

Potential of the *in vitro* dissolution method DissolvIt® to predict pharmacokinetic outcomes

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Conclusion

Dissolution and absorption data generated in the DissolvIt *in vitro* dissolution method correlates well with lung specific absorption data generated in the *ex vivo* model isolated perfused and ventilated rat lung (IPL), for both fast-dissolving active pharmaceutical ingredient (API), salmeterol (Sal), and the slow dissolving API, fluticasone propionate (FP). DissolvIt FP data were also used for physiologically based biopharmaceutical modelling (PBBM), and the calculated plasma-time profile predicted the observed clinical plasma-time curve which indicates an *in vitro-in vivo* relationship (IVIVR) of DissolvIt.

Background

A general goal within inhalation research is to establish an *in vitro* dissolution method that can predict pharmacokinetic (PK) outcomes of inhaled APIs. DissolvIt was previously developed with the aim to physiologically resemble the airways in design and generate more clinically representative data, such as concentration-time graphs that describe maximum plasma concentration (C_{max}) and time to maximum concentration (T_{max}) of the inhaled API obtained from PK measurements (1). Here, DissolvIt dissolution data of FP and Sal was directly compared with lung-specific PK data from the rat isolated perfused lung (IPL). Furthermore, the DissolvIt FP data were used for PBBM in order to evaluate its potential IVIVR.

Experimental Methods

Seretide Evohaler pressurized metered dose inhaler (pMDI) (WEP Clinical, USA and Apoteket, Sweden) was used as a test formulation. Each dose contains 250 µg FP and 25 µg Sal. The PreciseInhale® aerosol generator (Inhalation Sciences, Sweden) was used to aerosolize the test material and precisely dose the following different objects: glass cover slips for *in vitro* dissolution testing in DissolvIt (1) (Figure 1), an IPL of the rat or humans (2),(3).

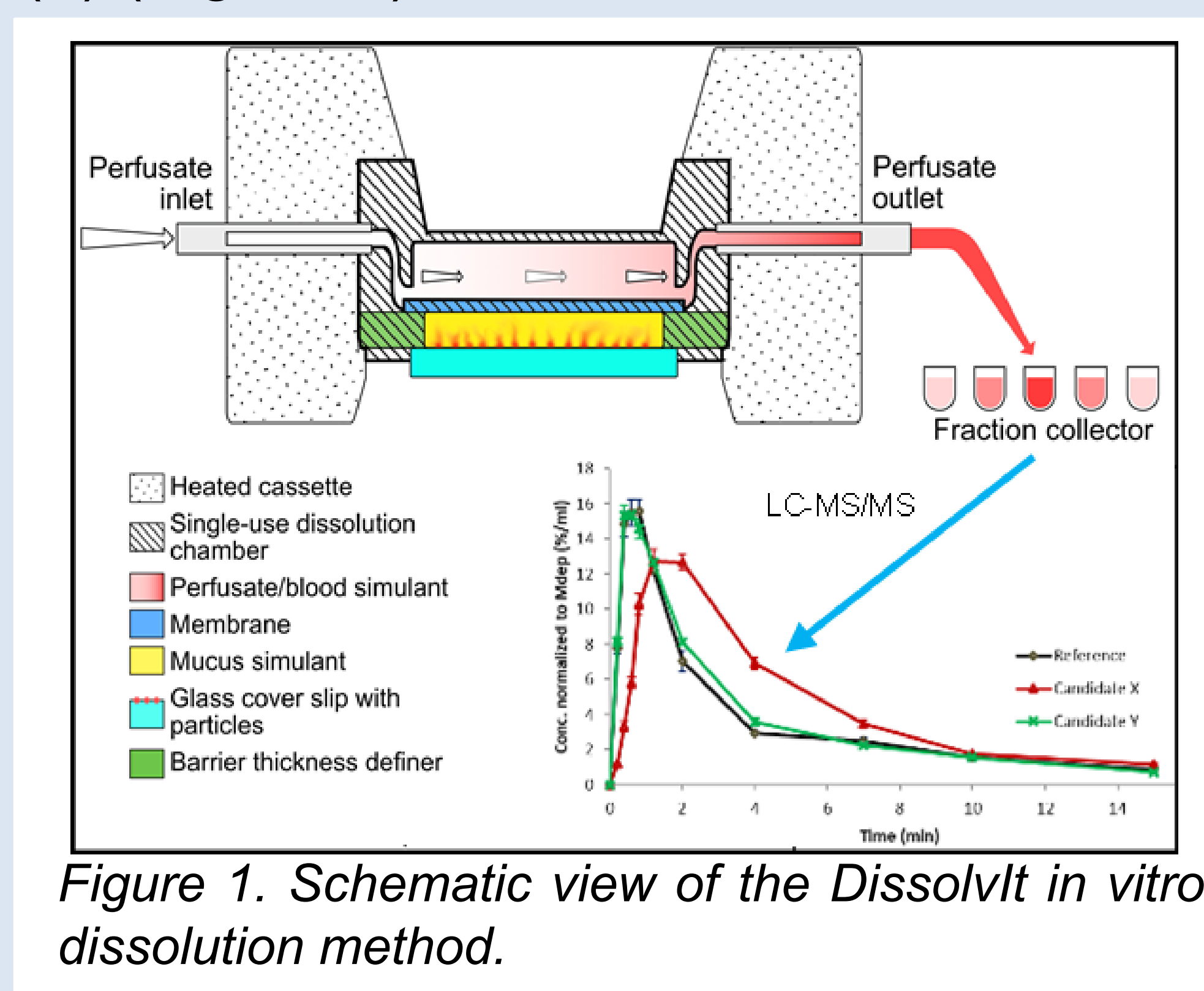


Figure 1. Schematic view of the DissolvIt *in vitro* dissolution method.

