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Research paper

Preparation and characterisation of controlled release co-spray dried drug–polymer microparticles for inhalation 1: Influence of polymer concentration on physical and in vitro characteristics

Rania Salama, Susan Hoe, Hak-Kim Chan, Daniela Traini, Paul M. Young *

University of Sydney, Sydney, Australia

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Abstract

A series of co-spray dried microparticles containing di-sodium cromoglycate (DSCG) and polyvinyl alcohol (PVA – 0%, 30%, 50%, 70% and 90% w/w, respectively), were prepared as potential controlled release (CR) viscous/gelling vehicles for drug delivery to the respiratory tract. The microparticles were characterised in terms of particle size, crystal structure, density, surface morphology, moisture sorption, surface energy and in vitro aerosolisation efficiency. The co-spray dried particles were amorphous in nature and had spherical geometry. High-resolution atomic force microscopy analysis of the surfaces of the DSCG/PVA suggested no significant differences in roughness between microparticles containing 30–90% w/w PVA (ANOVA, $p < 0.05$), while no specific trend in either size or density was observed with respect to PVA concentration. In comparison, a linear decrease in the relative moisture sorption ($R^2 = 0.997$) and concurrent increase in total surface free energy ($R^2 = 0.870$) were observed as PVA concentration was increased. Furthermore a linear increase in the aerosolisation efficiency, measured by inertial impaction, was observed as PVA concentration was increased ($R^2 = 0.993$). In addition, the increase in aerosolisation efficiency showed good correlation with equilibrium moisture content ($R^2 = 0.974$) and surface energy measurement ($R^2 = 0.905$). These relationships can be attributed to the complex interplay of particle forces at the contiguous interfaces in this particulate system.
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1. Introduction

A key criterion for a successful inhalation dosage form is that the therapeutic agent is generated in an optimum respirable size range, consistently and reliably. In general, to achieve respiratory deposition, the primary particulates require an aerodynamic diameter $\leqslant 6.0$ μm [1]. As a consequence, for dry powder inhalation (DPI) therapy, the properties of the respirable powder are critical to the aerosolisation efficiency, since the high surface area to mass ratio results in a highly cohesive system. Subsequently, for many DPI formulations, it becomes difficult to impart sufficient energy to overcome inter-particulate forces and sufficiently de-aggregate the respiratory fraction during inhalation. Consequently, many DPI devices have inherently poor aerosolisation efficiency, and in general less than 20% of the emitted dose generally can be considered as the respirable fraction [2].

Since the inter-particulate adhesion is the critical factor for efficient aerosolisation performance, the two major components, which will influence formulation performance, will be the morphology of the particulates and their surface chemistry. In general, the total force of adhesion between two contiguous bodies can be considered equal to the contact area multiplied by the difference in Gibbs

* Corresponding author. Advanced Drug Delivery Group, Faculty of Pharmacy, University of Sydney, Sydney, NSW 2006, Australia. Tel.: +61 2 9036 7035; fax: +61 2 9351 4391.
E-mail address: py@pharm.usyd.edu.au (P.M. Young).

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free energy. Although in principle such theoretical prediction of inter-particulate adhesion seems simple, particulates used in inhalation are not uniform in size, morphology or surface chemistry. In addition, such systems are often complicated by multiple formulation components (such as drug, inert fines and carrier).

Since the performance of such particulate systems is dependent on many variables, the fundamental study of the relationship between morphology, surface energy and aerosol performance is generally limited, and performance related theories are based on empirical observation, since modification of one variable (for example particle shape) inherently alters other physical variables (for example surface chemistry). Although multiple variables pose a significant problem when attempting to understand the intricacies of these systems, significant advancement in understanding has been achieved through empirical study. For example, Chan and Gonda [3] showed that the aerosol efficiency of sodium cromoglycate was significantly improved with increased particle elongation ratio. In such cases it is suggested that the increase in performance and respiratory deposition may be due to airstream orientation effects. Furthermore, recent studies by Chew et al. have demonstrated that increasing the degree of corrugation of primarily spherical spray dried BSA particles increased their aerosolisation efficiency (through presumed reduction in contact geometry [4,5]. In comparison, Pilcer et al. demonstrated that the aerosolisation efficiency of micronised tobramycin could be increased if the powder was spray-coated with lipids [6], altering the surface chemistry, increasing the hydrophobicity and reducing the relative contact angle of the powder. In more recent studies, other factors have been identified as playing a major role on drug aerosolisation efficiency. For example work by Young and Price demonstrated how small amounts of amorphous content on the surface of crystalline particles potentially reduced aerosolisation efficiency through particle instability and inter-particle fusion [7]. It is clear from these previous studies, that if we are to truly understand the complex nature of particle interaction and aerosolisation efficiency, these factors need to be studied independently in greater detail.

Understanding the interplay of these different formulation variables is even more important when investigating composite formulations, which are designed with a modified release component.

The advantages of controlled release of drugs to the respiratory tract is well documented [8] and most methods involve the encapsulation or formation of matrix particles containing drug and excipient. The excipient component may be a natural cross-linked polymer or protein (e.g. Hyaluronic acid [9] or albumin [10]), polysaccharide based gum (e.g. xanthan gum [11]) synthetic polymer (e.g. ether-anhydride co-polymers [12,13] or poly(lactic-co-glycolic acid) polymers [8]), or phospholipid based formulation (e.g. dipalmitoylphosphatidylcholin [14,15]). In general, previous studies of such matrix systems have shown a potential for sustained release in the respiratory tract, with particle characteristics conducive to respiratory deposition. However, a systematic study of how matrix components influence the physico-chemical properties, aerosolisation efficiency and controlled release rates of microparticles for inhalation has still not been investigated in great detail.

As part of an ongoing study, the authors investigated a model dry powder polymer–drug matrix system containing di-sodium cromoglycate (DSCG) and polyvinyl alcohol (PVA). Specifically, the influence of polymer concentration on the physico-chemical properties of the microparticles (size, morphology, moisture sorption, contact angle, etc.) and in vitro aerosolisation efficiency were studied. DSCG was chosen as a model drug, since it is a commonly used drug in the treatment of asthma, while PVA was chosen due to its simple structure, biodegradability, and good toxicology [16]. Furthermore, recent in situ studies by Yamamoto et al. have shown simple viscous vehicles containing 1% w/w PVA to have a significant influence on the pulmonary absorption rate [17].

