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Dissolution testing for inhalation formulations

Developing an in vitro method for evaluating how inhaled APIs dissolve in lung fluids for systemic absorption

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Dissolution testing is one of the most common analyses performed on solid and semi-solid dosage forms, but the industry currently lacks an *in vitro* test capable of analyzing the dissolution of loose powders such as those used in DPI formulations. For solid dosage forms, this type of testing allows developers to generate data for the comparison and optimization of formulations, and manufacturers routinely use these tests in quality control (QC) studies such as batch to batch consistency, stability, and detection of manufacturing deviations. A high throughput, cost-effective method of understanding how inhalation powders dissolve in the lungs would provide these same benefits to developers and manufacturers of DPI formulations.

The ability to perform dissolution testing on loose powders would provide a number of benefits beyond QC studies that would be specific to pulmonary delivery. For example, developers of inhaled large molecule drugs could obtain *in vitro* data on the length of time that the API would take to dissolve in lung fluids before systemic absorption could occur, information that might influence initial dosing levels and intervals. Furthermore, these types of tests could provide data needed to optimize particle size distribution. For instance, within the 1-5 μm size range that has the ability to reach the lower airway, what size would provide the best dissolution characteristics for the desired activity?

Since lung residence time depends on dissolution rate, dissolution testing could also help to determine the likelihood of accumulation of drug in the lungs over time or whether a topical drug such as tobramycin would remain in the lung long enough for effective action. This data would also aid development of controlled release products for inhalation and help to evaluate the use of surfactants, salts, and solubility enhancers in DPI formulations.

Necessary testing conditions

Given that most inhalation products target the lower airways where the alveolar surface area (as large as 60-90 m^2) is covered by a thin diffusion layer of aqueous fluid and lung surfactant, replicating the exact conditions would prove impossible. However, since, as with dissolution testing of solid dosage forms, the point is not to obtain a universally applicable *in vitro-in vivo* correlation, but instead to provide data that in conjunction with later *in vivo* studies may produce an IVIVC for a particular drug, exact replication of the lung environment is unnecessary.

Dissolution test methods for pills and capsules create an environment meant to simulate the gastric fluids in which oral dosage forms will dissolve: relatively large volumes of an acidic fluid in an agitated vessel. Simulating the environment in which powders dissolve in the lungs requires instead a relatively small volume of a neutral aqueous solution with salt components to approximate the same tonicity as natural lung fluid. Testing has shown that the addition of a surfactant such as that which occurs in the lungs is not always necessary.

In addition to simulating lung fluids, a dissolution test for DPI formulations must be able to retain the powder in a thin layer to simulate the uniform deposition of drug in the lungs because any aggregation would affect the dissolution rate. The most familiar and well-established pharmacopoeial methods for testing dissolution of solid dosage forms involve placing a pill or capsule in the bottom of an agitated vessel while the paddles turn above the drug.

However, because loose powders would float on top of the liquid initially, they would likely clump or cling to the stirrer or vessel, so the standard method of introducing the sample to the dissolution apparatus will not work for inhalation formulations.

A prototype testing apparatus

Development of a method for inhalation powder dissolution testing has centered around preparation of samples for use in a standard USP dissolution apparatus. For the initial tests with the prototype, micronized hydrocortisone (HC) mixed with a larger lactose carrier has served as a model inhalation formulation for testing. The sample preparation involves deposition of the API onto a polycarbonate membrane using an NGI cascade impactor. The membrane is then fixed securely in a cassette that can be dropped into the dissolution test vessel (Fig. 1).

As a preliminary test of its potential usefulness, a dissolution testing method for dry powders must demonstrate that it can detect anticipated changes in dissolution in response to physicochemical changes in the powder properties. For example, the test should show faster dissolution rates for smaller particles than for larger particles. Separating out various particle size fractions using cascade impaction provides an opportunity to analyze the method's ability to differentiate between samples.

The prototype method for creating a powder-holding cassette requires cutting pieces of membrane to line the collection surfaces of the NGI. The analyst then cuts wax paper templates to fit over the membranes (Fig. 2). Each template features a rectangular hole with the same dimensions as each of the other templates, creating a uniform area for powder collection for each collection plate (Fig. 3). Once the membranes and templates are in place, the NGI is closed, and the analyst performs a cascade impaction, using a DPI to fire a dose of the HC/lactose mixture.