Mimetikos Preludium™ (Emmace, Sweden) was recently adapted to include DissolvIt by augmenting and modifying the system of differential equations that describes this process (4). The PBBM used was Preludium (v1.2.1.1), parametrized for FP as previously described (5). Together with dose deposition data from the literature, the FP dissolution data generated in DissolvIt for Seretide

Evohaler 250/25 pMDI were used for PBBM of a clinical FP plasma concentration-time profile. This simulated profile was compared with observed clinical data in order to evaluate the predictive potential of DissolvIt (3).

Results

It is clear from Figure 2A and 2B that the dissolution /absorption curves for both FP and Sal look very similar in shape between the DissolvIt (*in vitro*) and IPL (*ex vivo*) experiments. The percent dissolved and absorbed API of the deposited dose is also shown to be very similar in DissolvIt and IPL after 2 h for both FP (11% in DissolvIt, 14% in IPL) and Sal (75% in DissolvIt, 71% in IPL) (Figure 2C). *In vitro-ex vivo* relationship (IVEVR) is demonstrated for both Sal and FP.

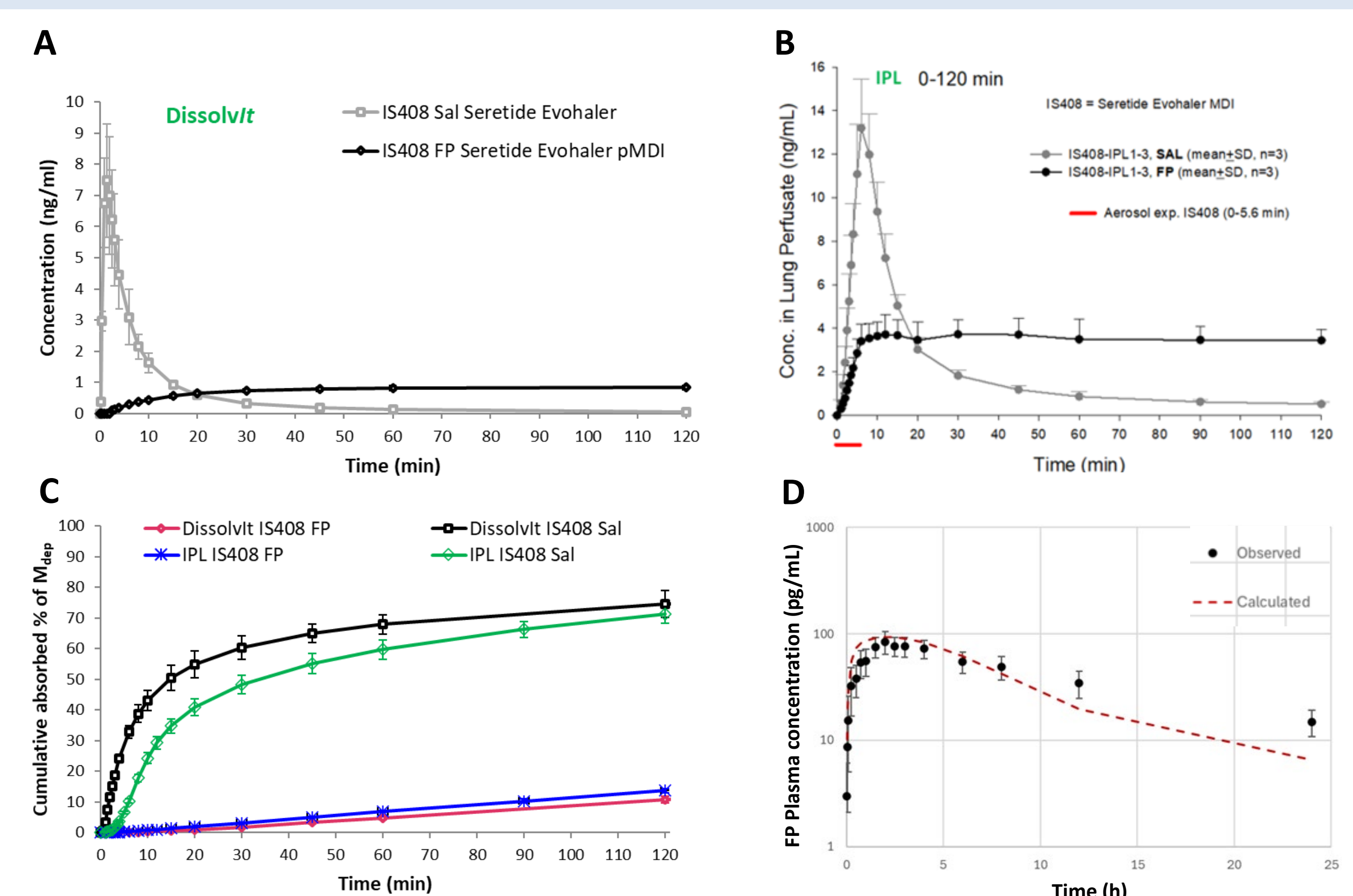


Figure 2. Dissolution and absorption profiles of Sal and FP in (A) DissolvIt and (B) IPL. (C) Cumulative dissolution graphs of Sal and FP in DissolvIt and IPL. All curves in A-C are based on mean values $\pm$ standard deviation (SD), N=3. (D) PBB modelled DissolvIt data of FP in Seretide Evohaler (calculated) compared to observed clinical data for FP in the same product (observed). The observed data points are mean values $\pm$ SD, N=12.

The comparison of the model-simulated concentration of FP in plasma (red dashed line in Figure 2D), with observed clinical data (black dots in Figure 2D) shows that the DissolvIt dissolution method correctly identified a clinically relevant dissolution rate of FP in Seretide Evohaler 250/25.

References

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