2. Materials and methods

2.1. Materials

Di-sodium chromoglycate (DSCG) was obtained from Sanofi-Aventis (Cheshire, England). Polyvinyl alcohol (PVA) was supplied from BDH Ltd. (Biolab, Victoria, Australia). The molecular weight of PVA was approximately 22,000 and the minimum degree of hydrolysis was 98%. Water used throughout the experiments was prepared by reverse osmosis (Milli-Q, Sydney, Australia).

2.2. Spray drying

Microparticles of DSCG with different percentages of PVA were prepared by co-spray drying aqueous solutions of DSCG and PVA. Final percentages of 0%, 30%, 50%, 70%, 90% and 100% (w/w) of PVA were obtained by dissolving pre-calculated amounts of PVA in water, heating to 90 °C for 5 min to ensure solubilisation [16], followed by cooling and addition of drug solution. All solutions were prepared with a constant PVA concentration in water, 1.5% (w/v), in order to keep the viscosity of the final solutions constant. All solutions were spray dried using a laboratory scale spray dryer (Büchi Mini Spray Dryer B-191, Switzerland), with the following conditions: inlet temperature 140 °C, measured outlet temperature 70–75 °C, air flow 700 L h^{-1} and solution feed rate 4 ml min^{-1}.

After spray drying, samples were stored in containers at 45% RH for a minimum of 48 h prior to use.

2.3. Particle sizing

Particle sizing was performed by laser diffraction (Malvern Mastersizer 2000, Malvern Instruments Ltd., UK)

using the Scirocco dry dispersion unit (Malvern, UK) at a feed pressure of 4 bars and feed rate of 50%. All samples were analysed in triplicate over 10 s intervals when obscuration values were between 0.5% and 5%.

2.4. Density

The true density of the co-spray dried particles was assessed using a buoyancy method described elsewhere [5,18]. Briefly, samples (approximately 2 mg) were dispersed in a series of liquids, which had a density gradient. Liquids used were bromoform and 1-hexanol (Biolab Ltd., Victoria, Australia). Samples were centrifuged (Jouan CT422, Saint Herblain Cedex, France) at 3500 rpm (corresponding to 2359*g*) for 30 min. The particle density was equal to the density of the liquid when the particles remained suspended after centrifugation.

2.5. X-ray diffraction

The X-ray diffraction patterns for the co-spray dried DSCG/PVA microparticles, were obtained by X-ray powder diffraction (D5000, Siemens, Germany) using Cu κα radiation, 40 keV and 30 mA. Settings were as follows: 5–35° 2θ, step size 0.05° 2θ, and temperature 25 °C.

2.6. Scanning electron microscopy

Particle morphology of the spray dried particles was visualised using scanning electron microscopy (SEM) (505 Philips, Japan) at 10 keV. Samples were mounted on carbon sticky tabs and gold-coated (10 nm thickness) before imaging (Edwards E306A Sputter coater, UK).

2.7. Atomic force microscopy

The morphology of the co-spray dried particles was further analysed using conventional tapping mode, atomic force microscopy (AFM) (Nanoscope IIIa controller with Multimode AFM, Veeco, Cambridge, UK). Samples were mounted on carbon sticky tabs and imaged in air using tapping mode tips (MikroMash, Oregon, USA) at a scan rate of 1 Hz.

2.8. Dynamic vapour sorption

Dynamic vapour sorption (DVS) was used to assess the moisture sorption characteristics of the spray dried particles. Sorption profiles were determined using an automated water sorption analyser (DVS-1, Surface measurement systems Ltd., London, UK). Approximately 30 mg of sample was weighed into the sample pan of the DVS and subjected to two 0–90% relative humidity (RH) sorption cycles, over 10% RH increments. Equilibrium sorption at each humidity was determined by a change in mass to time ratio of 0.001 dm/dt.

2.9. Contact angle measurement

Measuring the contact angle (θ) of powders is a useful indicator of wettability, giving information on surface energies. Contact angle measurements were measured on model compacts of the co-spray dried DSCG/PVA microparticulates. Compacts were prepared by direct compression using a servo hydraulic press (Model 25010, Specac Ltd., Kent, UK). Approximately 200 mg of the sample material was weighed into a 10 mm stainless steel die, spread evenly in the die and compacted with a compression force of 10 kN. Compacts were stored in sealed containers in a controlled environment (45% RH, 25 °C) for at least 24 h prior to use. It is important to note that the surface energy values, in this case, are derived from contact angle measurement on compacts, made from the microparticulate systems. This approach was chosen since more recent techniques such as inverse gas chromatography only evaluate high-energy sites and give dimensionless numbers for the polar component of surface free energy [19]. However, the particles used in this study are amorphous in nature and contain long chain polymers, which under compression would have limited orientation effects as opposed to crystalline samples.

The contact angle of the powder compact surfaces was measured using the sessile drop method [20–24] with a NRL goniometer (Model 200-00, Ramé-Hart, Inc., New Jersey, USA) equipped with Dropimage® Standard software. A liquid drop was introduced onto the substrate surface via a microsyringe. The advancing contact angles (e.g. the angle the drop makes when it has ceased advancing) were measured for three different liquids (water, diiodomethane and ethylene glycol) at room temperature (25 °C). A summary of the surface tension components of the liquids used in the direct contact angle determination [22] is presented in Table 1.

2.10. Spectrophotometric quantification of DSCG

The concentration of DSCG in the co-sprayed microparticles, and after in vitro testing was determined spectrophotometrically (U2000 Spectrophotometer, Hitachi, Japan), at a wavelength of 245 nm. All samples and standards were prepared in water. In addition, co-spray dried

Table 1
Surface tension components and parameters of liquids used in CA measurements at 20 °C (Vanoss [22])

	Surface tension components and parameters (mJ m^{-2})			
	γ^{LW}	γ^{+}	γ^{-}	γ^{AB}
Diiodomethane	50.8	~0	0	0
Water	21.8	25.5	25.5	51.0
Ethylene glycol	29.0	1.92	47.0	19.0

Where γ^{LW} is the dispersive component of the total surface energy, γ^{+} is the electron-acceptor parameter, γ^{-} is the electron-donor parameter and γ^{AB} represent the polar or Lewis acid–base interactions.

samples were heated in a waterbath at 90 °C for 5 min to ensure dissolution of the PVA polymer. Standards indicated linearity over a concentration range of 1.0–20.0 μg ml^{-1} ($R^2 = 0.999$). Addition of PVA to samples did not interfere with the calibration curve.

