# Optimization of an In Vitro Dissolution Test Method For Inhalation Formulations

Y-J. Son[1], M. Horng[1], M. Copley[2], J. T. McConville[1]

[1]College of Pharmacy, The University of Texas at Austin

[2]Copley Scientific Limited, Colwick, Nottingham, NG4 2JY. U.K.

## OBJECTIVES

- To develop standardized dissolution method for inhalation formulations
- To adapt a USP2 dissolution aparatus for high throughput analysis
- To validate an optimized *in vitro* dissolution method using newly manufactured membrane holder
- To study the broad applicability of this method to a wide range of inhaled pharmaceutical products

## INTRODUCTION

Standardized dissolution test methods allow comparisons between various pharmaceutical dosage forms to be conducted *in vitro*. A predictive estimates of *in vivo* behavior may also be established.

While there are many standardized dissolution test methods for solid dosage forms such as tablets and capsules, there is no applicable standardized method to estimate the dissolution behavior for inhaled pharmaceutical formulations.

For inhalation products, only a fraction of the API emitted from standard delivery devices is usually delivered to target site, due to the fine particle size distribution for most inhaler products (1). Thus, an ideal dissolution test procedure for inhalation formulations would involve particle classification followed by an evaluation of the dissolution behavior of those sorted drug particles that may deposit at various sites in the respiratory tract. However, most existing dissolution procedures on powders have been performed with no aerodynamic classification due to the existing experimental difficulties in dose collection (2-4).

## MATERIALS

- **Active pharmaceutical ingredients (APIs) & excipients**
  - Budesonide : Sigma Chemical Co.( St. Louis, MO)
  - Albuterol Sulfate : Spectrum Chemical Co.(Gardena, CA)
- **DPI devices**
  - PulmicortFlexhaler™180 mcg : AstraZenexa (Wilmington, De) (Lot No: KC 2148, KC 2154, KD 2163)
  - Ventolin®HFA 108mcg: GSK (Research Triangle Park, NC) (Lot No: 3ZP8971)
- **Membrane**
  Polycarbonate membranes (0.05 m): Whatman (Florham Park, NJ)
- **Dissolution tester**
  Hanson SR-8 plus test station: Hanson Co. (Chatsworth, CA)
- **Phamrceutical impactor**
  Next Generation Impactor (NGI) : Copley Scientific Limited (Nottingham, UK)
- **Membrane holder**
  Stainless steel membrane holder : Copley Scientific Limited (Nottingham, UK)

## METHODS

### Dissolution Tester Design

- Paddle (Dissolution apparatus 2, USP)
- Vessel
- Membrane holder

**Schematic diagram of the dissolution apparatus**

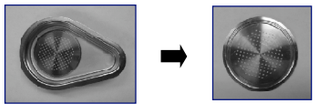
### Dose Collection (Aerodynamic Particle Separation)

**Membrane holder assembly (Copley Scientific)**


**NGI setup with membrane holder**

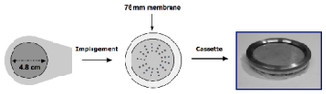
**a) Quick release dose plate**
**b) Dose collection body (stainless steel)**
**c) Sealing ring (stainless steel)**

- The PulmicortFlexhaler™ device, or the Ventolin® HFA device were fired into the NGI.
- Following actuation, the dose collection body was removed from the quick release collection plate.



### Dissolution Test

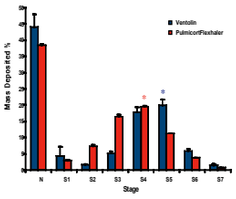
- A pre-soaked membrane was placed onto the top and sealed in place with the top part of the new membrane holder.




- The sealed membrane holder was then placed into each dissolution vessel containing 300 mL of dissolution media.

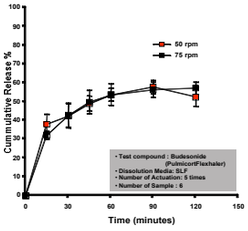
## RESULTS

### Dose Collection for Dissolution Study




- Aerodynamic separation study
- Analyze the amount of API accumulated on each dose-plate
- Dose collection plate 4 and plate 5 were selected for PulmicortFlxhaler™ device and Ventolin® device, respectively as these consistently displayed the maximum deposition

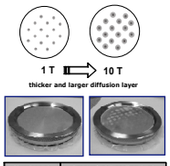
### Rotating Speed



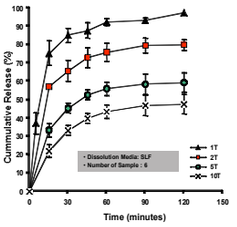

- Data obtained at 75 rpm show less variable release profile
- For the paddle apparatus, 50 rpm is most commonly used, however, a higher paddle speed was required due to the "dead" volume
- An eddy was observed at an agitating speed of 100 rpm

### Amount of Drug Loading

**• PulmocortFlexhaler™ (Budesonide)**




| Number of Actuation (T) | Amount of Loading (㎍) (N=6) |
|---|---|
| 1 | 29.4 ± 5.1 |
| 2 | 55.2 ± 3.8 |
| 5 | 151 ± 12.7 |
| 10 | 224 ± 5.3 |

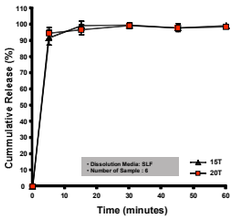



- Thicker, larger and more compressed diffusion layer were created as an actuation time increases
- Multi-layer powder bed is not appropriate for dissolution study because of dry portion inside the powder bed (for hydrophobic APIs)
- Ideally, the device needs to be actuated one time to obtain well dispersed particles in an approximately single layer
- The release amount of budesonide show significant differences
- Variability in release rate increases as diffusion layer increases
- Early time points (0, 5 and 10 minutes) are very useful

