

## Rapid Pre-formulation Screening of Drug Salts for Dry Powder Inhalers

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### Summary

Salt formation is a simple means of endowing a molecule with properties to overcome some undesirable feature of the parent drug. In order to optimize dry powder inhaler (DPI) dosage forms, the selections of salt forms based on surface interfacial properties is vital. The aim of this study was to use the CAB approach to colloid probe AFM to investigate the surface interfacial properties of different salt forms of salbutamol. Furthermore, the aerosolisation properties of the different salt forms of salbutamol were assessed using inertial impaction. The aerosolisation performance of binary and ternary DPI formulations was correlated to the CAB ratio of the different salts. These data suggest CAB may be used in the selection of optimal salts to be formulated in DPI dosage forms.

### Background

Salt formation is a simple means of endowing a drug with unique properties to overcome some undesirable feature of the parent drug in relation to its physicochemical, biopharmaceutical and processing properties<sup>1</sup>. Hence, the selection of optimal salt forms in the development of dry powder inhaler (DPI) dosage forms may enable the optimization of DPIs in terms of stability, processability and performance. Currently, screening for optimal salt forms is based on physicochemical stability profiling<sup>1</sup>. However, in order to optimize DPI aerosol dosage forms, the selections of salt forms based on key functional physicochemical properties, which relate to DPI drug product performance may enable rapid screening of active ingredient salt forms for DPI drug product development.

It is widely accepted that the complex array of interfacial interactions that occur between components of a DPI drug product ultimately governs performance<sup>2</sup>. Therefore, the surface interfacial properties of drug entities are a key functional property that governs the overall performance of DPI products. Hence, selection of drug salt forms on the basis of their interfacial properties with components of DPI products may enable the selection of salt forms that provide some functional benefit to the drug product.

Interparticle interactions between components of DPI formulations have largely been conducted using scanning probe microscopy techniques such as colloid probe atomic force microscopy (AFM). The most useful AFM-technique thus far has been the cohesive-adhesive balance (CAB) approach, which has been shown to successfully relate to DPI performance<sup>3, 4, 5</sup>.

### Aim

The aim of this study was to use the CAB approach to colloid probe AFM to investigate the surface interfacial properties of different salt forms of salbutamol. The aerosolisation properties of the different salt forms of salbutamol were assessed using inertial impaction and then related to the cohesive-adhesive properties of the different salt forms.

### Experimental

Salbutamol base was sourced commercially from PFC Italiana (Milan, Italy) and salbutamol sulphate was purchased from Miza Pharmaceuticals (UK) Ltd (Runcorn, UK). All other reagents and solvents were purchased from Fisher Scientific Ltd (Manchester, UK).

The following salts were employed to form different salt forms of salbutamol: 1-hydroxy-2-naphthoate (xinafoate), tartrate, acetate and propionate. The selection of the salts was based on physicochemical acceptance and relevance to the delivery of therapeutics to the lung. The sulphate salt was not prepared as it was commercially available. The different salt forms were prepared by addition of the acid to a solution of salbutamol base in methanol. Following this, the liquid was completely evaporated, which resulted in a white precipitated material. In order to remove any excess acid present in the salts produced, as well as any other impurities, the reaction products were all re-crystallized from solution twice by slow addition of a suitable anti-solvent. The base and sulphate were also re-crystallized using the same approach. The resultant crystalline salt forms of salbutamol were freshly micronised to the inhalable size range using a MC One Jet Mill (Jetpharma SA, Switzerland).

The morphology of the micronized products was assessed using scanning electron microscopy (SEM, Joel, Japan). Particle size analysis was performed using a HELOS/BF laser diffraction sensor. The powder sample was fed via an ASPIROS micro dosing unit into a RODOS dry dispersing unit (all from Sympatec GmbH, Clausthal-Zellerfeld, Germany). The dispersing pressure was set at 2 bar, the vacuum applied was 20 mbar, and the feed velocity was 20 mms<sup>-1</sup>. Approximately 20mg of sample was used for each analysis. All analyses were carried out in triplicate and the mean and standard deviation calculated. The water-sorption of the micronized powders was also assessed using a DVS-1 (Surface Measurement Systems Ltd, London, UK). The sample of micronized drug (10-20mg) was weighed into a tared sample holder and was hermetically sealed into the equipment. The system was allowed to equilibrate at 25°C and 43%RH to eliminate the possible build-up of electrostatic charges. The relative humidity was then reduced to 0% for 5 hours, increased to 100% for 15 hours and then reduced to 0% for 5 hours. The temperature was constant at 25°C throughout the experiments.

Using three colloidal probes of each of the micronized products, the CAB ratio (ratio between cohesive and adhesive forces) of each of the salt forms of salbutamol was determined with respect to lactose monohydrate, as described in detail elsewhere<sup>2</sup>. In this way, when the CAB ratio was >1, the cohesion of the drug was greater than its adhesion to the carrier and when the ratio was <1, the opposite adhesive situation applied.

