AAPS PharmSciTech, Vol. 13, No. 3, September 2012 (© 2012)
DOI: 10.1208/s12249-012-9822-3

Review Article

Challenges with Developing *In Vitro* Dissolution Tests for Orally Inhaled Products (OIPs)

Trevor Riley,[1] David Christopher,[2] Jan Arp,[3] Andrea Casazza,[4] Agnes Colombani,[5] Andrew Cooper,[6] Monisha Dey,[7] Janet Maas,[8] Jolyon Mitchell,[9] Maria Reiners,[10] Nastaran Sigari,[11] Terrence Tougas,[12] and Svetlana Lyapustina[13,14]

Received 3 April 2012; accepted 18 June 2012; published online 14 July 2012

Abstract. The purpose of this article is to review the suitability of the analytical and statistical techniques that have thus far been developed to assess the dissolution behavior of particles in the respirable aerodynamic size range, as generated by orally inhaled products (OIPs) such as metered-dose inhalers and dry powder inhalers. The review encompasses all analytical techniques publicized to date, namely, those using paddle-over-disk USP 2 dissolution apparatus, flow-through cell dissolution apparatus, and diffusion cell apparatus. The available techniques may have research value for both industry and academia, especially when developing modified-release formulations. The choice of a method should be guided by the question(s) that the research strives to answer, as well as by the strengths and weaknesses of the available techniques. There is still insufficient knowledge, however, for translating the dissolution data into statements about quality, performance, safety, or efficacy of OIPs in general. Any attempts to standardize a dissolution method for compendial inclusion or compendial use would therefore be premature. This review reinforces and expands on the 2008 stimulus article of the USP Inhalation *Ad Hoc* Advisory Panel, which "could not find compelling evidence suggesting that such dissolution testing is kinetically and/or clinically crucial for currently approved inhalation drug products."

KEY WORDS: diffusion cell; dissolution; flow through cell; inhaler; paddle.

INTRODUCTION

In vitro dissolution testing is well established for solid oral dosage forms as both a quality control test to assess batch-to-batch consistency and to predict *in vivo* drug release profiles for both immediate and modified release dosage forms (1,2). For many solid oral products, an *in vitro–in vivo* correlation can be established between *in vitro* dissolution data and pharmacokinetic (PK) data. Such a correlation enables use of dissolution data as an important tool for assessing postapproval changes to the formulation or manufacturing process, as well as for the development and approval of generic products.

The clinical safety and efficacy of orally inhaled products (OIPs) is understood to be influenced by the total aerosolized dose delivered to lung and by the aerodynamic particle size distribution (APSD). Consequently, dose content uniformity and APSD are generally viewed as critical quality attributes of inhaled products and corresponding testing is required by regulatory guidances for characterization and quality control purposes (3–6). Testing for these attributes is also required for

[1] Inhaled Product & Device Technology, GlaxoSmithKline, Hertfordshire, UK.
[2] Nonclinical and Pharmaceutical Sciences Statistics, Merck, West Point, Pennsylvania, USA.
[3] Analytical Development Respiratory R&D, Teva, Haarlem, The Netherlands.
[4] Drug Product Development R&D CMC, Chiesi, Parma, Italy.
[5] Pharmaceutical Development, AstraZeneca, Mölndal, Sweden.
[6] Global Respiratory Group, Mylan, Sandwich, UK.
[7] Non-Clinical Statistics, Merck, Kenilworth, New Jersey, USA.
[8] Pharmaceutical and Analytical Development, Novartis, Horsham, UK.
[9] Trudell Medical International, London, Ontario, Canada.
[10] Respiratory Drug Delivery, Boehringer Ingelheim, Ingelheim am Rhein, Germany.
[11] Respiratory Product Development, Merck, Summit, New Jersey, USA.
[12] CMC Development, Boehringer Ingelheim, Ridgefield, Connecticut, USA.
[13] Pharmaceutical Practice Group, Drinker Biddle & Reath LLP, 1500 K Street NW, Washington, District of Columbia 20005-1209, USA.
[14] To whom correspondence should be addressed. (e-mail: svetlana.lyapustina@dbr.com)

