

Dissolution Behavior of Inhalable Dry Powder Formulations: Unravelling the Influence of Solubility Across IBCS Classes

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Summary

Dissolution of orally inhaled dry powder products (OIDPs) plays a central role in determining the rate and extent of drug absorption within the respiratory tract. It is particularly critical for poorly water-soluble compounds, where dissolution can be the rate-limiting step for pulmonary absorption. Accurate characterization of dissolution behaviour is essential for optimizing formulation performance and ensuring therapeutic efficacy and consistency. Dissolution testing methodologies were employed to investigate the dissolution behaviour of the fine particle fraction of two inhaled Biopharmaceutics Classification System (iBCS) class Active Pharmaceutical Ingredients (APIs), fluticasone furoate (FF) and salmeterol (SA). A Fast-Screening Impactor (FSI) and Glass Twin Impinger (GTI) were used to collect fine particle fractions and dissolution profiling was performed using the Paddle Over Disk (POD) USP Apparatus II and the Transwell® system. The results demonstrate the impact of API solubility on dissolution performance. SA, a highly soluble drug, was fully dissolved in 5 minutes. In contrast, FF exhibited significantly lower solubility, reaching 92% after 12 hours. The POD system showed lower variability compared to Transwell®, likely due to amount of recovered API, media volume, and setup complexity. However, both methods met criteria and produced comparable dissolution profiles, nearly reaching FF's maximum solubility (1 µg/mL) in 8 hours. This study demonstrated consistent dissolution profiles across two distinct apparatuses, confirming the method's robustness and reliability by reflecting the formulation's intrinsic dissolution behavior under defined conditions, independent of apparatus effects. Comparative studies as these are critical for moving toward regulatory acceptance of dissolution methods as drug development tools.

Key Message

Understanding the dissolution behaviour of inhaled drugs is crucial for optimizing formulation and therapeutic performance. This study shows that solubility significantly impacts dissolution, with POD and Transwell® offering reliable assessment tools. Tunable formulation attributes aligned with drug delivery needs can better support *in vivo* predictability, especially for poorly soluble compounds.

Introduction

Drug absorption and bioavailability of OIDPs depends on the dissolution of their fine particle fraction in the fluid lung epithelial lining fluid and is influenced by formulation properties beyond aerodynamic particle size distribution (aPSD) [1]. Even with similar aPSDs, variations in excipients or manufacturing can affect critical quality attributes such as porosity, wettability, and solubility. Unlike oral dosage forms, no standardized methods exist for OIDP dissolution testing. This work aimed to investigate two approaches to predict the dissolution of OIDPs, using formulation fine particle fractions as lung-representative samples for FF and SA, which are model APIs in the inhalation field with different solubilities. The methods include: 1) fine particle fraction collection via FSI followed by POD USP apparatus II, and 2) lung fraction collection using Transwell® inserts incorporated in a GTI setup, for quality control dissolution test and biorelevant dissolution purpose, respectively (Figure 1) [2,3]. A novel High Performance Liquid Chromatography (HPLC) with a single quadrupole mass detector (QDa)-based method, was also implemented for API recovery from low-dose dissolution media [4].