2.11. In vitro aerosolisation studies

The in vitro performance of the spray dried particles was assessed using a 5-stage Marple Miller Impactor (MMI) (Model 160, MSP Corporation, USA) which at 60 L min^{-1} produced aerodynamic cut-off diameters of 10.0, 5.0, 2.5, 1.25, and 0.625 μm, for stages 1–5, respectively. In addition the MMI included a United State Pharmacopoeia throat and filter stage. Prior to analysis the MMI sample cups were coated with silicone lubricant (Slipicone®, DC products, Australia) to prevent particle bounce.

The flow rate through the MMI was controlled by a rotary vein pump and solenoid valve timer (Copley scientific, Nottingham, UK). Prior to testing, a 60 L min^{-1} flow rate through the MMI was set using a calibrated flow meter (TSI, 4000 series, Buckinghamshire, UK). The aerosolisation performance of each sample was investigated using a Cyclohaler™ DPI device (Novartis, Surrey, UK). Size 3, hard gelatine capsules (Capsugel®, NSW, Australia) were manually filled with 30.0 ± 2.0 mg of each sample and tested at 60 L min^{-1}, using the Cyclohaler, for 4 s. The mass of drug deposited on each stage of the MMI was collected by dissolving in a suitable volume of water. After each experiment, the MMI was rinsed with methanol and dried prior to re-use. All samples were run in triplicate and were randomized for PVA concentration. Temperature and humidity during the in vitro investigation was 25 °C and 50% RH, respectively.

Samples recovered from each MMI experiment were analysed by UV using the method described earlier. The concentration of drug from the MMI, device and capsule was calculated and represented as follows: total dose (TD) drug concentration recovered from all stages of MMI device and capsule; emitted dose (ED) drug concentration recovered from all stages of the MMI; fine particle dose (FPD) drug recovered from stages 3 to 5 and filter, representing the 'respirable' particle with an aerodynamic diameter <5 μm; and the fine particle fraction (FPD/TD × 100).

3. Results

3.1. Particle size analysis

Particle size distributions for all co-spray dried DSCG/PVA microparticles are shown in Fig. 1. In general, all samples exhibited a similar particle size distribution, with the average median particle diameter across all samples being 3.15 ± 0.375 μm, suggesting that the manufacturing method generated particles within a narrow size distribution regardless of polymer concentration. Although small variations in median diameter were observed for different samples, there was no direct relationship between PVA concentration and diameter. Furthermore, analysis of the particle distribution revealed that 90% of the particles were less than 7.82 ± 1.78 μm, suggesting a size range suitable for inhalation purposes.

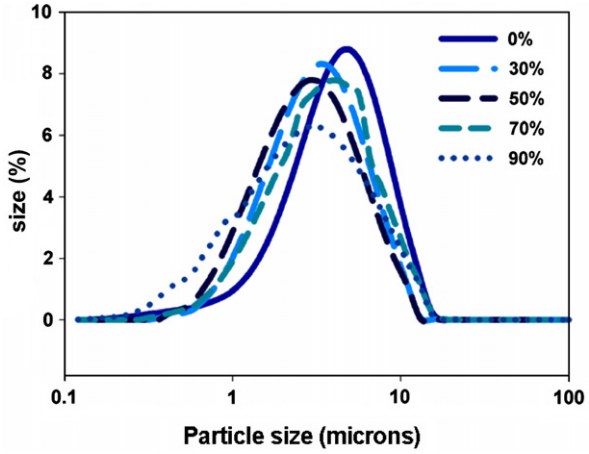

Fig. 1. Particle size distribution of the raw DSCG as well as the co-spray dried samples with different % w/w of PVA.

3.2. Density

Analysis of the particle density data suggested significant variation in density as PVA concentration was increased (ANOVA, $p < 0.05$). However, post-hoc Fishers-Pairwise analysis, suggested that paired samples were not significantly different. In general, the density of spray dried DSCG was 1.55 ± 0.05 g m^{-3}, which was in agreement to data reported previously [18]. As the percentage of PVA was increased in the co-spray dried formulations a decrease in density was observed: density values of 1.45 ± 0.05, 1.45 ± 0.05, 1.30 ± 0.05 and 1.30 ± 0.05 g m^{-3} were observed for 30%, 50%, 70% and 90% w/w PVA co-spray dried microparticles, respectively. This is in good agreement with the reported density of PVA which has a density between 1.2 and 1.3 g m^{-3} (approximated from reported specific gravity data) [16].

3.3. X-ray powder diffraction

Analysis of the X-ray diffraction patterns for spray dried DSCG, spray dried PVA and co-spray dried DSCG and PVA 50% (w/w) is shown in Fig. 2. Fig. 2 showed a single diffuse peak characteristic of a material with no long-range order, indicating the amorphous nature of the spray dried samples.

3.4. Scanning electron microscopy

Representative electron micrographs of the co-spray dried DSCG with 0%, 50% and 90% w/w PVA are shown

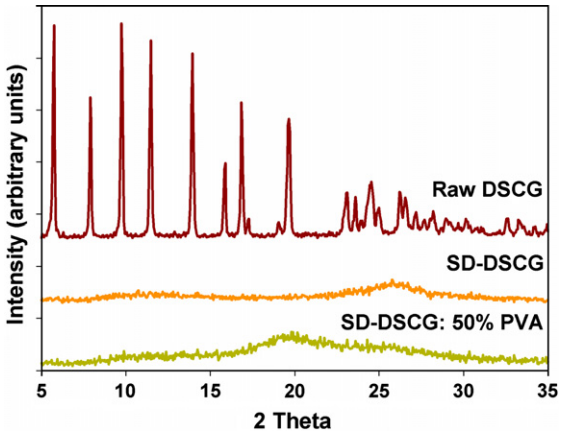

Fig. 2. X-ray powder diffractograms of crystalline, spray dried DSCG and spray dried DSCG with 50% w/w PVA.

in Fig. 3A–C, respectively. In general, all particulate systems appeared to be spherical in shape and had a diameter that were both similar and in good agreement with particle size data reported previously. It is interesting to note, however, that the DSCG microparticulates prepared in the absence of PVA had a more irregular morphology. Such observations are in good agreement with previous studies [18]. In comparison, the co-spray dried systems containing PVA had smooth spherical morphologies that suggested no variability with PVA concentration.

