Paddle over disk as a dissolution test for orally inhaled drugs: discriminating composite from carrier-based formulations

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Summary

Dissolution testing can be a way of discriminating between different pharmaceutical formulations. Even though dissolution testing of oral drugs is widespread and routinely used for both quality control and R&D to identify the influence of critical manufacturing variables on dissolution profiles and for in vitro-in vivo correlations, none of the standard USP apparatus are readily adapted for investigating inhaled products. Son et al. developed a potential standardized test method, the paddle over disk apparatus, which can be conjugated with the Next Generation Impactor (NGI) allowing for a dissolution profile assessment of a respirable fraction of the aerosol. The aim of this work was to investigate the discriminatory power of the newly developed paddle over disk apparatus when analysing dry powder formulations aimed for pulmonary delivery. The obtained results show that the apparatus can be successfully employed to discriminate between different formulations of dry powders, although further research is required to optimize the parameters used.

Introduction

One of the most important steps with *in vitro* performance testing of inhalation products is the characterization of the delivery of a given API from a specified inhaler using a pharmaceutical impactor/impinger, to estimate the actual dose that can potentially deposit on the target site of the lung. However, aerodynamic characterization does not completely describe the particles behaviour once inhaled. It completely misses the assessment of the drug absorption profile, which depends in great extent on the dissolution of the pharmaceutical dosage form. An ideal dissolution test procedure for inhaled formulations would involve particle classification followed by an evaluation of the dissolution behaviour for the classified drug particles that may deposit at various sites in the respiratory tract.

Although dissolution testing for oral drugs is widespread and routinely used for both quality control and R&D to identify the influence of critical manufacturing parameters on dissolution profiles and for establishing *in vitro-in vivo* correlations, none of the standard USP apparatus 1, 2, 3 and 4 are readily adapted for assessing inhaled products. Few reports of powder or nanoparticle dissolution testing are based on apparatus suited for oral drugs, and studies failed to discriminate between formulations [1,2], as the dry powders are difficult to disperse homogenously and tend to adhere to the walls and paddles. Several authors have attempted to develop systems capable of overcoming the mentioned drawbacks [3-6]. Son *et al.* [7,8] developed a potential standardized test method applicable to various formulations, as a variation of USP Apparatus 2 (paddle), designated paddle over disk apparatus. A stainless steel support disc is placed under the paddle to hold the test article at a precise distance from the bottom edge of the paddle. This method is amenable for inhaled products as particles with a known aerodynamic diameter can be collected using a NGI and can be directly positioned inside the vessel, guaranteeing that the tested powder is within the respirable fraction.

The present work aims to utilize the paddle over disk apparatus to characterize dry powder inhaler (DPI) formulations of composite particles produced by spray drying and blend formulations of active pharmaceutical ingredient (API) and lactose aimed for pulmonary delivery, specifically.

Experimental methods

Aerosol formulation and characterization

To produce two different composite powders, C_1 and C_2, solutions with 2% w/w of solids in a water/ethanol (50/50, % w/w) solvent mixture were prepared, according to Table 1. The powders were spray dried at an outlet temperature (T_{out}) of 95 ºC, a solution feed flow of 7 g/min, atomization pressure of 8 bar and atomization gas flow at 50 mm in the rotameter, using a Büchi model B-290 unit. The inlet temperature of the drying gas was adjusted to obtain the target outlet temperature (T_{out}). The particle size distribution (PSD) of the particles were analysed by laser diffraction (Sympatec). To obtain three different carrier based blend powders, B_1, B_2 and B_3, homogeneous mixtures of 100 g of coarse (SV003) and fine (LH300) lactose with 1% w/w of micronized Fluticasone Propionate (FP) where prepared in a TURBULA® Shaker-Mixer, following geometric dilution of FP. Content of fine excipient in the prepared blends was of 5, 10 and 15% w/w for B_1, B_2 and B_3 respectively. For all formulations (C_1, C_2, B_1, B_2 and B_3), HPMC size #3 capsules were hand filled with a target fill weight of 12.5 mg, with acceptance limits of +/- 0.5 mg. The aerodynamic performance was assessed by NGI. Composite particles were actuated with a Plastiape Monodose inhaler (40L/min at 4 kPa pressure drop) and its deposition profile determined with a gravimetric analysis of collected NGI deposits - gravimetric NGI - (n=3), using one capsule per replicate. Carrier based blend aerodynamic profile was assessed by chemical NGI (n=3) with 10 capsules per replicate, using PowdAir® inhaler (40L/min at 4 kPa pressure drop). Each formulation was also analyzed by scanning electron microscopy (SEM).

Table 1 – Composition of the spray dried solutions.