ABBREVIATIONS: ACI, Andersen Cascade Impactor; API, active pharmaceutical ingredient; APSD, aerodynamic particle size distribution; BDP, beclomethasone dipropionate; COPD, chronic obstructive pulmonary disease; DDW, double distilled water; DPI, dry powder inhaler; DPPC, dipalmitoylphosphatidylcholine; ELF, epithelial lung fluid; FP, fluticasone propionate; ICS, inhaled corticosteroid; IPAC-RS, International Pharmaceutical Aerosol Consortium on Regulation and Science; IVIVC, *in vivo in vitro* correlation; LABA, long-acting beta agonist; MDI, metered dose inhaler; NGI, Next Generation Pharmaceutical Impactor; OIP, orally inhaled product; PBS, phosphate-buffered saline; PC, phosphatidylcholine; PD, pharmacodynamic; PK, pharmacokinetic; PVDF, polyvinylidene difluoride; SLF, simulated lung fluid; USP, US Pharmacopeia.

demonstrating *in vitro* equivalence of generic/second-entry or modified OIPs to the original (reference) product (7–10), with an understanding that these *in vitro* tests are not fully predictive of *in vivo* performance and that *in vivo* assessment may also be required. In particular, it has been emphasized that multistage cascade impactors are not surrogates for the human respiratory system and that an APSD does not have a direct relationship to pulmonary deposition profile (11,12).

Many commonly used inhaled products such as metered-dose inhalers (MDIs), dry powder inhalers (DPIs) and suspensions for nebulization deliver the active pharmaceutical ingredient (API) to the lung in a solid form. A variety of competing mechanisms exist for the clearance of aerosol particles after deposition in the airways (13). Undissolved particles may be cleared either from the conducting airways by the mucociliary escalator to the trachea and into the gastrointestinal tract or from the lower airways by uptake into alveolar macrophages and elimination through the lymphatic system. However, the bioavailability and therapeutic action, as well as systemic absorption of inhaled APIs, depend on the dissolution of the deposited aerosol particles in the limited volume of fluid that lines the respiratory tract.

Currently, there are no regulatory requirements or pharmacopeial techniques for dissolution testing of OIPs. In 2008, the Inhalation *Ad Hoc* Advisory Panel of USP evaluated the scientific rationale for *in vitro* dissolution tests for inhalation dosage forms and concluded that there was no compelling evidence that dissolution was "kinetically and/or clinically crucial for currently approved" OIPs (14). Nevertheless, there has continued to be considerable academic and industrial interest in the development of *in vitro* techniques to determine the dissolution profile of inhaled products (15).

The nature and strength of relationships among dissolution and PK, pharmacodynamic (PD), and/or other clinical data have yet to be demonstrated, and they may well be product- and patient-specific, *i.e.*, dependent on the inhalation maneuver, inspiratory flow profile, physiology and anatomy of lungs in the target population, treated condition (*e.g.*, asthma *vs* COPD), disease state (moderate *vs* severe), *etc.*

The purpose of this article is to review the suitability of the analytical and statistical techniques that have been developed to date to assess the dissolution behavior of particles in the respirable aerodynamic size range. The current state of knowledge concerning clinical relevance of dissolution data is discussed with the objective of making a recommendation on the utility of measuring dissolution profiles for orally inhaled products.

This article is authored by the Dissolution Working Group of the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS), which is an international association of companies that develop and manufacture OIPs.

OVERVIEW OF ANALYTICAL METHODS

A range of techniques to measure dissolution rates of inhaled products have been reported in the literature. Figure 1 represents the potential steps involved in a dissolution experiment. In addition to selection of the dose collection and dissolution techniques, the choice and volume of the dissolution medium are also critical to performing and comparing experiments.