3.5. Atomic force microscopy

Since variation in particle morphology may have a significant impact on the aerosolisation efficiency, the nanoscopic surface characteristics of each system were studied using AFM in conventional tapping mode. Topographical images of DSCG spray dried alone, with 50% and 90% w/w PVA, are shown in Fig. 4A–C, respectively. From Fig. 4 it can be seen that all the microparticle formulations were spherical in geometry, however, the particles containing PVA appeared to have a lower degree of irregularity. To assess the variation in surface morphology, 250 nm^2 areas across each particle surface were processed to produce root mean square roughness values (R_{RMS})

$$R_{RMS} = \sqrt{\frac{1}{n}\sum_{i=1}^{n} y_i^2} \quad (1)$$

where n is the number of data points in a topographical profile and y_i is the distance of asperities (i) from the centre line.

Analysis of the spray dried DSCG indicated roughness values of 64.05 ± 4.31 nm. As expected the roughness of the spray dried DSCG was significantly greater than the co-spray dried samples containing PVA (ANOVA, $p < 0.05$). Analysis of the R_{RMS} of the co-spray dried powders indicated roughness values of 12.59 ± 2.05, 12.54 ± 1.98, 12.06 ± 1.86 and 12.96 ± 1.26 nm for 30%, 50%, 70% and 90% w/w PVA, respectively. No significant differences in roughness were observed between samples containing different concentrations of PVA (ANOVA, $p < 0.05$).

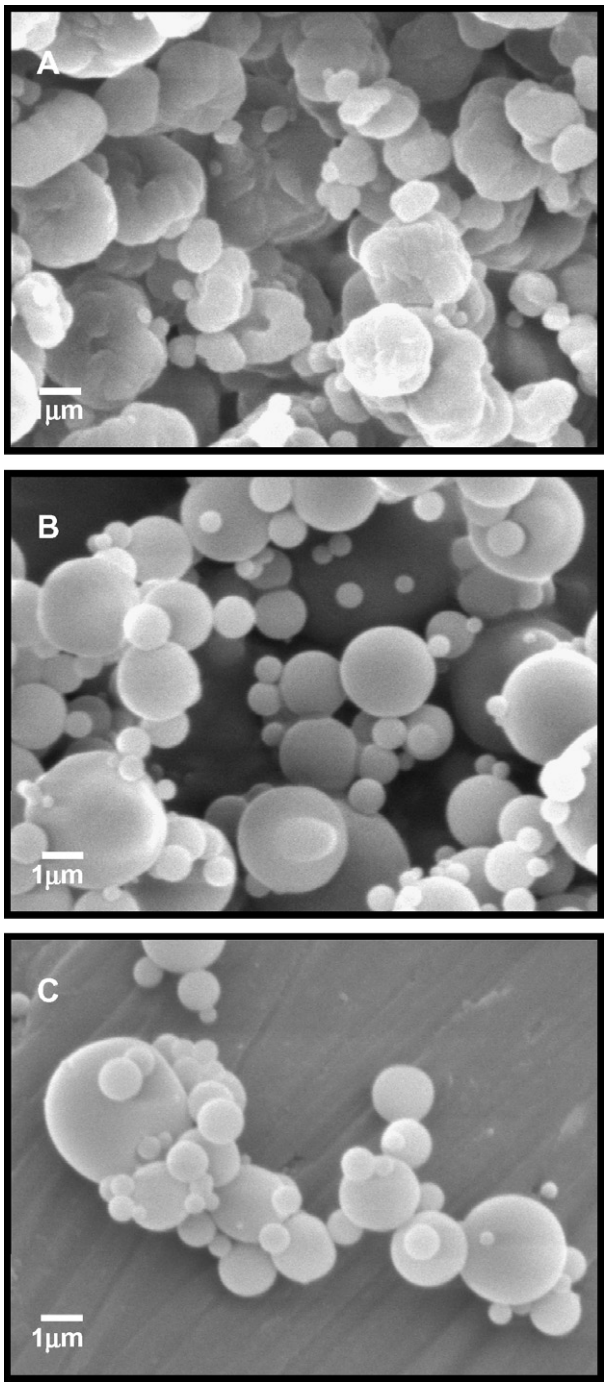

Fig. 3. Representative electron micrographs of (A) spray dried DSCG, (B) co-spray dried DSCG and PVA 50% w/w and (C) co-spray dried DSCG and PVA 90% w/w.

3.6. Dynamic vapour sorption

As previously discussed, analysis of the vapour sorption characteristics of the co-spray dried DSCG/PVA

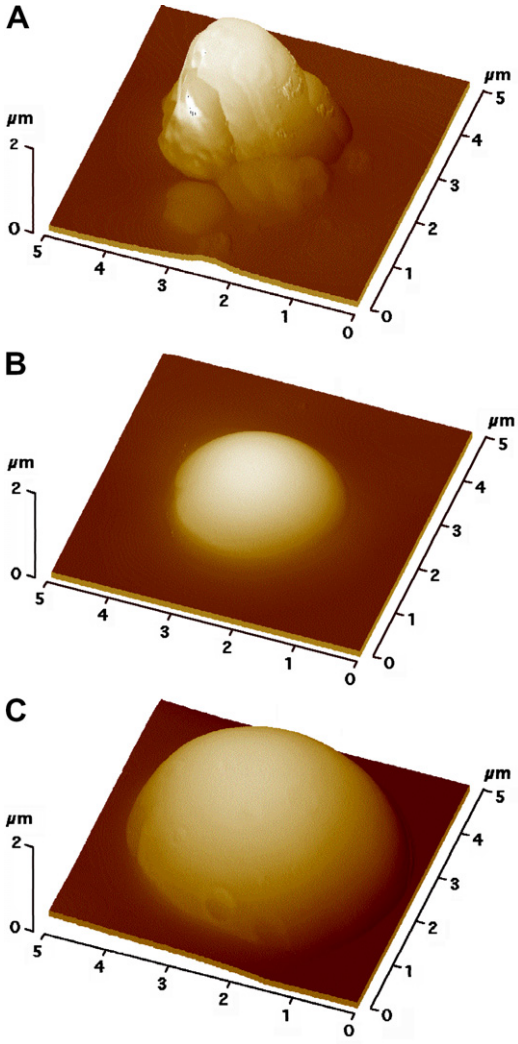

Fig. 4. AFM topographical images of (A) spray dried DSCG, (B) co-spray dried DSCG and PVA 50% w/w and (C) co-spray dried DSCG and PVA 90% w/w.

microparticulate samples were investigated by DVS. The equilibrium moisture sorption isotherms (first sorption cycle) for each of the samples are plotted in Fig. 5. Although two cycles were conducted for each material, moisture de-sorption from the first cycle was reversible. Subsequently, such data were omitted to aid clarity between DSCG/PVA samples. Analysis of the moisture sorption isotherms for each co-spray dried DSCG/PVA microparticulate sample suggested that as PVA concentration increased, the relative moisture sorption decreased. To further investigate the relationship between moisture sorption and the relative concentration of PVA in the DSCG/PVA microparticulate systems, the equilibrium mass content of each sample at 50% RH was plotted against PVA concentration (Fig. 6). Analysis of Fig. 6, suggested a direct linear relationship between moisture sorption at 50% RH and PVA concentration ($R^2 = 0.998$), with increased PVA resulting a decreased affinity for moisture sorption.

