

The Aerodynamic Deposition of Drugs from Combination DPI Formulations: The Influence of Particle Size and Drug-Drug and Interactions.

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Summary:

The delivery of multiple actives from a combination inhaler provides a useful option for treating some patients suffering from chronic respiratory diseases. However, complex interactions exist between the different components of combination formulations. Changes in the particle size of salmeterol xinafoate (SX) had a significant effect on the deposition of SX and fluticasone propionate (FP) but the converse was not true. FP deposition was more dependent on the particle size of SX than its own size. Such drug-drug interactions may result in significant differences in drug deposition and efficacy when drugs are aerosolised from combination formulations. Knowledge of the factors and mechanisms affecting drug aerosolisation and deposition from combination formulations can be very useful in designing better formulations for the local and systemic delivery of inhaled medicaments.

Introduction:

Patients suffering from asthma and chronic obstructive pulmonary disease (COPD) may need to inhale more than one active ingredient with many sufferers requiring the concurrent administration of inhaled corticosteroids and long acting β_2 -agonists. One of the strategies that have been adopted is to present the treatment as a combination inhaler. This approach offers some benefits to patients including the simplification of their often complex medication regimes (1, 2).

Published research suggests that the use of a combination of inhaled corticosteroids and long acting β_2 agonists is at least as effective as the administration of the two products separately (3, 4). Two inhaled combination products are already well established: Seretide[®] Accuhaler[®] combining SX and FP and Symbicort[®] Turbohaler[®] which combines formoterol fumarate with budesonide, while several other combination products are under development (5). Such combinations have been approved for the treatment of asthma and chronic obstructive pulmonary disease (COPD). The British Thoracic Society (BTS) Asthma Guidelines and the European Respiratory Society (ERS) / American Thoracic Society (ATS) Task Force on COPD recommend the regular use of such combinations in patients who cannot be controlled by the use of an inhaled corticosteroid alone (6, 7).

There have been several suggestions that improvements seen with the combination product over two separate single-active inhalers are not solely due to the possible increase in patient compliance, but rather as a result of pharmacological and/or pharmaceutical interactions between the two active components (8). Considering the potential physico-chemical interactions in a combination formulation, including drug-drug and drug-carrier interactions, it becomes apparent that a complex multi-factorial scenario may be present.

The role of fine particles in DPI formulations has been extensively researched over the past two decades (9-11). Today, it is widely accepted that fines can significantly alter the aerodynamic performance of formulations although the mechanisms by which they exert their effects are far from being fully understood. It is likely, however, that a multi-factorial process takes place to produce such effects. Consequently, the introduction of combination formulations moves the problem to another level, and reasserts the importance of understanding the fundamental inter-particulate interactions further. While fine-exipient particles may be included to improve the aerosolisation and/or deposition of an active pharmaceutical ingredient (API), in a combination formulation *both* actives are required to be delivered to their required site of action.

Due to the number of variables involved, it is important that deposition studies are designed to allow the investigation of each factor individually while controlling as many variables as possible. This allows even small but significant changes in the mass-median aerodynamic diameter (MMAD) and fine particle fraction (FPF) to be detected. Such small changes might not be clinically significant for current therapies inhaled by asthma or COPD patients but may be important in developing predictable formulations for the systemic delivery of narrow therapeutic window medicines in the future.

Despite a significant body of research into inter-particulate interactions in inhaled dry powder formulations and several advances in technology, understanding the complex nature of such interactions remains a challenge. However, explaining interparticulate interactions is a valuable step if drug delivery to the lung is to become a generic route for treating systemic diseases.

Previously, we have shown that the in-vitro deposition of SX from Seretide Accuhaler may be significantly influenced by the concentration of FP (12). Here we have studied bespoke formulations containing SX, FP or a combination of both that have been 'matched' with respect to fine lactose (FL) and coarse lactose (CL) in terms of particle size and size distribution, concentration, mixing ratio, mixing order and carrier load such that the nature and magnitude of potential interactions can be measured in terms of in vitro aerodynamic deposition using the NGI.

Methods:

Coarse lactose (CL; Friesland Domo, Netherlands) was sieved in triplicate to obtain a fraction between 63-90 μm . SX (Vamsi Labs Ltd. Maharashtra, India), FP (Coral Drugs Ltd. New Delhi, India) and FL (Friesland Domo, Netherlands) were micronised in-house. Two size fractions of each of SX and FP were prepared and mixed with CL either as binary or ternary formulations (Table 1). Before mixing, the larger fractions (SX_L and FP_L) were shown to be aerodynamically equivalent. This was also shown for the smaller fractions (SX_S and FP_S).

A sample of 150 mg (5x30mg) was accurately weighed into hard gelatine capsules and the contents of each were aerosolised using an Aerolizer device into a next generation impactor (NGI) at a flow rate of 60 Lmin^{-1} . The NGI "collection cups" were coated in a mixture of 11 g of polypropylene glycol (Riedel-de Haen AG, Seelze, Germany) in 100 mL of isohexane (Fisher Scientific, Loughborough, UK) and air dried. Samples were recovered using a validated HPLC method.

Table 1: Particle size measurements determined using a Malvern Mastersizer.

	SX_L	SX_S	FP_L	FP_S	CL
VMD (μm)	6.22 ± 0.37	3.18 ± 0.20	3.26 ± 0.14	1.70 ± 0.12	100.01 ± 0.63

To ensure consistency throughout the various formulations, a primary mix was made for each of SX_L , SX_S , FP_L , FP_S , FL_L and FL_S . This was achieved by geometrically mixing each fine powder with coarse lactose at a ratio of 1:15 (w/w), respectively. All combinations of similar and different size fractions were prepared producing 8 formulations each containing 1.5% (w/w) of each active in binary mixes and 1.5%+1.5% (w/w) of SX+FP in ternary mixes, with the remainder being CL. All mixes were validated by accurately weighing 10 x 2 mg (± 0.5) samples and dissolving them in 5 mL of HPLC mobile phase solution. Samples were analysed by HPLC.