Aerosol Particle Collection

Although dissolution measurements of inhaled products can and have been performed on API, micronized API and bulk formulations, it is arguably preferable to perform the dissolution test on aerosolized particles in the potentially respirable size range, in order to maximize the probability of generating data reflective of *in vivo* pulmonary dissolution. Several approaches have been used to collect the aerosolized dose using either the Andersen Cascade Impactor (ACI) or the Next Generation Pharmaceutical Impactor (NGI). Arora *et al.* (16) collected particles on the impaction stages of an ACI simply by placing polyvinylidene difluoride (PVDF) membrane filters on the stainless steel collection plates. One has to keep in mind, however, that the aerodynamic flow profiles of the particles could be influenced by a filter on the plates.

More elegantly, Son *et al.* (17–19) developed a modified NGI cup with a removable impaction insert as shown in Fig. 2. In an alternative approach, stainless steel or glass fiber filters may be used to capture particles in the impactor. Feddah and Davies (20) described positioning a fiber filter at the base of the USP induction port. To avoid the capture of coarse particles when analyzing lactose-containing dry powder inhaler formulations, other researchers have positioned particulate filters above stage 3 of the NGI (21,22), as in Fig. 3. The filter approach has the advantage of collecting the aerosolized drug dispersed over a greater surface area than is the case when particles are collected directly under the air jets in an impactor stage.

Dissolution Media

A variety of dissolution media, usually at pH=6.8–7.4, ranging from simple phosphate-buffered saline (PBS) to simulated lung fluid (SLF) have been used for dissolution testing of inhaled products (Table I). In this article, we use the term 'simulated lung fluid', wfhich has become customary in the literature, with an understanding that SLF does not fully simulate the interstitial or epithelial lung fluid (ELF) given that it will not contain protein components, mucus, *etc.* (23) In the studies to date, SLF has simply been an aqueous solution of mineral salts and sometimes a surfactant (24).

Pulmonary surfactant found in epithelial lung fluid is an array of phospholipids, neutral lipids, and proteins with phosphatidylcholine (PC), and in particular the phospholipid disaturated dipalmitoylphosphatidylcholine (DPPC)—the most abundant lung surfactant (25). Consequently, a surfactant could be included in the dissolution medium, particularly for analyzing poorly soluble drug substances. DPPC solutions can be difficult to prepare due to lengthy and variable preparation times; synthetic surfactants have, therefore, also been used for *in vitro* dissolution comparisons.

Few systematic investigations of the effect of dissolution medium composition on dissolution rate have been reported. The most comprehensive discussion is probably that of Davies and Feddah (20), who found that surfactant DPPC increased the dissolution rate, but they did not compare different surfactants. The authors also observed that the buffer type and pH had no effect on dissolution rate for a neutral drug such as beclomethasone dipropionate (BDP).

Dissolution experiments have typically been performed at 37°C to mimic normal human body temperature. It should

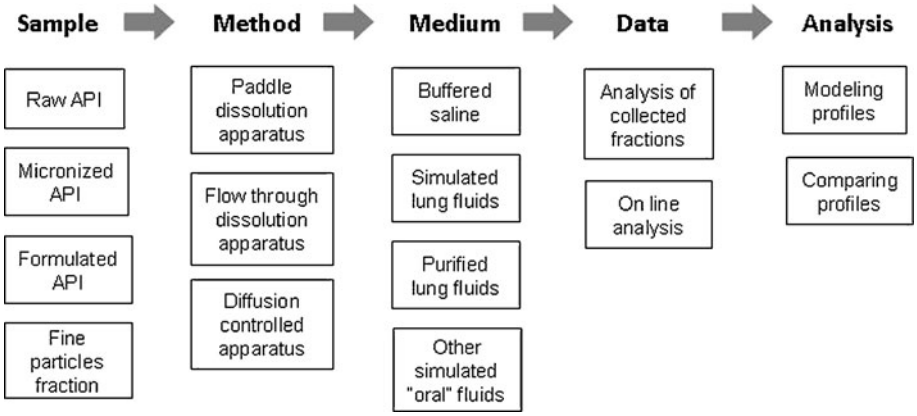

Fig. 1. Illustration of the range of options at each stage of a dissolution experiment for inhaled compounds

