

# In-situ fine particle excipient as dispersion modifier for a dry powder inhalation product

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## Summary

To achieve a better fine particle fraction (FPF), dry powder inhaler formulations can make use of fine particle excipients acting as dispersion modifiers. This is mostly fine particle lactose. In this study, the use of hydroxypropyl methylcellulose (HPMC) acting as dispersion modifier is described for two different formulation approaches for a combination of salmeterol and fluticasone, being wet milling and co-precipitation, followed by a spray drying step respectively. With the addition of HPMC to the dispersion prior to spray-drying, an in-situ formation of HPMC spheres takes place and with this, the FPF can be remarkably enhanced (from 0.8% without HPMC to 39% with 0.6% HPMC). The addition of a water soluble excipient as dispersion modifier is a feasible improvement in formulation, especially if a spray drying step is included in the manufacturing procedure anyway.

## Introduction

A dry powder formulation needs to be capable of being readily dispersed resulting in a good proportion of fine particles with an aerodynamic diameter below 5  $\mu\text{m}$  which will enter the lung during inhalation. Several papers have been published dealing with the use of fine particle excipients as dispersion modifier in DPI formulations. Fine particle lactose can be added to an interactive mixture of micronised drug and coarse carrier to cover the 'active sites' of the carrier and, with this, lower the interaction of the drug with the carrier resulting in a good separation during inhalation and an improvement in fine particle fraction (FPF) [1]. Other scientists use fine particulate leucine as ternary agent to enhance the dispersion capability of a dry powder mixture and, with this, the FPF [2]. In every dry powder mixture, the homogeneity of distribution is a crucial aspect in formulation and can be difficult to obtain especially if only small amounts of substance are present.

In this work, a method for the in-situ formation of a fine particle dispersion modifier in a DPI formulation is described.

## Materials and Methods

A dry powder formulation comprising the two active ingredients salmeterol xinafoate and fluticasone propionate was produced. To achieve a primary particle size in the respirable range, wet co-milling with a ball mill or a co-precipitation process has been used.

For wet milling, a stock dispersion of both drugs (4.5% w/w) in water was prepared. Salmeterol xinafoate and fluticasone propionate were used in a ratio of 1.45 plus 2, corresponding to the ratio used in therapy. In order to allow the drugs to be acceptably dispersed, 1% (w/w) polysorbate 80 was added to the suspension. This suspension has been transferred into the milling chamber of the ball mill (MM 2000, Retsch, Haan, Germany) afterwards. The milling chamber has a total volume of 25 mL and was prefilled with 30 g (7 mL) cer-stabilised zirconium oxide milling beads (0.7 – 1.2  $\mu\text{m}$  diameter). The swing mill was operated at an amplitude of 30% for 120 min. The suspension was immediately separated from the milling beads and stored in the refrigerator until further processing. Aliquots of the suspension have been spray dried subsequently with a Mini-Büchi B-290 (Büchi, Flawil, Switzerland) in order to obtain a dry powder for inhalation. For this, the stock suspension was diluted 1:100 with water containing different amounts (0.00% to 0.06%) of hydroxypropyl methylcellulose 50 (HPMC, Shin Etsu Chemicals, Japan) by mixing in a glass beaker and each batch was spray dried immediately after dilution. Spray drying conditions were 120°C inlet temperature and an outlet temperature below 50°C with a drying air volume of 40m<sup>3</sup>/h.

The precipitation process has been described in detail elsewhere [3]. In brief, an organic solution of both drugs was mixed with water as non-solvent containing 0.01% polysorbate 80 and different amounts (0% to 0.05%) of HPMC using a micro mixer (IMM, Mainz, Germany). The obtained dispersion was spray dried afterwards to obtain a dry powder.

From each batch, SEM micrographs (S240, Carl Zeiss AG, Oberkochen, Germany) were taken to allow a morphological characterisation of the batches.

The aerodynamic behaviour of the powders was assessed with the Next Generation Pharmaceutical Impactor (NGI, MSP Corporation, Shoreview, USA) using the Aerolizer<sup>®</sup> device at an air flow rate of 100 L/min. The powder was weighed directly into capsules (hard gelatine capsules size 3, Capsugel, Colmar, France), which were individually placed into the device for testing. In order to avoid particle bouncing, all stages were coated with a coating fluid. The amounts of both drugs deposited on the impactor stages, preseparator, throat and remaining in the capsule were analysed by HPLC afterwards. The FPF as percentage of drug particles below a size of 5  $\mu\text{m}$  was calculated from a log-linear distribution utilising stages 2 to MOC and is related to the total recovery of drug.

## Results and Discussion

The aerodynamic properties of precipitated or milled formulations with polysorbate 80 as sole stabiliser are poor as they show a low redispersion capability in the airflow as tested with the NGI resulting in an FPF of only 0.8%. But if a dispersion modifying excipient as hydroxypropyl methylcellulose 50 is added, which can already be incorporated in the dispersion prior to spray drying, the FPF is remarkably enhanced up to 39%. HPMC is a water soluble excipient with surface activity. When added to the dispersion prior to spray drying, the excipient dissolves

in the dispersion. During spray drying, HPMC forms small dispersion modifying spheres in-situ, which are very evenly distributed throughout the product (Figure1) and inhibit close particle-to-particle contact already in the product vessel of the spray dryer.