The HPLC instrument used for analysis was a SpectraPHYSICS™ system (Thermoseparation Products Inc., California, USA). The column used was a ThermoQuest (Cheshire, UK) Hypersil column (C18, 4.6 mm, 5 μm , 25 cm). The mobile phase was a mixture of methanol (BDH International, Poole, UK) and a solution of 0.2% (w/v) ammonium acetate buffer (BDH International, Poole, UK) in a ratio of 75:25, respectively, at pH 5.5 (± 0.01). The flow rate was 1.0 mL min^{-1} , the temperature was 40° C, and a UV detector set at a wavelength of 228 nm was used. The method was shown to be linear, accurate, precise and reproducible in the range 0.5-100 $\mu\text{g/mL}$.

Results from 4 replicates were obtained and the mass median aerodynamic diameter (MMAD) and fine particle fractions (FPF) were calculated from regression equations fitted to log-probability plots as per the method described in the European Pharmacopoeia. Two FPF values were calculated as the percentage of the recovered dose having an aerodynamic diameter < 3 μm ($\text{FPF}_{<3 \mu\text{m}}$) or < 5 μm ($\text{FPF}_{<5 \mu\text{m}}$). Results were analysed for significance using m-ANOVA and t-test.

Results and discussion:

It is widely accepted that particle size is a key factor in determining the aerodynamic deposition of particles both in vitro and in vivo with particles smaller than 5 μm regarded as 'respirable'. However, there are no specific limits as to which particles would be regarded to be similar aerodynamically. Results in **Error! Not a valid bookmark self-reference.** show that changes in particle size led to large changes in the FPF. This was seen for both SX (eg. 1 vs 6) and FP (eg. 4 vs. 5). Changes in the particle size of both drugs produced a significant effect on deposition from binary formulations with the larger size fractions producing higher FPF values. While a higher FPF value was also produced by the larger size fractions in SX ternary formulations, changing the particle size of FP had no effect on its deposition from ternary formulations (**Error! Not a valid bookmark self-reference.**).

M-ANOVA tests results showed that small changes in particle size significantly affected the deposition of both drugs ($p < 0.001$). The fine particle fraction of SX from binary and ternary formulations was similar for each size (**Error! Not a valid bookmark self-reference.**; SX_L : 1, 2 and 3; SX_S : 6, 7 and 8).

However, ternary formulations produced higher FP FPF values than binary formulations (FP_L: 2 and 7 vs. 4; FP_S: 3 and 8 vs. 5). While changes in the particle size of FP had no effect on the deposition of SX, the converse was not true. The deposition of FP was dependent on the particle size of SX but not its own particle size with the larger SX size fraction producing double the FP FPF compared to the smaller SX size. These results show significant drug-drug interactions in the SX-FP combination formulation. The magnitude of the difference in FPF may be observable in vivo but the clinical consequence of these findings is uncertain.

Table 2: MMAD, GSD and FPF results of SX and FP obtained from the different formulations.

number	size fraction		Deposition results (mean ±SD; n=4)							
	SX	FP	SX				FP			
			MMAD	GSD	FPF _{<3 μm} (%)	FPF _{<5 μm} (%)	MMAD	GSD	FPF _{<3 μm} (%)	FPF _{<5 μm} (%)
1	L	-	2.23 ±0.0	1.64 ±0.0	18.07 ±1.5	23.59 ±1.8	-	-	-	-
2	L	L	2.28 ±0.1	1.62 ±0.0	18.63 ±1.3	24.68 ±1.4	2.38 ±0.1	1.66 ±0.0	13.73 ±0.9	18.84 ±1.0
3	L	S	2.22 ±0.1	1.64 ±0.0	20.39 ±0.6	26.58 ±0.9	2.13 ±0.1	1.66 ±0.0	14.85 ±0.5	18.89 ±0.7
4	-	L	-	-	-	-	2.47 ±0.1	1.65 ±0.0	4.98 ±0.6	7.03 ±0.7
5	-	S	-	-	-	-	2.38 ±0.1	1.69 ±0.0	3.22 ±0.3	4.43 ±0.3
6	S	-	2.10 ±0.0	1.64 ±0.0	12.21 ±0.4	15.31 ±0.4	-	-	-	-
7	S	L	2.30 ±0.1	1.60 ±0.0	10.30 ±1.0	13.71 ±1.1	2.59 ±0.1	1.64 ±0.0	6.88 ±0.7	10.12 ±0.7
8	S	S	2.31 ±0.0	1.61 ±0.0	10.56 ±0.6	14.12 ±0.7	2.40 ±0.1	1.63 ±0.0	6.78 ±0.5	9.37 ±0.7

These results suggest that such effects might have resulted from significant changes in the inter-particulate interactions within the formulations, possibly by affecting agglomeration. The observation that relatively small changes in the particle size of one component in a combination formulation significantly affect the deposition of another appears to support this view. Interestingly, SX appears to affect FP much more than it is affected by the latter. It might be suggested that less cohesive particles may have a greater ability to interact with more cohesive agglomerates that have similar physico-chemical properties. The latter particles, as a result of their cohesiveness, may not greatly affect the less cohesive species. This might explain the observation that the apparently less cohesive SX improved the deep impactor deposition of the more cohesive FP, while the FP had no effect on the deposition of SX.

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