	C_1 (g)	C_2 (g)
Water/Ethanol (50/50% w/w)	392	392
Trehalose di-hydrated, from Pfanstiehl	6.34	-
Raffinose pentahydrate, from amresco	-	6.34
L-Leucine, from Merck	1.58	1.58
Fluticasone Propionate	0.08	0.08

Dissolution profile determination

The DPI formulations were actuated in a gravimetric NGI following the conditions previously described in order to obtain particle separation and collect a known amount of API and a powder with a narrow and known aerodynamic particle size distribution. The collection was conducted by placing a dissolution cup assembled with an impactor insert in stage 4 of the NGI (**Error! Reference source not found.**, left) - stage with greater amount of powder – and actuating 3 and 10 capsules for composite and blend formulations, respectively. Following the impaction, the stainless steel collector was removed from the NGI dissolution cup and covered with a pre-soaked polycarbonate membrane (Copley Scientific), which was sealed in place with the securing ring of the membrane holder, to be finally placed inside a dissolution vessel (**Error! Reference source not found.**, right). To assess the dissolution profiles, a Tablet Dissolution Tester DIS 6000 from Copley Scientific was employed as USP apparatus 2 with and without a membrane holder. The apparatus consisted of vessels containing 350 mL of dissolution medium (0.01 M phosphate buffer saline from Sigma-Aldrich, with a pH of 7,4, containing 0.4% w/v of an anionic surfactant), maintained at 32 ± 0.5 ºC and stirred with paddles at 75 rpm, placed 25 ± 2 mm above the bottom of the vessel or the membrane holder. The described disposition allows for a complete submersion of the paddle, securing an effective drug dispersion after membrane release and continuous circulation of the medium in the vessel. For the collected powder, the membrane holder was placed carefully, as its orientation may influence the dissolution rate, and pre-warmed medium was added to the vessel. The dissolution profile of the hand filled capsules was also assessed by opening and pouring a pre-punched capsule (12.5 ± 0.5 mg) into a pre-warmed medium. Aliquots of 3 mL of dissolution medium were withdraw manually, filtrated and centrifuged at 120 000 rpm for 3 min, then replaced with pre-warmed medium. All experiments were done in duplicate and concentrations were determined using a Waters HPLC system with UV detection.

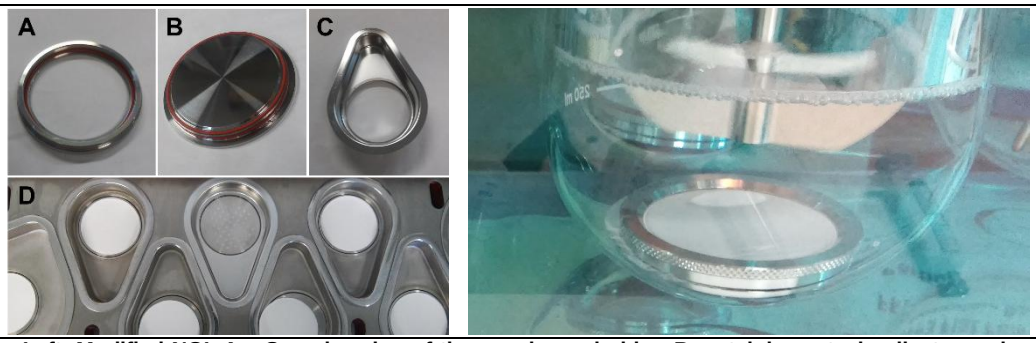

Figure 1 – Left: Modified NGI. A – Securing ring of the membrane holder; B – stainless steel collector and membrane holder; C – Dissolution cup; D – NGI with dissolution cup after actuation. Right: Dissolution vessel with membrane holder.

Results and Discussion

The PSD analysis of the composite aerosols C_1 and C_2 showed a similar particle size distribution, with 90% of particles having a diameter below 3.3 and 3.2 µm, and a span of 2.0 and 2.1, respectively. Additionally, the SEM analysis (Figure 2, G-J) show a similar morphology for these formulations, as well as an alike particle agglomeration for the produced blends (Figure 2, A-F) – smaller agglomerates of fines (≈10 µm), and fines attached to the carrier lactose particles. The aerodynamic performance of the formulations is illustrated in Figure 3. Blends show an increase in fine particle fraction (FPF) with the percentage of fines, and composite particles present a similar FPF. Plate 4 was selected for powder collection for all formulations as it consistently displayed the maximum deposition of API and the collected particles are within the respirable fraction (aerodynamic cutpoint, $D_{50} \approx 3.5 < 5$ µm). Considering the amount of FP collected in stage 4 for each formulation, the number of actuations was defined in order to obtain approximately 100 µg of FP in stage 4 (Table 2).