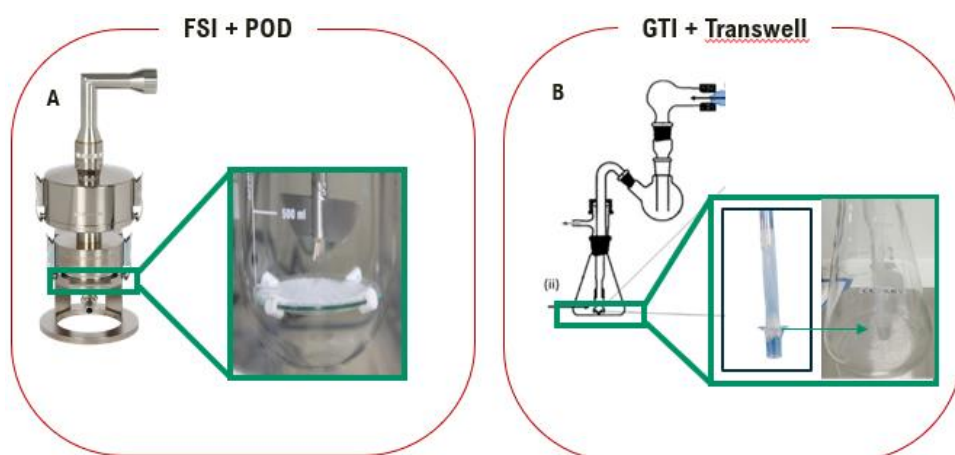


Figure 1 - A) Fast-Screening Impactor (FSI) with Paddle Over Disk (POD) USP apparatus II; B) Glass Twin Impinger (GTI) with Transwell®.

Materials and Methods

FF and SA were produced at Hovione FarmaCiência. LactoHale 100, LactoHale 230 and SV003 were purchase from DFE Pharma. Micronized FF was mixed at a concentration of 20% w/w with a 90:10 blend of LactoHale 100 (coarse) and LactoHale 230 (fine) to create a model dry powder inhaler (DPI). Micronized salmeterol (SA) was formulated at 15% w/w with 85:15 blend of SV003 (coarse) and Lactohale LH230 (fine). Vcaps capsules size 3 were filled with 20mg of powder for both formulations.

For dissolution purposes, one capsule of each formulation was placed into RS01 Plastiapipe 65L/min and actuated during 4 seconds for FSI and 5 seconds for GTI [2]. Before the actuation, both systems were properly assembled, and the flow was adjusted for 60 ± 5 L/min. After the actuation, the filters were collected from the FSI, placed on the dissolution setup and then in the USP II apparatus glass vessels. For GTI, the Transwell® were placed on a 24-well plate in a rotating oven. At each timepoint, 600 μ L of dissolution medium was removed from the basal side and replaced with the same volume of pre-heated fresh medium. Table 1 shows the dissolution conditions for both strategies. All the experiments were carried out in triplicate.

Table 1 - Dissolution conditions for Paddle Over Disk and Transwell®.

	Paddle Over Disk	Transwell®
Dissolution medium	Phosphate Buffer with 0.2% Tween 80	
Agitation speed	100 rpm	
Volume of dissolution medium	300 mL	100 μ L in the apical compartment 600 μ L in the basal compartment
Temperature of dissolution medium	$37.5 \text{ }^{\circ}\text{C} \pm 0.5 \text{ }^{\circ}\text{C}$	

Each API was also dissolved individually under the conditions described in Table 1 to determine its maximum solubility. Additionally, in a separate experiment, the API content from both FSI and GTI was recovered to assess the Fine Particle Dose.

Drug quantification was performed using High-Performance Liquid Chromatography with QDa and PDA detectors to ensure accurate API quantification above 0.2 μ g. An Acquity UPLC BEH C18 column was used, at 35 $^{\circ}\text{C}$ column temperature, 8 $^{\circ}\text{C}$ auto sampler temperature and 0.4mL/min of flow rate, with QDa detector acquired in positive SIM mode for a m/z of 539.00 Da for fluticasone furoate and PDA detector acquired at 240 nm for Salmeterol.

Results and Discussion

The POD system demonstrated lower variability across three replicate runs, with relative standard deviations (%RSD) ranging from 2% to 14%, compared to 24% to 30% observed with the Transwell® system (Figure 2). The higher variability in the Transwell® setup may be attributed to several factors, including the low quantities of API quantified in the Transwell® (0.2–0.8 μ g FF), the limited dissolution volume in the basal compartment (600 μ L), and the overall complexity of assembling the aerodynamic

performance and dissolution apparatuses, which could result in sample losses and impact repeatability. Furthermore, the GTI cut-off is 6.4 μm compared to 5 μm with the FSI. A slightly higher cut-off can lead to a more varied and higher PSD at the deposition site, increasing dissolution complexity and potentially contributing to inter-replicate variability. Despite the observed variability, the results from both methods remained within the predefined internal acceptance criteria established from prior studies. For the POD system, the %RSD at the first time point was required to be $\leq 20\%$, with all subsequent time points $\leq 10\%$. For the Transwell® system, an RSD of $\leq 30\%$ was considered acceptable across all time points. Nevertheless, the overall dissolution profiles obtained from both methods were comparable, with both almost achieving the FF solubility limit in PBS with 0.2% Tween 80 after 8h of dissolution (1 $\mu\text{g/mL}$).

