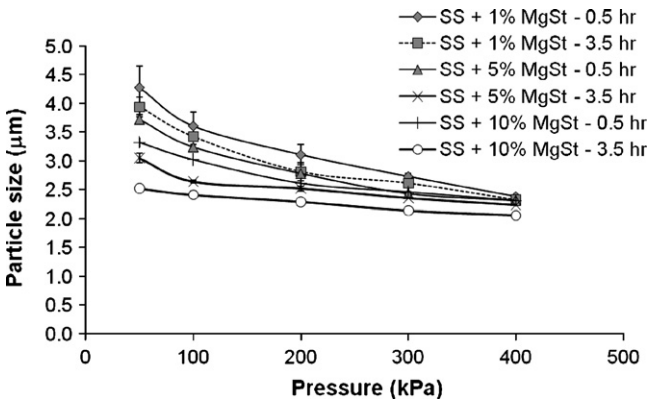

Fig. 5. Particle size–shear pressure profiles of salbutamol sulphate (SS)–magnesium stearate (MgSt) mixtures containing different concentrations of MgSt (d_{50} = 5.6 μm) (1, 5, 10%, w/w) and mixed for different durations (0.5 and 3.5 h), as measured by the Mastersizer 2000 at various shear pressures.

For each of the mixtures containing 1, 5 and 10% of MgSt, longer mixing times of 3.5 h produced an agglomerate structure that required lower shear pressures for particle de-agglomeration than for mixtures prepared at shorter times of 0.5 h. For example, when 10% MgSt was used, the particle size of the 3.5 h mixture was reduced to 2.5 μm even at 50 kPa, and to 2.1 μm at the maximum shear pressure of 400 kPa. In contrast, the 0.5 h mix required higher shear pressures to de-agglomerate the mixture; the particle size of the agglomerate gradually decreased from 3.3 to 2.3 μm as the shear pressure increased from 50 to 400 kPa. This indicated that SS powders mixed for longer mixing times with MgSt resulted in more dispersible agglomerates which required lower shear pressures to de-agglomerate, thus allowing for improved SS dispersibility.

When examining the effect of MgSt concentration on the agglomerate strength, the magnitude of shear pressure required for de-agglomeration decreased with increasing amounts of MgSt added to the mixtures. For example, over the shear pressures of 50–400 kPa for both the 3.5 h mixes, the particle size was reduced from 3.9 to 2.3 μm for the 1% MgSt mixture, compared to a reduction from 2.5 to 2.0 μm when higher concentrations of 10% MgSt was used. Increasing the percentage of MgSt in the mixture lead to the formation of a weaker agglomerate structure that was easier to de-agglomerate, consistent with the higher FPF values of SS obtained when 10% MgSt was used.

These findings suggest that increased mixing time and increased MgSt concentrations in the mixture give mixtures that disperse more easily, and although the particle size changes are small, they are significantly different. MgSt could act as an agglomerate modifier, similar to that of fine lactose (Adi et al., 2006). However, the mechanism by which it reduces the strength of the agglomerates is uncertain, but, since the SS particles have been shown to undergo some form of coating during mixing, the reduction in adhesion between particles is likely to contribute to the effects seen. One can make no comments about the influence of packing fraction on the agglomerate strength changes.

4. Conclusions

The outcomes of this study demonstrated that the addition of MgSt to SS improved its dispersion. When mixed with MS1 (d_{50} = 5.6 μm) the *in vitro* deposition of SS increased with mixing times and with increased percentages of MgSt added. Three possible mechanisms were investigated to explain the enhanced dispersion.

Firstly, SEM images demonstrated the presence of micro-interactive units containing some SS adhered onto larger particles of MgSt. The work of adhesion between SS and MgSt particles were significantly less than the work of cohesion between SS particles in agglomerates. Thus, enhanced detachment of SS particles from the MgSt micro-carriers resulted with corresponding increases in SS dispersion. In addition, when the use of a smaller size fraction of MgSt (d_{50} = 3.1 μm) reduced the concentration of large MgSt carrier particles, the extent of dispersion decreased.

Secondly, when MgSt was completely immobilized and mixed with SS powders, increases in the FPF values were still present indicating a possible coating effect of MgSt onto the surface of SS. This was further supported by shifts in the dispersive energy profiles of the SS with and without immobilized MgSt treatment, measured by IGC. The resultant coating layer of MgSt onto the surface of SS would therefore reduce particle interaction and facilitate the dispersion of SS.

Thirdly, particle sizing conducted at different shear pressures indicated an increased rate of de-agglomeration for SS mixed with MgSt at longer mixing times as well as higher concentrations of MgSt added. These outcomes were consistent with the MgSt acting as an agglomerate modifier in improving drug dispersion by changing either packing fraction, work of adhesion or both; however, the outcomes are also consistent with decreased agglomerate strength due to SS coating and reduced work of cohesion between the SS particles.