**• Ventaline®HFA (Albuterol Sulfate)**

| Number of Actuation (T) | Amount of Loading (㎍) (N=6) |
|---|---|
| 15 | 259.5 ± 42.4 |
| 20 | 320.7 ± 17.7 |

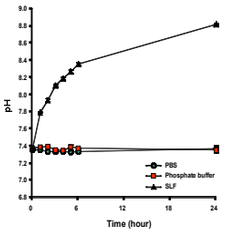
Total amount of loading :
Total released amount of drug + Remaining drug inside the cassette




- Accumulated drugs are immediately dissolved and released
- Amount of loading may not influence the dissolution of hydrophilic APIs
- Early time points (0, 5 minutes) are very important

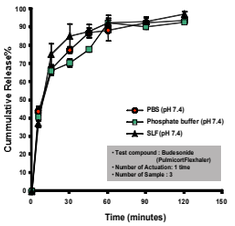
### Dissolution Media Selectioin

**• pH stability of dissolution media**




- The pH of SLF increases from 7.4 to 8.8 for 24 hours without continuous $CO_2$ bubbling.
- Bubbling the solution with 95 % $O_2$ -5 % $CO_2$ to maintain pH at 7.4 (6)
- Not appropriate for routine QC study
- The use of SLF media would not be recommended for evaluating inhalation dosage forms that show pH-dependency or sustained-release manner in dissolution profile

**• Release profiles in different media**



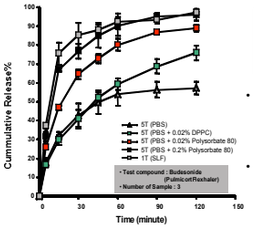

- Similarity factor

| Comparison | PBS | Phosphate buffer |
|---|---|---|
| $f_2$ | 63.4 | 51.6 |

◦ Reference : SLF

- The dissolution profiles from three media were similar
- Either phosphate buffer, or PBS could be used as an alternative dissolution media.

**• Surfactant selection for hydrophobic compounds**




- Similarity factor

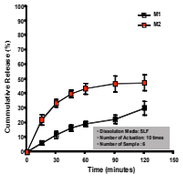
| Comparison | PBS/DPPC (0.02 %) | PBS/Polysorbate 80 (0.02 %) | PBS/Polysorbate 80(0.2 %) |
|---|---|---|---|
| $f_2$ | 25.1 | 40.7 | 64.7 |

◦ Reference : 1T (SLF)

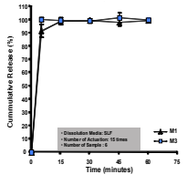
- Care must be taken when the loading dose is obtained by multiple device actuations, especially for poorly water soluble drugs
- For very poorly soluble compounds, dissolution media may contain a percentage of surfactant to enhance drug solubility
- PBS containing 0.2% w/v polysorbate 80 was found to be an ideal dissolution media to evaluate 5 times actuated budesonide
- The concentration of surfactant needs to be justifed by showing profiles at several different concentrations for variety of different dose loadings.

### Sampling/Filtering Method

**• PulmocortFlexhaler™ (Budesonide)**



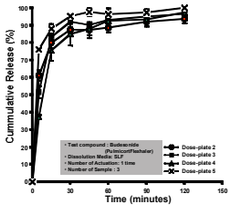

**• Ventolin®HFA (Albuterol Sulfate)**




- M1 : plastic syringe + filter tip
- M2 : glass syringe + add organic solvent + filter tip
- M3 : glass syringe + no filter

- No drug adsorption on the filter was found from albuterol sulfate samples
- Significant drug adsorption was found from budesonide samples (samples were diluted with mobile phase to dissolve budesonide before filtering)

### Influence of Particle Size Cut-off on Dissolution




• Similarity factor

| Comparison | Plate 2 | Plate 3 | Plate 5 |
|---|---|---|---|
| $f_2$ | 52.5 | 59.7 | 48.7 |

-Reference: Plate 4

• Stage cut size at 60 L/min (5)

| Stage | $D_{50}$ (microns) |
|---|---|
| 2 | 4.46 |
| 3 | 2.82 |
| 4 | 1.66 |
| 5 | 0.94 |

- The release profiles of particles accumulated on collection plates 2, 3, and 4 reached 80 % after 15 minutes, and the overall dissolution profiles are not statistically different
- Particles accumulated on collection plate 5, the overall dissolution profile is not equivalent to the reference test (dose-plate 4)
- Smaller particles have better wettability and dissolve quickly due to their larger surface area

## CONCLUSION

A new easy to use dissolution membrane holder for evaluating the *in vitro* dissolution behavior of inhalation formulations was designed. The dissolution rates of commercially available drug formulations were successfully estimated by analyzing the amount of drug released from this attachment for the NGI.

This dissolution method may be used for a qualify control studies for various dry powder inhalers, in particular, the *in vitro* dissolution profiles of drug may provide an estimate of its dispersion characteristics which directly relate to the device or aerosol performances.

## REFERENCES

1) J. S. Patton, *et al.* Advn. Drug Delivery Reviews 19; 3 (1996)
2) M. N. Davis, *et al.* Int. J. Pharm. 255; 175 (2003)
3) R. O. Cook, *et al.* J. Controlled Release 104; 79 (2005)
4) S. Jaspart et al.,Eur. J. Pharm. Biopharm. 65; 47 (2007)
5) V. A. Marple, et al. *J. Aerosol Med.* 16 ;3 (2003)
6) Q. R. Moss, *Health Phys.* 36; 447 (1979)