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An Optimized Dissolution System for Orally Inhaled Drug Products: Development and Validation

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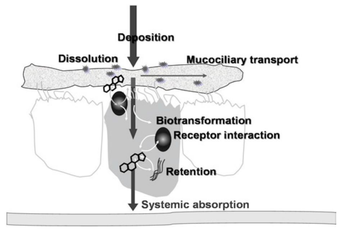
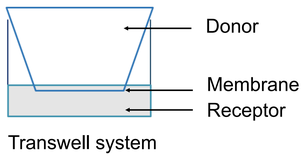
INTRODUCTION

The establishment of an *in vitro in vivo* correlation (IVIVC) of orally inhaled products (OIPs) is challenging because of the complex fate of these drugs in the lungs after inhalation.





Transwell system

In the present study, an *in vitro* dissolution test was developed that could be used as a tool for understanding the absorption behavior of OIPs *in vivo*. The goal was to develop a robust and sensitive dissolution test method and use the profiles generated from this test to establish an IVIVC.

This dissolution test method, after optimization, could be used as a pharmaceutical development tool to assess bioequivalence, and also for developing formulations of OIPs using a quality-by-design approach.

AIMS AND OBJECTIVES

Aim 1
Optimize the parameters of the dissolution test

- **Membrane**
  - Should allow fast diffusion.
- **Surfactant**
  - Increase solubility of hydrophobic drugs.
  - Sensitive to differences in formulation parameters.
- **Sample deposition method**
  - Size differentiated fractions (NGI).
  - Respirable fraction (mouth - throat model).
  - Emitted dose.

Aim 2
Use the optimized test to compare and contrast inhaled formulations

- **Commercially available**
  - MDIs and DPIs of Fluticasone Propionate, Budesonide and other ICS.
- **Custom-made MDIs**
  - Mometasone furoate formulations differing in particle sizes and excipient concentrations.
- **Custom-made DPIs**
  - Fluticasone propionate formulations differing in particle sizes.

Methods for comparison of profiles
- Model dependent
- Model independent

Aim 3
Establish an *in vitro in vivo* correlation (IVIVC)

- **Compare with pharmacokinetic data**
  - Obtained from literature/in house clinical studies

METHODS

A Transwell® system was used for the dissolution test[1].

0.5% SDS in water was used to optimize the membrane. For all other experiments, 0.5% Tween in water was used. Stirring was incorporated in the receptor compartment of the Transwell. Drug samples were deposited on a GF/C glass microfiber filter.

Two types of inhaler fractions were evaluated:

1) The single size fractions of various aerodynamic sizes, ranging from 6.4 micron to 0.84 micron, of fluticasone propionate (FP) metered dose inhaler (MDI) (Flovent® HFA) and FP dry powder inhaler (DPI) (Flovent® Diskus), collected on different stages of the Next Generation Impactor (NGI) were used to evaluate the system and optimize the conditions of the experiment.

2) The ex-throat fractions of Flovent as well, collected on a filter paper using a realistic mouth -throat model, were used to compare different formulations and doses of inhaled drugs. Flovent Diskus and MDI as well as Pulmicort Turbuhaler®, containing Budesonide, were used for this analysis.

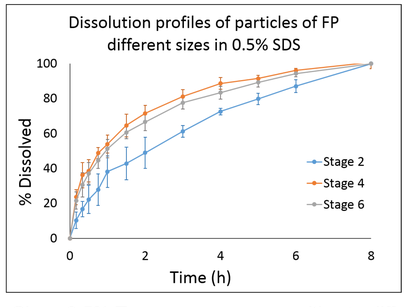
The *in vitro* mean dissolution time (MDT) was compared with pulmonary mean absorption time (MAT) *in vivo*.

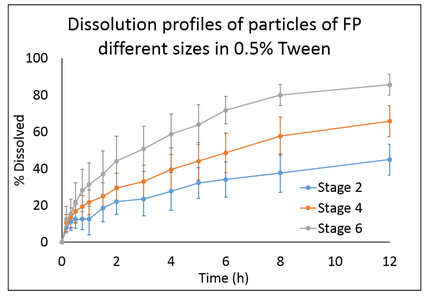
RESULTS

Membrane - We observed the fastest diffusion of dissolved FP when an 8 micron pore size polycarbonate membrane was used, with a stirrer in the receptor compartment.