In addition, binary and ternary DPI formulations of each of the salbutamol salt forms (0.4% w/w) were prepared with a coarse lactose carrier (SV003, DMV, Vehgel, Netherlands). Binary formulations were prepared on a 5g scale such that 20mg of the formulation would contain 200µg salbutamol (1%w/w drug content). The blends were prepared by geometric mixing of the powders in a 30ml glass test tube fitted with a glass stopper. For the ternary blends, a 50g pre blend of carrier lactose and fine lactose (Sorbolac 400, Meggle, Germany) was prepared containing 10.1%w/w fine lactose and 89.9%w/w carrier lactose. This mixture was blended geometrically in a sealed 200ml glass jar using a Whirlimixer with 30 seconds of mixing per iteration. The ternary blends were then prepared using the same amount of drug material as the binary formulations and using the same blending regime. This produced ternary blends containing 10%w/w fine lactose. Formulations were aerosolized from ten 25 mg capsules using a Monohaler™ at 60 L.min<sup>-1</sup> into a Next Generation Impactor (NGI) with pre-separator. The fine particle dose (FPD) and fine particle fraction of the recovered dose (FPF<sub>RD</sub>) for each formulation was then determined.

## Results and Discussion

The physicochemical properties of the micronized salt forms of salbutamol were analysed using SEM, particle size analysis and dynamic vapour sorption (DVS). In addition, the respective cohesive-adhesive balance of each of the micronized products to lactose monohydrate was determined using the CAB approach to colloidal probe AFM. These data were then related to product functionality as determined by *n-vitro* inhalation performance.

### Physicochemical Characterisation

The morphology of the different micronized salt forms of salbutamol was similar (data not shown). Particle size analysis summarized in Table 1, suggested that 90 % of particles were less than 7 µm and presented a median equivalent volume diameter of approximately 2 µm. These data suggest that micronized products were suitable for pulmonary drug delivery. The differences in particle size between the various salt forms may be related to the mechanical properties of the primary crystal from which they were micronized.

Table 1. Particle size distribution analysis of the different micronized salt forms of salbutamol.

| Material          | d <sub>10</sub> (µm) | d <sub>50</sub> (µm) | d <sub>90</sub> (µm) |
|-------------------|----------------------|----------------------|----------------------|
| Base              | 0.71 (0.01)          | 2.56 (0.02)          | 5.29 (0.03)          |
| Sulphate          | 0.57 (0.01)          | 2.21 (0.02)          | 5.33 (0.18)          |
| Acetate           | 0.63 (0.01)          | 2.30 (0.06)          | 5.38 (0.03)          |
| Propionate        | 0.59 (0.01)          | 1.84 (0.01)          | 3.75 (0.02)          |
| Tartrate          | 0.56 (0.01)          | 1.81 (0.01)          | 6.60 (0.01)          |
| Hydroxynaphthoate | 0.66 (0.01)          | 2.99 (0.03)          | 6.94 (0.07)          |

All the salt forms showed significant difference in water uptake following exposure to high humidity as shown in Figure 1. These data may be related to chemical differences between the different salt forms and/or the presence of surface structural disorder. This may, therefore, suggest that the different salt forms may possess different mechanical properties that corresponded to each salt form attaining different levels of surface disorder upon micronization.

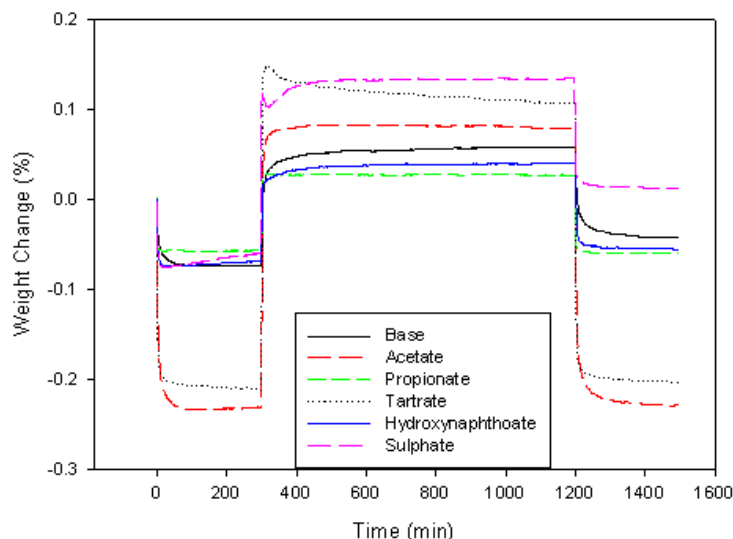


Figure 1. The change in mass of the different micronized salt forms following exposure to 100 % RH.