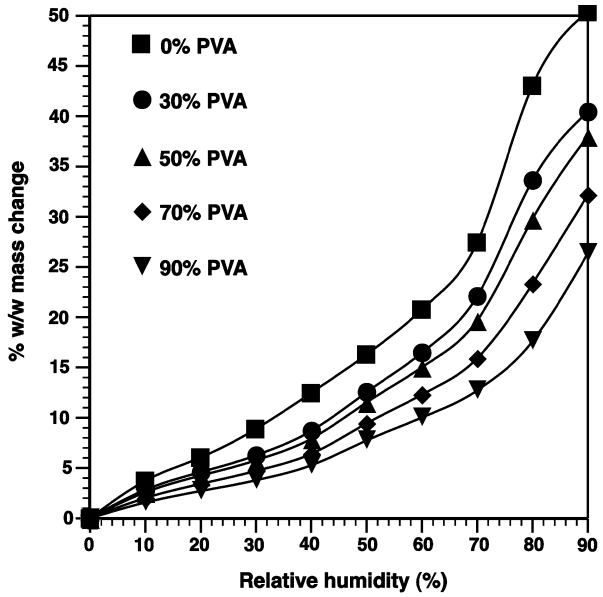

Fig. 5. DVS sorption isotherms for spray dried DSCG with varying percentages of PVA.

3.7. Contact angle measurement

The surface energy components obtained by CA measurements are presented in Table 2. In general, γ^{LW} is the dispersive component of the total surface energy, γ^{+} is the electron-acceptor parameter, γ^{-} is the electron-donor parameter and γ^{AB} the polar or Lewis acid–base interactions. Statistically significant differences were found between all surface energy values of the different DSCG/PVA compacts (ANOVA, $p < 0.05$). Interestingly, however, no relationship between the dispersive component

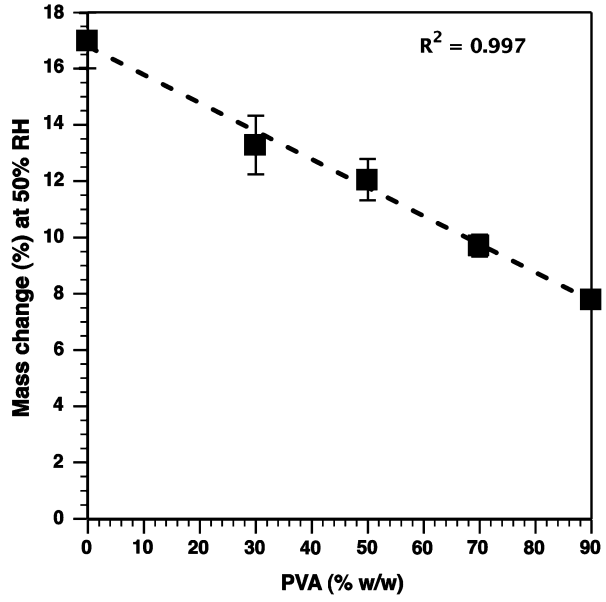

Fig. 6. Mean moisture sorption at 50% RH plotted as a function of PVA concentration.

Table 2
Surface free energy components obtained using CA measurement ($n = 3$, ±standard deviation)

PVA % w/w	Surface energy components from CA (mJ m^{-2})			
	γ^{LW}	γ^{+}	γ^{-}	γ^{AB}
0	45.89 ± 0.09	0.46 ± 0.03	22.55 ± 1.01	6.40 ± 0.08
30	44.79 ± 0.28	0.47 ± 0.04	27.49 ± 0.87	7.21 ± 0.44
50	43.88 ± 1.16	1.56 ± 0.18	39.61 ± 0.44	15.71 ± 0.82
70	47.86 ± 0.04	1.84 ± 0.09	46.30 ± 1.39	18.46 ± 0.72
90	45.94 ± 0.00	3.79 ± 0.03	61.10 ± 0.60	30.44 ± 0.25

Where γ^{LW} is the dispersive component of the total surface energy, γ^{+} is the electron-acceptor parameter, γ^{-} is the electron-donor parameter and γ^{AB} represent the polar or Lewis acid–base interactions.

of the surface energy and PVA concentration was observed, with a linear regression analysis of $R^2 = 0.086$. In comparison, regression analysis of the acid and basic component of the surface free energy indicated a positive linear relationship ($R^2 = 0.874$) where increased PVA concentration resulted in increased γ^{AB}.

By simple arithmetic addition of the dispersive and acid–base parameters ($\gamma^{LW} + \gamma^{AB}$) the total surface free energy (γ^{Tot}) may be calculated. A plot of γ^{Tot} vs. PVA concentration is shown in Fig. 7. From Fig. 7, it can be seen that a positive linear relationship between total surface free energy and PVA concentration was observed ($R^2 = 0.870$).

3.8. In vitro aerosolisation performance

The aerosolisation performance of the co-spray dried DSCG/PVA microparticles was studied using the MMI. Analysis of the deposition data suggested that the incorporation of PVA into the formulation had a significant impact on fine particle fraction (ANOVA, $p < 0.05$). The

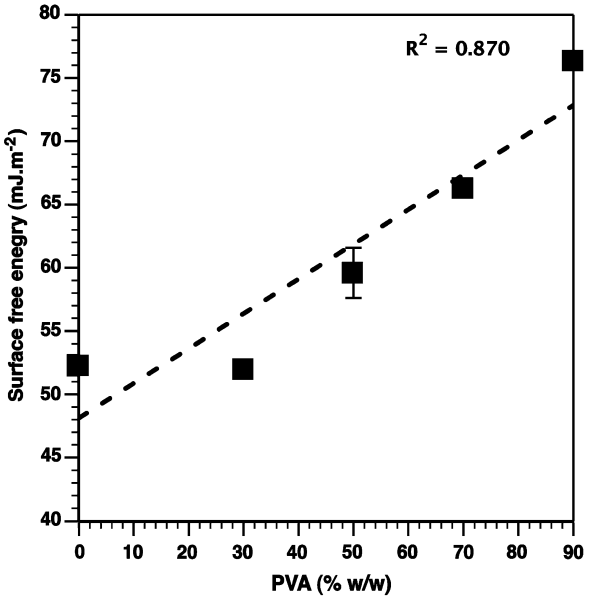

Fig. 7. Total surface free energy of formulation compacts measured as a function of PVA concentration.