This study has been significant because the mechanisms of increased dispersion performance due to added MgSt are seen to be more complex than previously described in the literature. This will mean that the development of strategies to improve dispersion using MgSt in mixtures will need to be cognizant of other factors. Thus, the selection of particle size and concentration of MgSt will not only influence drug coating during mixing but will enhance dispersion efficiency through optimization of drug–MgSt micro-interactive units and inherent mixture structure through a function as agglomerate modifiers.

The possible effect of MgSt on drug dissolution was not addressed in this study as the primary focus was to gain a mechanistic understanding of MgSt on improving the respiratory deposition of SS. Any in vivo aspects of drug action would require further investigation.

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References

Adi, H., Larson, I., Chiou, H., Young, P., Traini, D., Stewart, P., 2006. Agglomerate strength and dispersion of salmeterol xinafoate from powder mixtures for inhalation. Pharm. Res. 23, 2556–2565.

Allahham, A., Stewart, P.J., 2007. Enhancement of the dissolution of indomethacin in interactive mixtures using added fine lactose. Eur. J. Pharm. Biopharm. 67, 732–742.

Begat, P., Price, R., Harris, H., Morton, D.A.V., Staniforth, J.N., 2005. The influence of force control agents on the cohesive–adhesive balance in dry powder inhaler formulations. Kona 23, 109–119.

Bolhuis, G.K., Lerk, C.F., Zijlstra, H.T., de Boer, A.H., 1975. Film formation by magnesium stearate during mixing and its effect on tabletting. Pharm. Weekbl. 110.

Buckton, G., 1995. Surface characterisation: understanding sources of variability in the production and use of pharmaceuticals. J. Pharm. Pharmacol. 47, 265–275.

Bunker, M.J., Roberts, C.J., Davies, M.C., 2005. Towards screening of inhalation formulations: measuring interactions with atomic force microscopy. Expert Opin. Drug Deliv. 2, 613–624.

Chowhan, Z.T., Chi, L.H., 1985a. Drug–excipient interactions resulting from powder mixing. I. Possible mechanism of interaction with starch and its effect on drug dissolution. Pharm. Technol. 9, 84–97.

Chowhan, Z.T., Chi, L.H., 1985b. Drug–excipient interactions resulting from powder mixing. II. Possible mechanism of interaction with crospovidone and its effect on in vitro drug dissolution. Pharm. Technol. 9, 28–41.