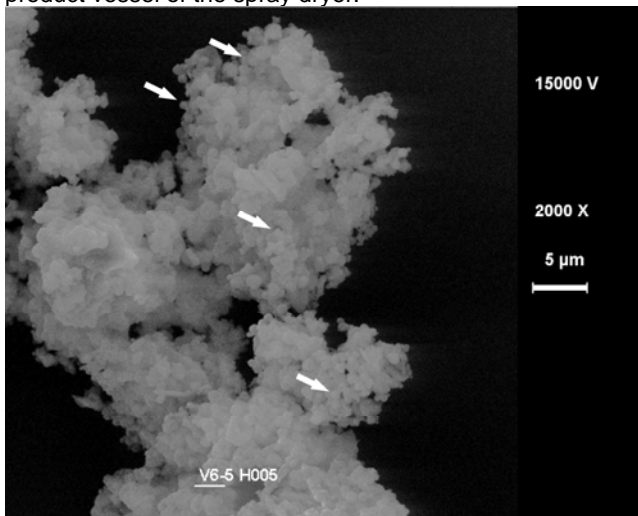


Figure 1: SEM micrograph of a formulation produced by wet milling comprising small spheres of HPMC (white arrows) acting as dispersion modifier (0.05% HPMC in dispersion media)

With this, a good redispersion of the dry powder can be achieved without the need of a carrier or further excipients. With increasing amounts of HPMC in the dispersion media, more spheres can be observed in the SEM pictures of the dried powder (Figure 2). In dependence on the concentration of HPMC, the FPF can be set to the desired range (Figure 3). It has to be emphasised that the FPF is only calculated from the active drug substances and does not account for fine particle excipients. This concept has also been proven for the precipitated product of Salmeterol xinafoate and fluticasone propionate (Figures 4 and 5).

Mixing with fine particle excipients after spray drying is difficult and does not give a comparable result with respect to the FPF. The addition of fine particles such as spray dried L-leucine, which could work as dispersion enhancer, has been tested for the co-precipitated product, but was shown to have an only limited effect [3].

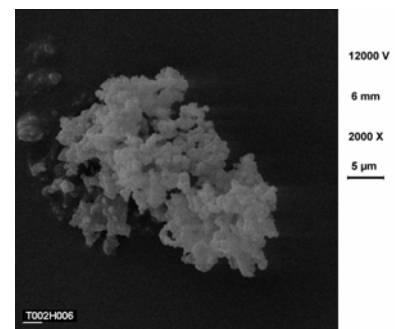
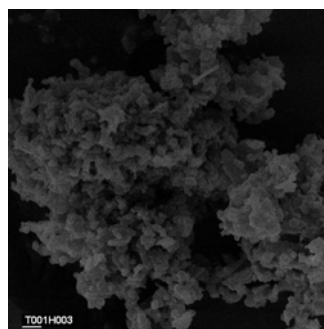
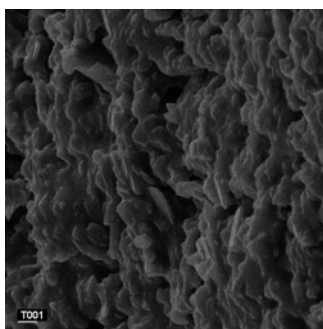


Figure 2: SEM micrographs of batches produced by wet milling with increasing amounts of HPMC in the dispersion media resulting in rising amounts of small spheres of HPMC acting as dispersion modifier in the dry product (left 0% HPMC, middle 0.03% HPMC, right 0.06% HPMC)

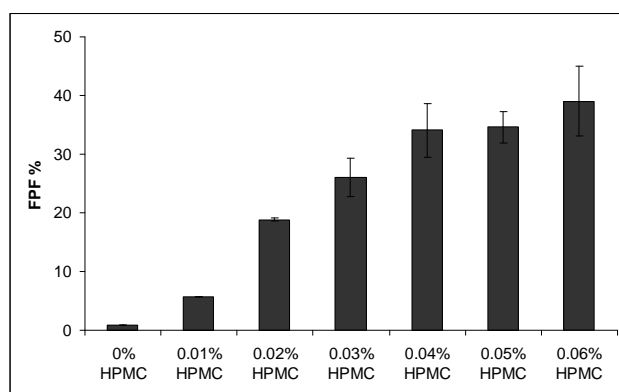


Figure 3: Fine particle fractions of formulations produced by wet milling with different concentrations of HPMC in the dispersion media

product resulting in a difference of filling volume for a single dose in the capsule. This is due to the different particle morphology of the drug particles in dependence on the manufacturing process and may also effect the dispersibility and with this the FPF.