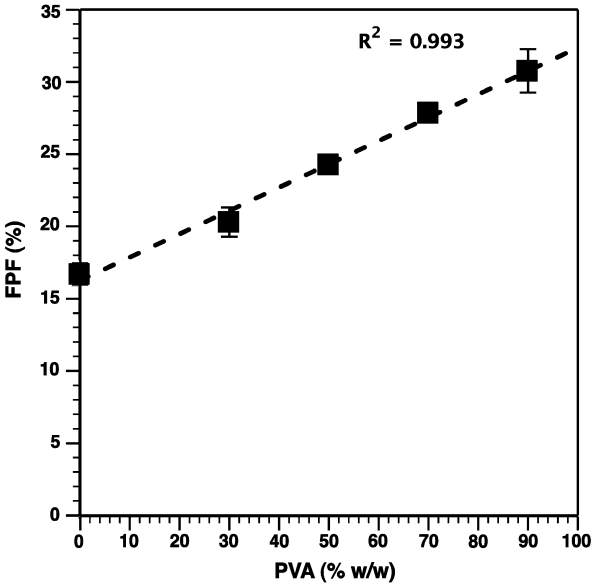

Fig. 8. Influence of % w/w PVA on the in vitro FPF obtained using the MMI.

relationship between PVA concentration and the FPF of the co-sprayed DSCG/PVA microparticles is shown in Fig. 8. In general, an increase in PVA concentration, within the DSCG/PVA microparticles, resulted in a subsequent increase in FPF. Furthermore, Fishers-Pairwise analysis indicated this to be significantly different between all paired samples across the range 0–90% w/w PVA (ANOVA, $p < 0.05$), with regression analysis suggesting a positive linear relationship ($R^2 = 0.993$). In general, the FPF_{LD} increased from 16.71 ± 0.73% to 30.76 ± 1.5% from 0% to 90% w/w PVA, respectively.

4. Discussion

Even for relatively simple single-particulate formulations, as studied here, the relationship between the physico-chemical properties of the co-spray dried microparticles, PVA concentration and the in vitro aerosolisation performance is complex. For example, as the PVA concentration in the co-spray dried microparticles is increased, a concurrent increase in both surface free energy and FPF is observed. However, simultaneously, a decrease in both the true density and relative moisture sorption occurs.

In order to further understand the role each physical parameter plays on the aerosolisation efficiency of the microparticle systems, the relationship between aerosolisation efficiency and the physical parameters, studied here, are discussed in turn.

It is well documented that the aerodynamic diameter (d_a) plays an important role in respiratory deposition [25], and the reduction in particle density (ρ) will result in a concurrent reduction in d_a, compared to the measured volume diameter (d_v) [26]

$$d_a = d_v\sqrt{\frac{\rho}{\rho_0}} \quad (2)$$

where ρ_0 is unit density. Using the mean median d_v (3.15 μm), measured by laser diffraction, calculation of the d_a for spray dried DSCG ($\rho = 1.55\ g\ cm^{-3}$) and co-spray dried DSCG with 90% PVA ($\rho = 1.30\ g\ cm^{-3}$) suggested values of 3.92 and 3.59 μm, respectively. Similar results were obtained when calculating the d_a for the mean 90th percentage undersize value of d_v (7.82 μm), where d_a values of 9.74 and 8.92 μm were calculated for pure spray dried DSCG and 90% PVA samples, respectively. Although a clear decrease in the aerodynamic diameter occurs when increasing the PVA concentration, the total difference in d_a is ⩽330 nm for 50th percentage undersize d_v values across the whole formulation range. Interestingly, post-processing of the laser diffraction particle distribution data, using Eq. (2), suggested the DSCG, spray dried alone, had a lower percentage of particles with a $d_a < 5$ μm (54%). However, analysis of the co-spray dried formulations indicated no clear rank order between PVA concentration and d_a percentage < 5 μm, where values of 68%, 72%, 65%, and 66% were observed for 30%, 50%, 70% and 90% PVA formulations, respectively. Furthermore, analysis of the relationship between FPF and the percentage particles with a $d_a < 5$ μm (the aerodynamic cut-off diameter chosen to represent FPF) suggested no correlation ($R^2 = 0.264$). Subsequently, it can be concluded that variations in both particle diameter and/or density were not a dominating factor affecting aerosol performance.

As with particle size, it may be concluded that particle morphology had little or no influence on the aerosolisation efficiency of the spray dried DSCG formulations. Since no significant differences between the R_{RMS} of the co-spray dried PVA particles were observed, no correlation between increased aerosolisation performance and R_{RMS} could be made. Furthermore, no deviation in linearity between FPF and PVA concentration was observed when analysing the spray dried DSCG (Fig. 8), suggesting that although a significantly higher roughness was observed, it had little or no influence on aerosolisation efficiency. Such observations are interesting, since previous studies by Chew et al. indicated that small variations in roughness resulted in significant improvements in aerosolisation performance [4,5]. However, in these previous studies, the microparticles under investigation were constructed of the same material (namely BSA) and subsequently, it is envisaged that particles with different roughness parameters had similar surface chemistry. In this study, the composition of each particulate system will be significantly different due to the variation in DSCG and PVA concentrations. Since a significant difference in FPF was observed, irrespective of density, size distribution or morphology, it can be concluded that dominant factor was the physico-chemical nature of the particulates.

As previously discussed, a linear relationship between both equilibrium moisture sorption (Fig. 6) or surface free energy (Fig. 7) and PVA concentration was observed, suggesting that variation in the composition of the microparticles affected both surface chemistry and internal structure. In order to fully evaluate how the influence of PVA concentration influenced FPF, with respect to both surface energy and moisture sorption, the relationships were evaluated and are shown in Fig. 9. Good linear correlations were observed between FPF and moisture sorption ($R^2 = 0.974$) and FPF and surface free energy ($R^2 = 0.905$). In general, as the equilibrium moisture sorption (at 50% RH) increased, the aerosolisation performance decreased (Fig. 9A). In comparison, as the total surface free energy increased, the aerosolisation efficiency increased (Fig. 9B). Importantly, the later observation is counterintuitive to what is understood about the relationships between adhesion, surface free energy and aerosolisation efficiency.