Chowhan, Z.T., Chi, L.H., 1986a. Drug–excipient interactions resulting from powder mixing. III. Solid state properties and their effect on drug dissolution. J. Pharm. Sci. 75, 534–541.
Chowhan, Z.T., Chi, L.H., 1986b. Drug–excipient interactions resulting from powder mixing. IV. Role of lubricants and their effect on in vitro dissolution. J. Pharm. Sci. 75, 542–545.
Conder, J.R., Young, C.L., 1979. Physicochemical Measurements by Gas Chromatography. John Wiley & Sons, Chichester.
Deryaguin, B.V., Krotova, N.A., Smilga, V.P., 1978. Adhesion of Solids. Consultants Bureau, New York.
Dorris, G.M., Gray, D.G., 1980. Adsorption of *n*-alkanes at zero surface coverage on cellulose paper and wood fibres. J. Colloid Interface Sci. 77, 353–362.
Fowkes, F.M., 1964. Attractive forces at interfaces. Ind. Eng. Chem. 56, 40–52.
Frijlink, H.W., de Boer, A.H., 2004. Dry powder inhalers for pulmonary drug delivery. Expert Opin. Drug Deliv. 1, 67–86.
Gold, G., Duvall, R.N., Palermo, B.T., Slater, J.G., 1968. Powder flow studies III—factors affecting the flow of lactose granules. J. Pharm. Sci. 57, 667–671.
Gonda, I., 1990. Aerosol delivery of therapeutic and diagnostic agents to the respiratory tract. Crit. Rev. Ther. Drug Carrier Syst. 6, 273–313.
Iida, K., Hayakawa, Y., Okamoto, H., Danjo, K., Luenberger, H., 2004. Effect of surface layering time of lactose carrier particles on dry powder inhalation properties of salbutamol sulphate. Chem. Pharm. Bull. 52, 350–353.
Jones, T.M., Pilpel, N., 1966. The flow of granular magnesia. J. Pharm. Pharmacol. 18, 429–442.
Kale, K., Hapgood, K., Stewart, P., 2009. Drug agglomeration and dissolution—what is the influence of powder mixing? Eur. J. Pharm. Biopharm. 72, 156–164.
Lahrib, H., Zeng, X.M., Martin, G.P., Marriott, C., Pritchard, J., 1999. The use of different grades of lactose as a carrier for aerosolised salbutamol sulphate. Int. J. Pharm. 191, 1–14.
Lucas, P., Anderson, K., Staniforth, J.N., 1998. Protein deposition from dry powder inhalers: fine particle multiplets as performance modifiers. Pharm. Res. 15, 562–569.
Malcolmson, R.J., Embleton, J.K., 1998. Dry powder formulations for pulmonary delivery. Pharm. Sci. Technol. Today 1, 394–398.
Newman, S.P., Clarke, S.W., 1983. Therapeutic aerosols. 1. Physical and practical considerations. Thorax 38, 881–886.
Pirre, P.Y.M., Heng, J.Y.Y., Thielmann, F., Williams, D.R., 2008. Inverse gas chromatographic method for measuring the dispersive surface energy distribution for particulates. Langmuir 24, 9551–9557.
Schultz, J., Lavielle, L., 1989. Interfacial properties of carbon fibre-epoxy matrix composites. In: Lloyd, D.R., Ward, T.C., Schreiber, H.P. (Eds.), Inverse Gas Chromatography: Characterization of Polymers and Other Materials. American Chemical Society, Washington, DC.
Schultz, J., Lavielle, L., Martin, C., 1987. The role of the interface in carbon fibre-epoxy composites. J. Adhes. 23, 45–60.
Shah, A.C., Mlodozeniec, A.R., 1977. Mechanism of surface lubrication: influence of duration of lubricant–excipient mixing on processing characteristics of powders and properties of compressed tablets. J. Pharm. Sci. 66, 1377–1382.
Staniforth, J.N., 1997. Improvement in dry powder inhaler performance: surface passivation effects. Proc. Drug Deliv. Lungs VIII.
Staniforth, J.N., Rees, J.E., 1982. Electrostatic charge interactions in ordered powder mixes. J. Pharm. Pharmacol. 34, 69–76.
Staniforth, J.N., Rees, J.E., Lai, F.K., Hersey, J.A., 1982. Interparticulate forces in binary and ternary powder mixes. J. Pharm. Pharmacol. 34, 141–145.
Steckel, H., Mueller, B.W., 1997. In vitro evaluation of dry powder inhalers. I. Drug deposition of commonly used devices. Int. J. Pharm. 154, 19–29.
Stewart, P.J., 1981. Influence of magnesium stearate on the homogeneity of a prednisone–granule ordered mix. Drug Dev. Ind. Pharm. 7, 485–495.
Strickland, W.A., Nelson, E., Busse, L.W., Higuchi, T., 1956. The physics of tablet compression. IX. Fundamental aspects of tablet lubrication. J. Am. Pharm. Assoc. Sci. Ed. 45, 51–55.
Swaminathan, V., Cobb, J., Saracovan, I., 2006. Measurement of the surface energy of lubricated pharmaceutical powders by inverse gas chromatography. Int. J. Pharm. 312, 158–165.
Swaminathan, V., Kildsig, D.O., 2002. Effect of magnesium stearate on the content uniformity of active ingredient in pharmaceutical powder mixtures. AAPS PharmSciTech 3, 1–5.
Thielmann, F., Burnett, D.J., Heng, J.Y.Y., 2007. Determination of the surface energy distributions of different processed lactose. Drug Dev. Ind. Pharm. 33, 1240–1253.
Thielmann, F., Pearse, D., 2002. Determination of surface heterogeneity profiles on graphite by finite concentration inverse gas chromatography. J. Chromatogr. A 969, 323–327.
Traini, D., Young, P.M., Thielmann, F., Acharya, M., 2008. The influence of lactose pseudopolymorphic form on salbutamol sulfate–lactose interactions in DPI formulations. Drug Dev. Ind. Pharm. 34, 992–1001.
van Oss, C.J., 1993. Acid–base interfacial interactions in aqueous media. Colloids Surf. A: Physicochem. Eng. Asp. 78, 1–49.
van Oss, C.J., Good, R.J., Chaudhury, M.K., 1988. Additive and nonadditive surface tension components and the interpretation of contact angles. Langmuir 4, 884–891.
Wang, L.-H., Chowhan, Z.T., 1990. Drug–excipient interactions resulting from powder mixing. V. Role of sodium lauryl sulphate. Int. J. Pharm. 60, 61–78.
Wells, J.I., Rubinstein, M.H., 1993. Pharmaceutical Technology: Tabletting Technology, vol. 2 (Compression). Ellis Horwood Limited, Great Britain.
Young, P.M., Cocconi, D., Colombo, P., Bettini, R., Price, R., Steele, D.F., Tobyn, M.J., 2002. Characterisation of a surface modified dry powder inhalation carrier prepared by particle smoothing. J. Pharm. Pharmacol. 54, 1339–1344.
Zimon, A.D., 1982. Adhesion of Dust and Powders. Consultants Bureau, New York.