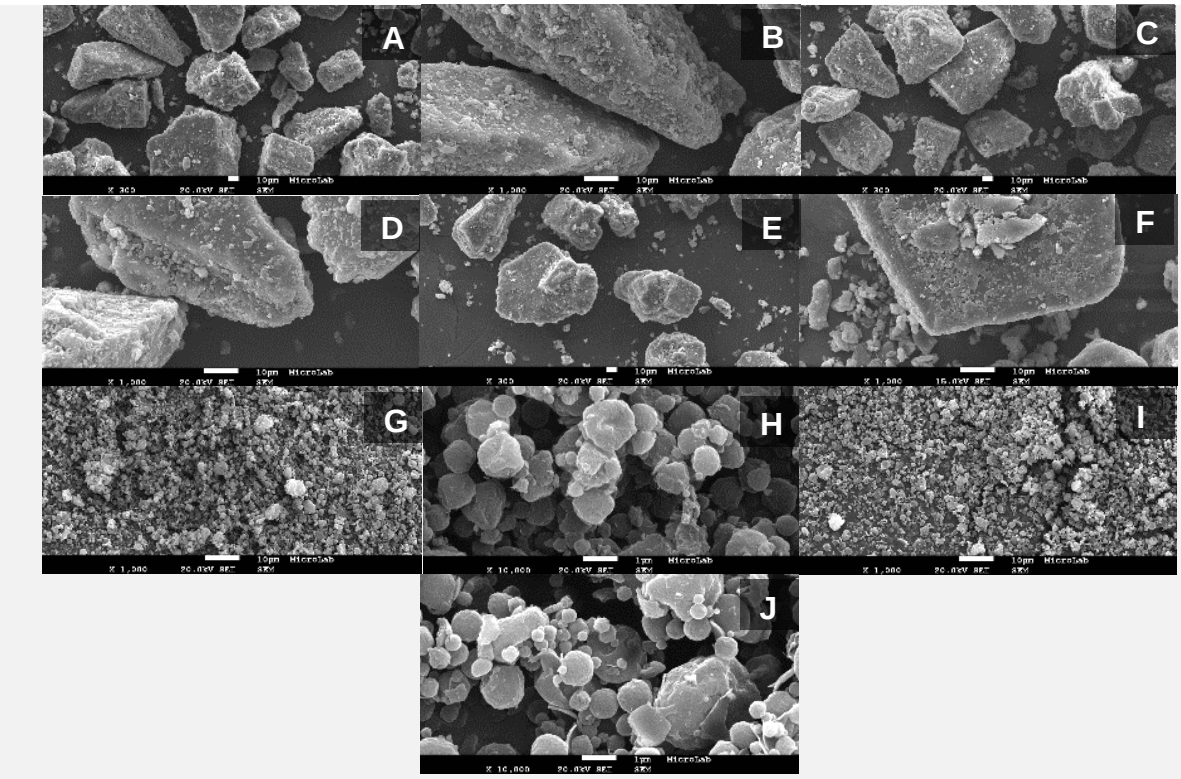

Figure 2 – SEM micrographs for blends with 5, 10 and 15% fines, B_1 (A and B), B_2 (C and D) and B_3 (E and F), x300 and x1000 respectively; and for composites containing trehalose and raffinose, C_1 (G and H) and C_2 (I and J), x1000 and x 10 000 respectively; at 20 kV.

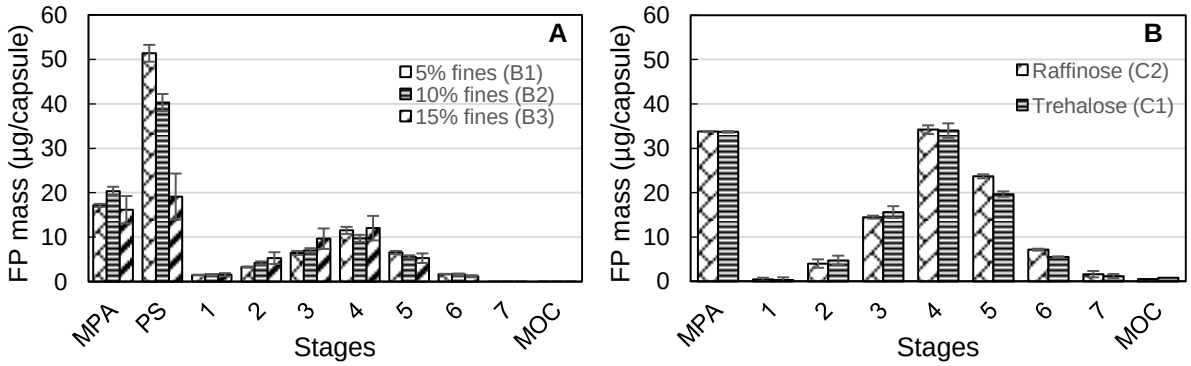

Figure 3 – API deposition at dose plate for blends B_1, B_2 and B_3 (A) after 3 repetitions of 10 actuations at 40 L/min using PowdAir inhaler; for composites C_1 and C_2 (B) after 3 repetitions of one actuation at 40 L/min using Plastiape Monodose inhaler. MPA is mouth piece adapter and induction port; PS is pre-separator and MOC is micro-orifice collector.