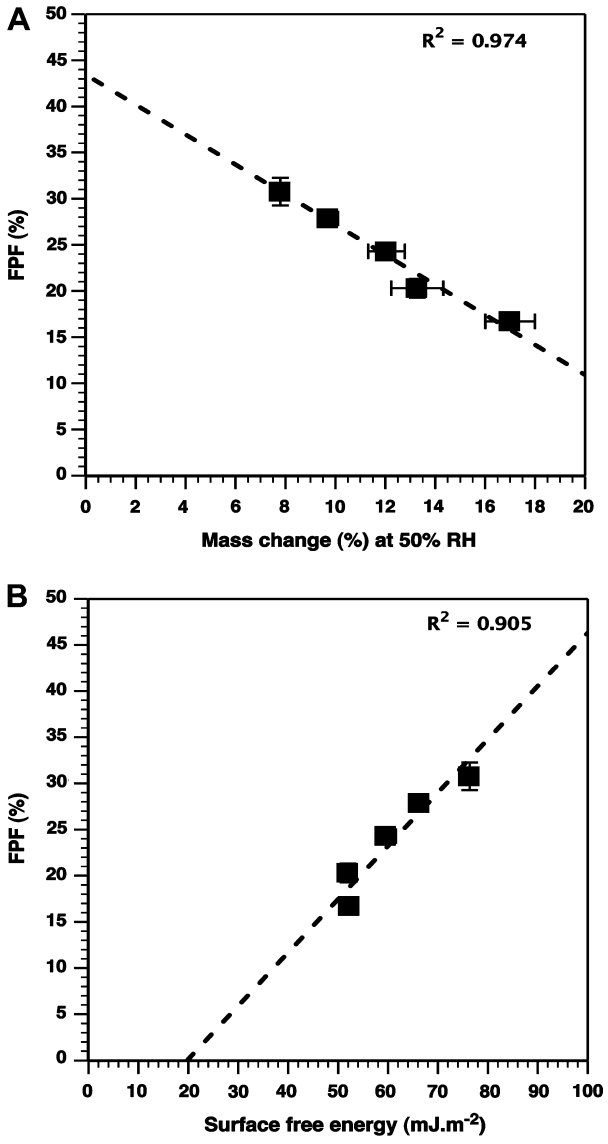

Fig. 9. Relationship between the FPF_{LD} of DSCG/PVA co-spray dried particulates and (A) DVS sorption at 50% RH (B) total surface free energy.

It is expected that the relative increase in equilibrium moisture sorption will be primarily due to internal absorbed water, since mono-multilayer water adsorption will have occurred at much lower humidities. Furthermore, it can also be assumed that any increase in mass due to water absorption has little influence on the FPF, since density measurements after storage at the 50% RH equilibrium humidity indicated no relationship. Subsequently, it can be assumed that the surface adsorbed moisture (not absorbed moisture) will play a dominant role in affecting aerosolisation efficiency of the co-spray dried microparticulate systems.

From Table 2 it can be observed that, although the dispersive component γ^{LW} of the surface energy for each of the PVA % w/w formulations did not vary significantly, the electron-acceptors/donor contribution (γ^- and γ^+) showed a large increase in surface free energy with relation to PVA concentration (the total polar surface tension component, γ^{AB}, being equal to twice the geometric mean of γ^+ and γ^-). As discussed, the major increase in surface free energy, with relation to PVA concentration, may be attributed to a large increase in γ^-, the electron-donating component of the surface free energy (Table 2). Since higher γ^- values suggest a greater hydrophilicity, this increase in surface free energy is most likely due to the relative increase in hydroxyl groups in the PVA polymer. In comparison, DSCG may be considered more hydrophobic than PVA and thus, many interactions arise from a combination of Lifshitz-van-der Waals forces and hydrogen bonds [22], where the contribution of the latter forces is the preponderant one by far (evident by the high amount of water absorbed into the mass of DSCG (Fig. 6)). Such observations were further corroborated by simple measurement of the water contact angle with 100% PVA or DSCG where values of $64.3 \pm 1.1°$ and $43.8 \pm 0.2°$ were observed, respectively. An increase in hydrophilic behaviour, by the addition of PVA, would indicate greater moisture sorption at the solid–air interface; as Israelachvili described "water simply loves itself too much to let some substances get in the way" [27]. This observation was made in the experimental contact angle measurements but was counterintuitive to the bulk moisture sorption and the aerosol performance. Consequently, it may be concluded that the dominant component to the formulation performance is the effect that bulk moisture sorption has on the contiguous particle interfaces in the powder bed before aerosolisation.

One explanation would be that the increase in hydrophilic hydroxyl groups on the surface of the microparticles, as PVA concentration is increased, results in a higher degree of surface bound water molecules, causing the formation of either repulsive hydration forces or the dissipation of charge. Alternatively, the increased bulk water in the sample containing low PVA concentrations may promote capillary formation and thus greater inter-particulate adhesion. However, generally it is considered that materials with increased wettability (high PVA w/w) would likely promote spontaneous formation of capillaries and thus increased adhesion [28].

Furthermore, aerosolisation performances were found to improve with decrease in moisture sorption and increased surface energy. It is postulated that increased surface energy may promote inter-particulate adhesion. This increased adhesion may result in the formation of larger and/or more locally stable agglomerates that experience greater shear (dispersion) forces during the aerosolisation process. Interestingly, recent studies by Cline et al. demonstrated similar findings in carrier based DPI systems, where increased surface energy resulted in a concurrent increase in aerosolisation efficiency [29].

Clearly, the cohesive interactions between DSCG microparticles containing PVA are complex, even without considering factors such as roughness and particle size distribution (which to an extent are eliminated variables in this study). In the current study, utilising primarily spherical microparticles, it may be concluded that surface chemistry and capillary formation, due to the nature of the model drug used in this investigation, interchange the dominating role in particle adhesion and thus aerosolisation efficiency. The direct physics of the interactions between these particles with respect to their surface chemistry is not clearly understood, and requires a fundamental and theoretical study that is outside the scope of this work.