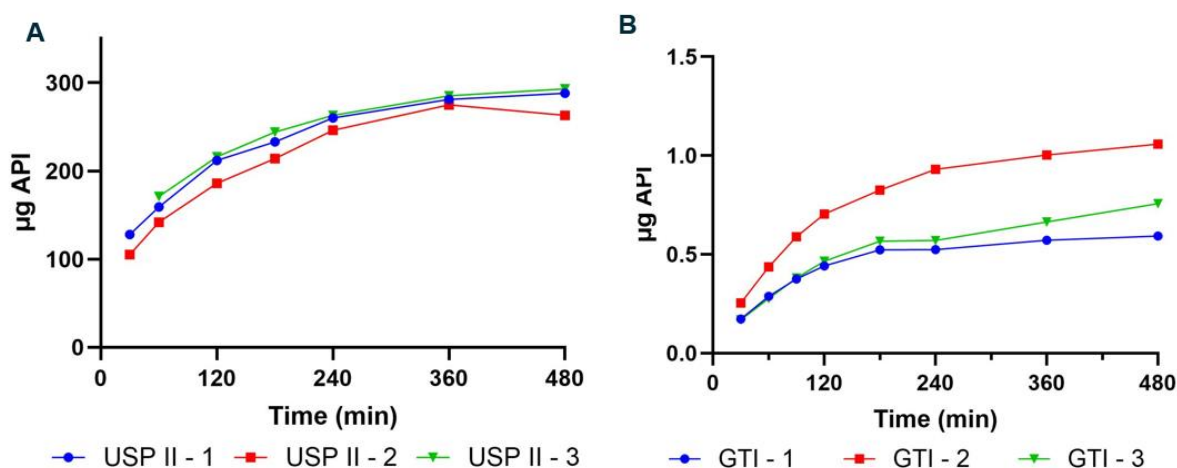


Figure 2 – Dissolution profile of a carrier-based fluticasone furoate (FF) formulation with 20% drug load using Paddle Over Disk (POD) USP II (A) and Transwell® inserts (B). FF solubility in the dissolution conditions is 1 $\mu\text{g/mL}$, establishing the plateau of the dissolution profile.

Figure 3 shows an overlay of the normalized %total dissolved FF vs time.

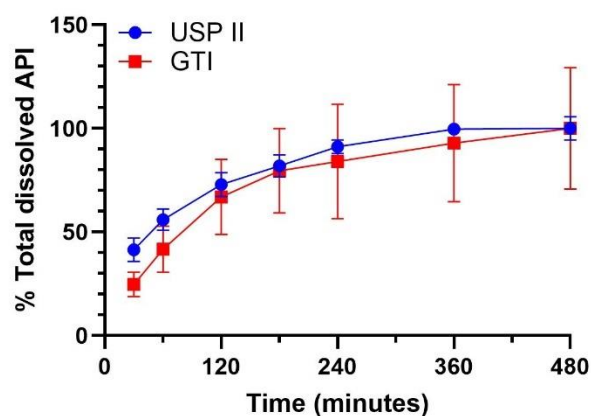


Figure 3 – % of FF dissolved using Paddle Over Disk (POD) USP II (blue) and Transwell® inserts (red) vs time. Each data point represents the mean percentage of drug dissolved at each sampling time point. Error bars indicate the standard deviation (SD) of the measurements. The n number corresponds to the number of replicate samples tested under the same dissolution conditions (e.g., $n = 3$).

As anticipated, the dissolution of crystalline FF, a poorly soluble compound classified as an iBCS class II API, was notably slow. Less than 50% of the available drug was dissolved at the 60-minute time point, with dissolution exceeding 80% only after approximately 6 hours. This slow dissolution rate is characteristic of low aqueous solubility APIs and suggests that dissolution could be a rate-limiting step in pulmonary absorption [3]. A prolonged dissolution profile could support sustained drug release within the lung, potentially contributing to longer local retention and extended pharmacological activity. The results demonstrated that both dissolution systems were robust when evaluating poorly soluble drug products, capable of quantifying very low API amounts ($\sim 0.2 \mu\text{g}$ FF) in a complex dissolution medium. This sensitivity was achieved through the use of a QDa detector, as shown in Figure 4, thereby avoiding the need for more complex analytical approaches.