If the deposition profile of the formulations is analysed for each individual drug substance, it can be shown, that both APIs are evenly distributed on the stages of the NGI. This is especially true for the co-precipitated formulations, where both APIs are processed together resulting in a combined product, with which both drugs are

This might be due to a high cohesiveness of the spray dried product consisting of evenly composed drug particles, which minimises the likelihood of separation and subsequent positioning of excipient particles reducing particle-to-particle contact during mixing.

Co-milling of substances is a common procedure for the formation of co-crystals in the dry state [4]. Here, a wet co-milling process is used for the formation of a combined formulation of SX and FP. The advantage of co-milling in comparison to a precipitation process is that the drug substance remains solid and with this might undergo fewer changes due to polymorphism and stability. The bulk density of the resulting dry powders is remarkably different with a median density of 0.03 g/cm<sup>3</sup> for the co-precipitated product and a median density of 0.17 g/cm<sup>3</sup> for the co-milled

co-distributed in the respiratory tract, but the co-milled formulations also show a good co-deposition as shown in Figure 6. As the formulations have been developed for pulmonary application, all excipients should show a good tolerability. With respect to polysorbate additives, this has been proven for many routes of application including the parenteral route [5] and there are inhalation products on the market using polysorbate 20 or polysorbate 80 as excipient. HPMC has been accounted for GRAS (generally recognised as safe) by the FDA and has already proven to be harmless when administered to the lung in animal studies [6].

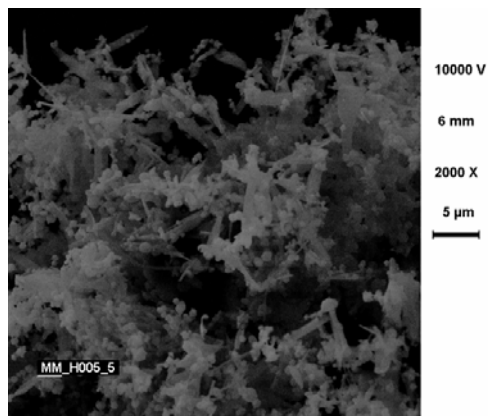


Figure 4:  
SEM micrograph of a formulation produced by co-precipitation comprising small spheres of HPMC acting as dispersion modifier (0.05% HPMC in dispersion media)

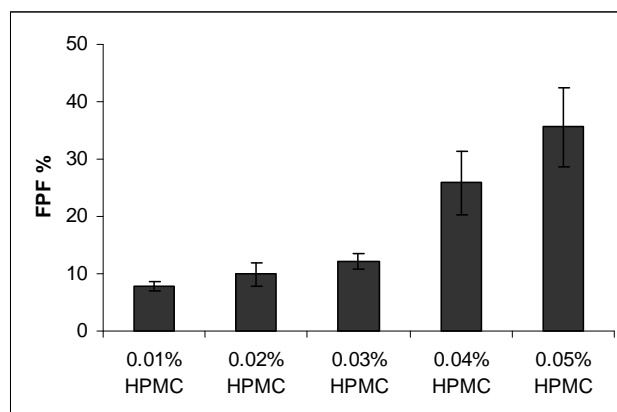


Figure 5:  
FPF of formulations produced by co-precipitation with different concentrations of HPMC in the dispersion media

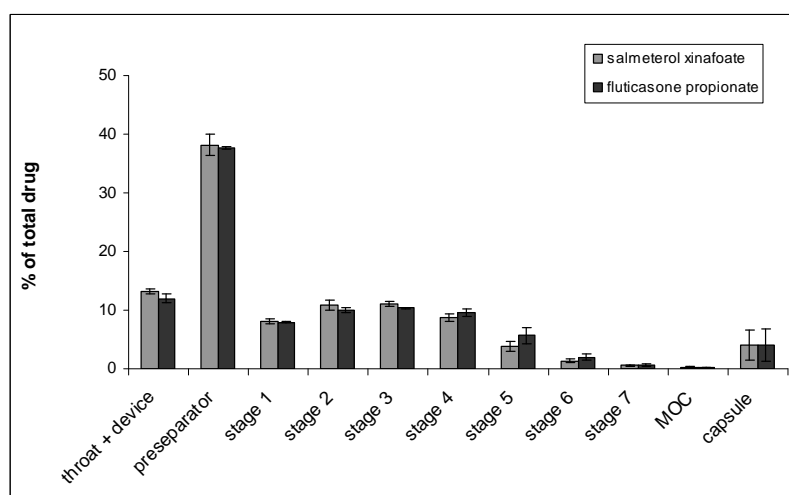


Figure 6:  
Deposition profile in the NGI of a formulation produced by co-milling with a resulting FPF of 35%. Both APIs are evenly distributed on every stage indicating a good co-formulation

### Conclusion

With the in-situ formed dispersion modifying HPMC spheres, an easy and reproducible possibility to improve the aerodynamic properties of dry powder formulations is introduced. Especially if a spray drying step is included in the manufacturing procedure anyway, the addition of a soluble excipient performing as dispersion modifier after drying is a simple option to enhance the respirable fraction of the product.

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