5. Conclusions

A series of CR microparticulate systems containing a model drug and a release-modifying polymer have been prepared. Characterisation of the powders suggested all formulations had similar densities, particle size distributions and morphology, but significantly different aerosolisation efficiency. It is suggested that, in this study, the chemical nature of the microparticles had the major influence. In general, an increase in percentage PVA resulted in decreased equilibrium moisture content (at 50% RH) and increased total surface free energy. Further study has shown that a relationship between these two parameters and aerosolisation efficiency exists ($R^2 \geqslant 0.905$), with the most likely dominating factor being capillary forces. In all cases the CR microparticles were of suitable size for respiratory delivery and aerosolisation efficiency was relatively high. Subsequently, these formulations will be used in future studies as a model to allow comparative evaluation of the in vitro and in vivo aspects of controlled release formulations for the respiratory tract.

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References

[1] J.N. Pritchard, The influence of lung deposition on clinical response, Journal of Aerosol Medicine-Deposition Clearance and Effects in the Lung 14 (2001) S19–S26.

[2] I.J. Smith, M. Parry-Billings, The inhalers of the future? A review of dry powder devices on the market today, Pulmonary Pharmacology & Therapeutics 16 (2) (2003) 79–95.

[3] H.K. Chan, I. Gonda, Aerodynamic properties of elongated particles of cromoglycic acid, Journal of Aerosol Science 20 (2) (1989) 157.

[4] N.Y.K. Chew, P. Tang, H.K. Chan, J.A. Raper, How much particle surface corrugation is sufficient to improve aerosol performance of powders? Pharmaceutical Research 22 (1) (2005) 148–152.

[5] N.Y.K. Chew, H.K. Chan, Use of solid corrugated particles to enhance powder aerosol performance, Pharmaceutical Research 18 (11) (2001) 1570–1577.

[6] G. Pilcer, T. Sebti, K. Amighi, Formulation and characterization of lipid-coated tobramycin particles for dry powder inhalation, Pharmaceutical Research 23 (5) (2006) 931–940.

[7] P.M. Young, R. Price, The influence of humidity on the aerosolisation of micronised and SEDS produced salbutamol sulphate, European Journal of Pharmaceutical Sciences 22 (4) (2004) 235–240.

[8] X.M. Zeng, G.P. Martin, C. Marriott, The controlled delivery of drugs to the lung, International Journal of Pharmaceutics 124 (2) (1995) 149–164.

[9] K. Surendrakumar, G.P. Martyn, E.C.M. Hodgers, M. Jansen, J.A. Blair, Sustained release of insulin from sodium hyaluronate based dry powder formulations after pulmonary delivery to beagle dogs, Journal of Controlled Release 91 (3) (2003) 385–394.

[10] X.M. Zeng, G.P. Martin, C. Marriott, Preparation and in-vitro evaluation of tetrandrine-entrapped albumin microspheres as an inhaled drug-delivery system, European Journal of Pharmaceutical Sciences 3 (2) (1995) 87–93.

[11] J.T. McConville, N. Patel, N. Ditchburn, M.J. Tobyn, J.N. Staniforth, P. Woodcock, Use of a novel modified TSI for the evaluation of controlled-release aerosol formulations. I, Drug Development and Industrial Pharmacy 26 (11) (2000) 1191–1198.

[12] J. Fu, J. Fiegel, E. Krauland, J. Hanes, New polymeric carriers for controlled drug delivery following inhalation or injection, Biomaterials 23 (22) (2002) 4425–4433.

[13] J. Fiegel, H. Fu, J. Hanes, Poly(ether-anhydride) dry powder aerosols for sustained drug delivery in the lungs, Journal of Controlled Release 96 (3) (2004) 411–423.

[14] R.O. Cook, R.K. Pannu, I.W. Kellaway, Novel sustained release microspheres for pulmonary drug delivery 1, Journal of Controlled Release 104 (1) (2005) 79–90.

[15] L. Dellamary, D.J. Smith, A. Bloom, S. Bot, G.R. Guo, H. Deshmuk, M. Costello, A. Bot, Rational design of solid aerosols for immunoglobulin delivery by modulation of aerodynamic and release characteristics, Journal of Controlled Release 95 (3) (2004) 489–500.

[16] R.C. Rowe, P.J. Sheskey, S.C. Owen, Handbook of Pharmaceutical Excipients, Pharmaceutical Press, London, 2006.

[17] A. Yamamoto, K. Yamada, H. Muramatsu, A. Nishinaka, S. Okumura, N. Okada, T. Fujita, S. Muranishi, Control of pulmonary absorption of water-soluble compounds by various viscous vehicles, International Journal of Pharmaceutics 282 (1–2) (2004) 141–149.

[18] N.Y.K. Chew, D.F. Bagster, H.K. Chan, Effect of particle size, air flow and inhaler device on the aerosolisation of disodium cromoglycate powders, International Journal of Pharmaceutics 206 (1–2) (2000) 75–83.

[19] N.M. Ahfat, G. Buckton, R. Burrows, M.D. Ticehurst, An exploration of inter-relationships between contact angle, inverse phase gas chromatography and triboelectric charging data, European Journal of Pharmaceutical Sciences 9 (3) (2000) 271–276.

[20] R.J. Good, Contact-angle, wetting, and adhesion – a critical-review, Journal of Adhesion Science and Technology 6 (12) (1992) 1269–1302.

[21] R.J. Good, L.A. Girifalco, A theory for estimation of surface and interfacial energies. 3. Estimation of surface energies of solids from contact angle data, The Journal of Physical Chemistry – US 64 (5) (1960) 561–565.

[22] C.J. Vanoss, Interfacial Forces in Aqueous Media, Marcel Dekker, New York, 1994.

[23] C.J. Vanoss, R.J. Good, M.K. Chaudhury, Additive and nonadditive surface-tension components and the interpretation of contact angles, Langmuir 4 (4) (1988) 884–891.

[24] C.J. Vanoss, M.K. Chaudhury, R.J. Good, Interfacial Lifshitz-Vanderwaals and polar interactions in macroscopic systems, Chemical Reviews 88 (6) (1988) 927–941.

[25] D.A. Edwards, J. Hanes, G. Caponetti, J. Hrkach, A. BenJebria, M.L. Eskew, J. Mintzes, D. Deaver, N. Lotan, R. Langer, Large porous particles for pulmonary drug delivery, Science 276 (5320) (1997) 1868–1871.

[26] W.C. Hinds, Aerosol Technology, John Willey & Sons, New York, 1999.

[27] J.N. Israelachvili, Intramolecular and Surface Forces, Academic Press, London, 1985.

[28] F. Podczeck, Particle–Particle Interactions in Pharmaceutical Powder Handling, Imperial College Press, London, 1998.

[29] D. Cline, R. Dalby, Predicting the quality of powders for inhalation from surface energy and area, Pharmaceutical Research 19 (9) (2002) 1274–1277.