### Pharmaceutical Functionality

In order to investigate the formulation performance of the different salt forms of salbutamol, 200 µg dose binary and ternary blends of the salts was prepared. The blend, after confirming acceptable blend uniformity, was added to size 3 HPMC capsules (y) and aerosolised into a NGI at 60 L.min<sup>-1</sup> using a Monohaler™. The fine particle dose (FPD) of binary preparations of the various salts of salbutamol varied between 30 – 80 µg, which suggests that formulations containing the different salt forms of salbutamol perform differently (Table 2). The FPD of the ternary formulations suggested that the delivery of the salbutamol salts had significantly ( $p < 0.05$ ) increased, which is the reported affect of including fines in DPI formulations<sup>6</sup>. These data suggest that there was no relationship between the particle size distributions and water-sorption properties of the salt forms of salbutamol and *in-vitro* performance.

Table 2. Aerosolisation of binary formulations of the different salt forms.

| Material          | FPD (µg ± S.D.) | FPF <sub>RD</sub> (% ± S.D.) |
|-------------------|-----------------|------------------------------|
| Base              | 73.17 (1.50)    | 32.95 (1.86)                 |
| Sulphate          | 76.97 (2.11)    | 35.12 (1.19)                 |
| Acetate           | 52.40 (1.31)    | 27.06 (2.25)                 |
| Propionate        | 45.93 (3.50)    | 27.49 (1.93)                 |
| Tartrate          | 31.30 (0.30)    | 19.18 (0.97)                 |
| Hydroxynaphthoate | 62.60 (1.06)    | 33.04 (2.28)                 |

Table 3. Aerosolisation of ternary formulations of the different salt forms.

| Material          | FPD (µg ± S.D.) | FPF <sub>RD</sub> (% ± S.D.) |
|-------------------|-----------------|------------------------------|
| Base              | 85.33 (2.94)    | 44.56 (0.31)                 |
| Sulphate          | 71.50 (4.94)    | 38.98 (1.16)                 |
| Acetate           | 58.10 (5.63)    | 31.51 (0.53)                 |
| Propionate        | 50.43 (1.36)    | 35.80 (0.73)                 |
| Tartrate          | 41.00 (1.65)    | 22.62 (0.36)                 |
| Hydroxynaphthoate | 70.30 (4.94)    | 38.13 (1.06)                 |

### Relationship between Formulation Performance and CAB

The CAB ratios of the different salts of salbutamol with respect to lactose are shown in Table 4. The CAB ratios of the salts varied between 0.3 – 1.0, indicating that the interactive properties of all the salts were different with respect to each other. This may be attributed to differences in the surface properties of the different salt forms.

Table 4. CAB ratios of the different salts of salbutamol and lactose monohydrate.

| Material          | CAB Ratio |
|-------------------|-----------|
| Base              | 0.85      |
| Sulphate          | 0.80      |
| Acetate           | 0.92      |
| Propionate        | 0.67      |
| Tartrate          | 0.55      |
| Hydroxynaphthoate | 0.34      |

This variation in the CAB ratio of the different salt forms of salbutamol was correlated to an increase in FPD of the binary formulations as the CAB ratio increased from 0.3 to 1.0, suggesting an optimal FPD was obtained when the system approaches a CAB ratio of 1 (Figure 2A). These data may be attributed to weaker drug-carrier adhesion as the CAB ratios of the drug particles move closer to 1, resulting in greater aerosolization of fine drug particles due to decreased force required to detach drug particles from the carrier. Figure 2B shows that as the different salts of salbutamol become adhesive to lactose the fine particle drug delivery increases. This may be related to formation of drug-fines agglomerates that are better aerosolized.

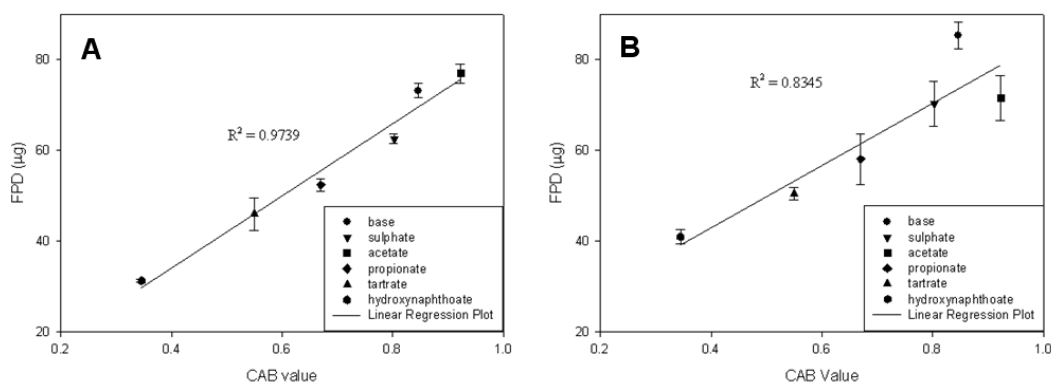


Figure 2. Relationship between fine particle dose of (A) binary and (B) ternary DPI formulation and the force balance of the different salt forms of salbutamol with respect to lactose.

## Conclusions

In conclusion, the CAB ratios of the different salt forms were correlated to fine particle drug delivery. These data suggest the CAB approach may present itself as a screening tool for the identification of optimal salt forms for DPI dosage forms.

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