Preparation of samples for the dissolution apparatus

After the procedure is completed, the analyst opens the lid of the NGI and removes the wax paper templates. Most of the lactose carrier impacts on stage 1, leaving mostly HC on stages 2-6 and in the fines collection, stage 7. The NGI produces sharp cut-offs, and scanning electron microscopy shows a uniform particle size distribution for the HC collected on each of the intermediate stages (Fig. 4).

Because removing the membranes without disturbing the HC particles impinged on them would be impossible, the analyst then places a second membrane, this one pre-soaked with dissolution media,

Figure 1

Dissolution testing apparatus

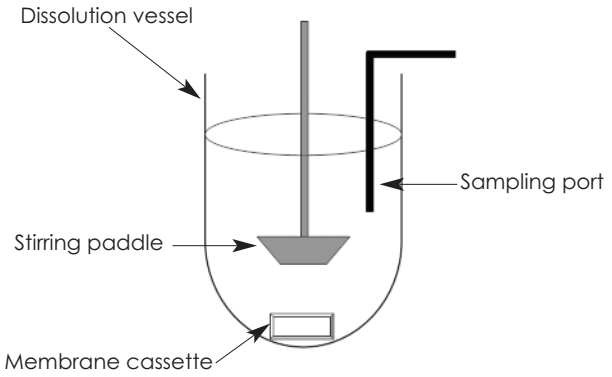

Figure 2

Modified Next Generation Impactor (NGI) setup before impingement

Figure 3

Modified NGI collection surface after impingement

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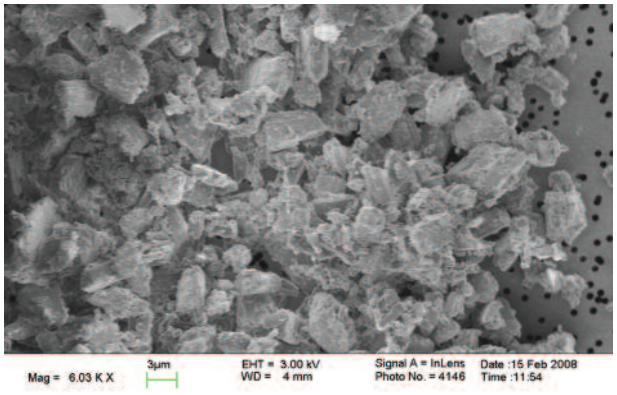
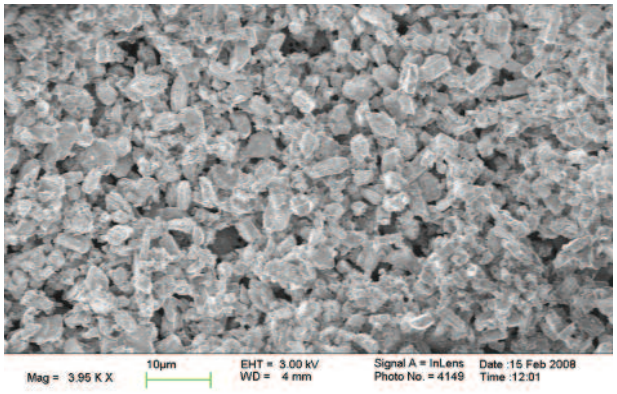
Figure 4

Scanning electron microscope (SEM) images of separated HC from stages 2 (a), 3 (b), 5 (c) and 6 (d)



(a)



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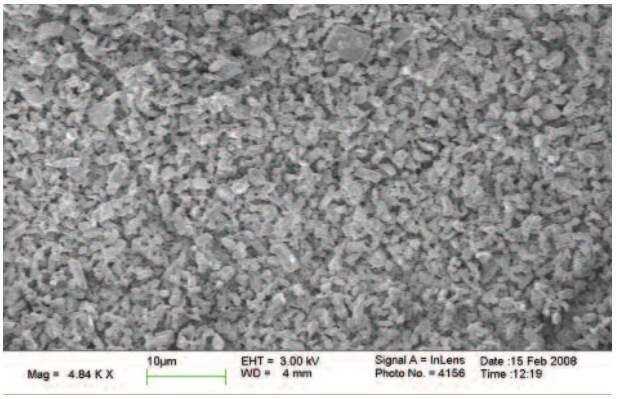
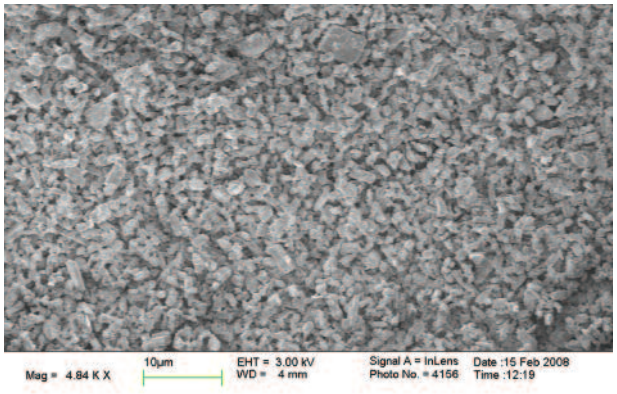