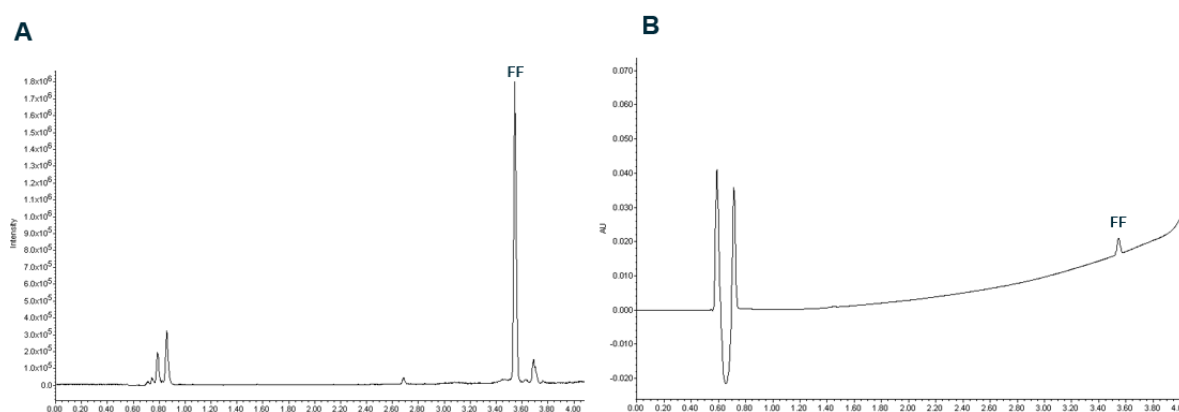


Figure 4 – Chromatogram of Fluticasone Furoate (FF) using QDa detector (A) and PDA detector (B), at 0.4 µg/mL.

To evaluate the dissolution profile of APIs from different iBSC classes, a formulation containing 15% SA was tested using both FSI and POD methods under the same conditions applied for FF (as outlined in Table 1). Table 2 presents a comparison of the two APIs. As expected for a highly soluble drug, SA completely dissolved from the FSI filter within 5 minutes. Furthermore, the dissolution medium effectively solubilized the entire SA content, yielding 1046 µg, comparable to the 1019 µg recovered using the diluent in the HPLC method. In contrast, only about half of the FF API was recovered from the filter using the same dissolution medium (310 µg), while the HPLC diluent yielded 746 µg. Moreover, even after 12 hours, only 92% of FF had dissolved, highlighting its limited solubility under these conditions.

Table 2- Fluticasone Furoate (FF) and salmeterol (SA) Fine Particle Dose and dissolution results.

	API quantification in FSI filter (µg)	API dissolved in dissolution medium (µg)	Timepoint for maximum solubility (min)	API dissolved in the last timepoint (%)
FF	746 (RSD=9%)	310 (RSD=5%)	1440	92
SA	1019 (RSD=14%)	1046 (RSD=6%)	5	101

Conclusion

POD and Transwell® systems are effective tools for assessing the dissolution of OIDPs. In this study, the dissolution profile of FF was examined under comparable dissolution conditions, including the type, volume, temperature and rotation speed of the dissolution medium. The findings indicate that the POD system can be applied for quality control testing, while the Transwell® holds potential for future biorelevant testing, where composition of alveolar and bronchial lung fluids and mucus need to be replicated. Overall, the differences observed in dissolution profiles emphasized the need for tailored formulation strategies based on the physicochemical properties of each API. Such data are essential not only for understanding *in vivo* performance but also for guiding formulation optimization and regulatory evaluation of inhaled products. These findings highlight that a clear understanding of dissolution behavior can help to adapt formulations to the intended therapeutic goals of the OIDP, especially for inhaled corticosteroids like FF, where a balance between onset, duration, and local *versus* systemic exposure is critical for clinical performance.

References

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