Table 2 – Amount of API loaded in plate 4 in one actuation (m_{stage4}) and respective amount (m_{disk}) after $N_{actuations}$, in µg.

Disk	m_{stage4} (µg)	$N_{actuations}$	m_{disk} (µg)
C_1	34.0	3	102.0
C_2	34.2	3	102.6
B_1	11.495	10	115.0
B_2	9.708	10	97.1
B_3	9.940	10	99.4

Following dose collection, the release profiles of the collected powders was assessed (Figure 4, left). To better compare the diffusion phenomenon through the membrane in each formulation, the dissolution profile of capsules containing 12.5 mg of powder was also assessed (Figure 4, right). The paddle over disk results do not show a meaningful discrimination between the two composite formulations when calculating the similarity factor, f_2=50.5>50, however, it shows an improvement when compared with the capsules' profile obtained with the paddle apparatus, pointing to a possible optimization of the system in order to obtain discrimination. This might be achieved by varying operational parameters such as paddle speed, or changing the dissolution media. A significant difference is observable between the dissolution profiles of the blend formulations. These results might be due to the interaction between the fine particles of lactose and API, as this is the varying factor in the formulations tested, although differences in interaction between fines and carriers are not clearly visible in the SEM micrographs. The influence of fine particles in formulation performance has been largely studied [9] with two hypotheses being prominent in the literature.

The first one states that the fine lactose particles occupy the stronger binding sites of the carrier particles, and the second that the fines form agglomerates with the API and these agglomerates are more easily dispersed and disaggregated. The present results could be a consequence of a particle behaviour described by the second theory: agglomerates of lactose and API may be formed as the percentage of fines increases in the formulation, decreasing the API solubility due to local saturation in FP. Further studies would be required to understand fully dissolution mechanism of these blends. A third difference that can be analysed in the obtained results is the profile variation between composites and blend formulations. Looking at the B_1 profile containing only 5% of fine lactose (Figure 4, right), with apparent similar equilibrium solubility of the composites, it differs mostly on the dissolution rate. This can be explained by the structural state of the particles, as the crystalline state of the API contained in the blends is expected to be more stable than the amorphous state in the composite formulations, which has been known to influence solubility [10].

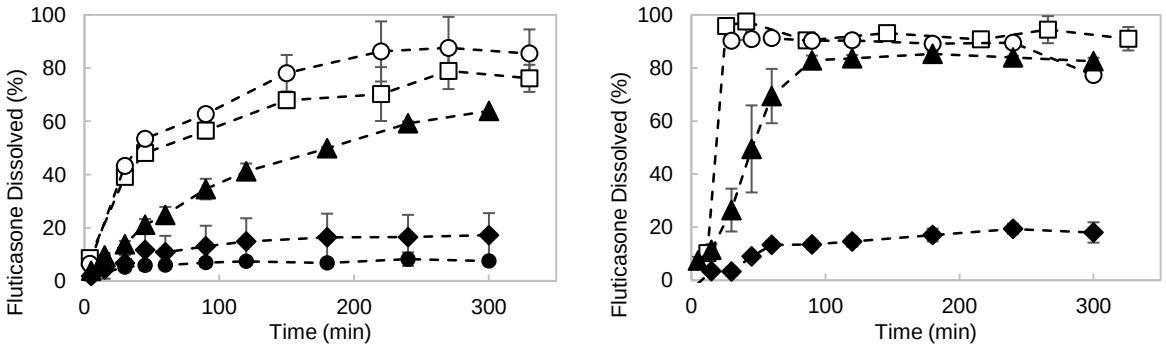

Figure 4 – Left: Dissolution profile in the paddle over disk apparatus of composites C_1 (○) and C_2 (□), and of blends B_1 (▲), B_2 (◆) and B_3 (●); right: dissolution profile in the paddle apparatus of hand filled capsules filled with of composites C_1 (○) and C_2 (□), and of blends B_1 (▲) and B_2 (◆). Each profile is given by two replicates.

Conclusions

The paddle over disk apparatus can be successfully employed to discriminate between different formulations of dry powders, and although the present results do not show the discriminating power regarding composite particles with similar morphology, an improvement was reached when comparing to the paddle apparatus, inspiring a design of experiments to achieve system optimization. The dissolution results of the blend formulations point towards significant differences between formulations with different percentages of fines; however, the exact dissolution mechanism is not yet fully understood and requires further research.

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