(c)



(d)

over the top, sandwiching and fixing the powder between the two membranes. The membrane "sandwiches" are then removed from each collection surface, and each is inserted into a plastic histology cassette.

Table 1

Amount of HC Loaded into membrane cassette for each stage tested

Stage	Stage cut-off size (µm)	HC mixed with Inhalac®70 (mg)		
		Run 1	Run 2	Run 3
2	4.46	0.76	0.60	0.80
3	2.82	0.37	0.46	0.59
5	0.94	0.32	0.36	0.29
6	0.55	0.045	0.067	0.053

Histology cassettes have positive lid closures and allow flow through of liquids because they normally hold tissue samples during dehydration and impregnation with wax or other embedding materials in preparation for microscopic examination. The membranes exceed the dimensions of the cassettes, so when the lids of the cassettes close, they crimp the two membranes of the sandwich together, creating a seal around the powder. Because this prototype method uses a pre-wetted membrane, the analyst must take care to prepare the cassettes in a standardized amount of time to prevent inconsistent dissolution of powder prior to introduction of the sample into the test vessel.

The dimensions of the rectangular collection area formed by the wax paper templates match the openings in the cassettes used, so the entire deposition surface on each membrane can be exposed to the dissolution media when the cassette is placed in the testing apparatus. Approximately 20µL of liquid permeates the cassette at any given time, and as the 100 mL of simulated lung fluid (SLF) in the vessel flows around and through the cassette, that volume is replenished constantly, immediately removing dissolved drug from the surface of the membrane.

Conclusions

Testing of the model inhalation formula using this method has demonstrated an ability to discriminate between various particle sizes of HC, with the release of drug particles collected from stage 2 occurring at a slower rate than those from stages 3-5, which in turn occur more slowly than the finer particles collected from stage 6 (Fig. 5). The standard deviation in the results over 3 tests, shown as error bars in Figure 5, appears relatively small, demonstrating the uniformity of the powder preparation and the reproducibility of the test method between samples.

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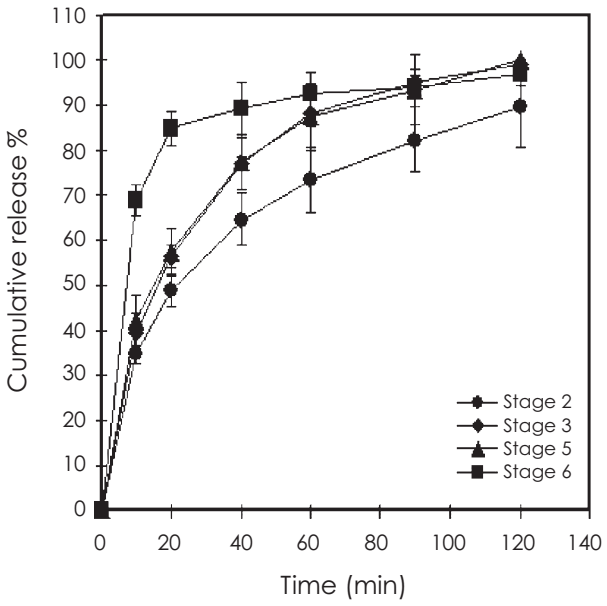
Figure 5

Release profiles of HC separated from the lactose carrier in SLF for dose plate 2, 3, 5, and 6. The error bars indicate the standard deviation of three tests.



This current method of preparing the membranes and removing the powder fractions from the NGI stages demonstrates a proof-of-concept procedure. In order to simplify the process, Copley Scientific has partnered with The University of Texas at Austin to design an insert for the NGI that would collect each sample, doing away with the need for the wax paper templates and histology cassettes. This modification will allow the analyst to open the NGI after a cascade impaction, remove an insert, and place the insert directly into the dissolution test vessel.

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