Surfactant - The importance of incorporating a surfactant in the dissolution medium was demonstrated by comparing the MDT to MAT of inhaled corticosteroids with different lipophilicities in different media. Solubility of the inhaled corticosteroids was tested in four different surfactant containing media, as well as water to systematically select a surfactant.

ICS	Log P [35]	Solubility in PBS (µg/ml)	Solubility in surfactant at 37°C (µg/ml)		MDT in setup B (h)	MAT (h)
			0.5% SDS/ PBS	0.5% Tween/ water		
Ciclesonide	4.08 -5.32	0.09	300	55.9	1.2 ± 0.2	≈ 0.4[2]
Fluticasone propionate	3.69-3.72	0.14	20 ± 3	12.34	5 ± 1.2	5-7[3]
Budesonide	2.42-2.73	23 - 42	470	111	0.6 ± 0.1	1 (0.3 – 1.8)[4]





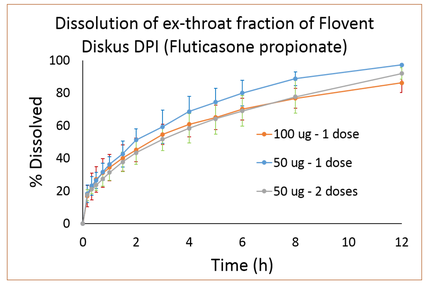
Since 0.5% Tween was more sensitive to differences in particle sizes, it was used in all further experiments.

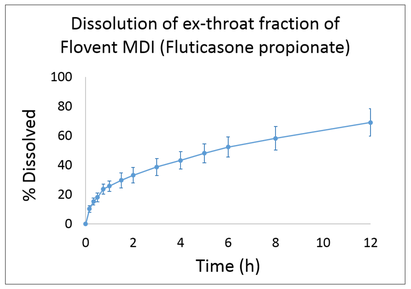
Sample deposition method - For optimization of the dissolution test parameters, single size fractions, deposited using the NGI, were used for simplicity.

The volume of medium in the donor compartment was adjusted to maintain an MDT that was independent of the sample amount, within the range of doses tested.

Once the parameters were optimized, a realistic mouth-throat model was used to deposit the respirable fraction of the inhaled formulation.

Comparison of commercially available inhaled formulations

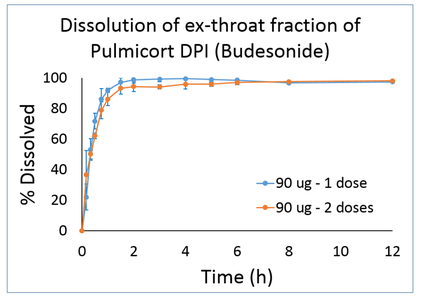




Strength (µg)	Doses	Ex-throat amount (µg)	MDT (h)	MAT in vivo (h)
100	1	22.99	3.1*	5.3 - 6.9[5]
50	1	11.36	3	
50	2	23.61	3.6*	

Strength (µg)	Doses	Ex-throat amount (µg)	MDT (h)	MAT (h)
110	1	38.14	†	7.2[5]

† MDT cannot be calculated as the measured profile has not reached 100% dissolution. Weibull model can potentially be used to predict the complete dissolution profiles (100%) when the complete profile is not measured, so that MDT can be calculated. This method is currently being validated.



Strength (µg)	Doses	Ex-throat amount (µg)	MDT (h)	MAT *in vivo* (h)
90	1	21.07	0.3	0.6[3]
90	2	38.26	0.6	

Methods for comparison of dissolution profiles

- **Model independent methods** - MDT is a useful metric that can be calculated for dissolution profiles that have reached 100% dissolution.
- **Model dependent method** - The parameters of appropriate models, such as the Weibull or first order kinetics model, can be used to compare profiles.

CONCLUSIONS

- **Aim 1** - The parameters of the dissolution test were optimized.
- **Aim 2** - Dissolution rates of different marketed formulations were tested and the effect of dose on dissolution rates was examined.

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