be considered good practice to determine the absolute solubility of the API in the medium of choice, at the intended pH and temperature. Without this information, it is difficult to determine whether sink or saturated conditions are achieved, which may, in turn, impact the interpretation. Some of the published papers, however, provide insufficient information about the methods and conditions used to determine the API solubility in the experiment.

Dissolution Apparatus

Three types of apparatus have been used in published reports of dissolution testing of inhaled products, namely, compendial (USP 2) paddle apparatus, custom-built flow-through apparatus and mainly diffusion-controlled cell systems (*e.g.*, Franz cell or Transwell® system (Corning Inc. Life Sciences, Lowell, MA)). For all techniques, the dissolution profiles are determined by HPLC assay of collected fractions or by online UV analysis. If using a membrane or fiber filter, then typically the remaining undissolved drug on the aerosol particle collector and holder (if used) is also determined at the end of the experimental procedure. Specific advantages and disadvantages of each technique are summarized below.

Paddle Dissolution Apparatus

The use of paddle dissolution apparatus, in "paddle over disk" mode, is illustrated in Fig. 4. The principle advantage of this approach is the use of a standard USP 2 apparatus, which can be used in conjunction with different types of aerosol particle collection filters placed into the vessel, as shown in Table II, and the different filter holders are described in "Aerosol Particle Collection".

The challenge in this approach resides in the set-up of the dissolution experiment in relation to the method of aerosol particle collection. Where the particles are collected on an impaction cup (Fig. 2), it is necessary to use a porous filter to retain the particles on the collection surface, supported in a holder. This retaining filter may act as a barrier to wetting and may increase the diffusion layer thickness. This effect can be minimized by optimizing the size and material of the membrane and by using the surfactant in the dissolution medium (18,19). Where a stainless steel filter has been used for collection (Fig. 3), it was placed directly in the dissolution bath (22). Unless the aerosol particle collector can be oriented reproducibly in the bath, its orientation may also influence the dissolution rate (18,22). The volume of the dissolution medium can be adapted to reflect the two extreme dissolution cases: sink conditions mimicking fast absorption and small dissolution medium volumes mimicking slow absorption.

Flow-Through Cell Apparatus

The flow-through cell systems reported in the literature for the dissolution of OIPs are custom-made systems often referred to as a modified USP 4 apparatus (Table II). This

Fig. 2. Modified NGI dissolution cup (reproduced with permission from Copley Scientific Limited UK)

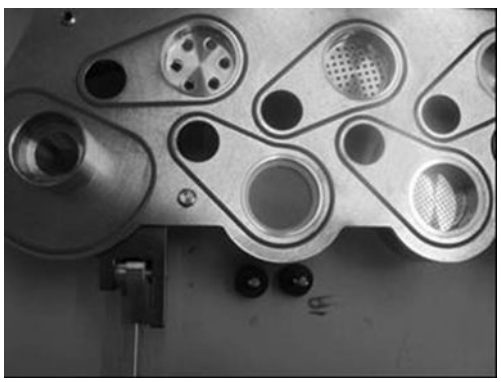

Fig. 3. Stainless steel filter placed above stage 3 of NGI. Reproduced with permission from Mees *et al.* (22)

apparatus is mostly used in conjunction with the particle filter approach to aerosol particle collection. The filter with the loaded particles is supported in a filter holder and the dissolution medium is pumped through the dissolution cell by means of an HPLC pump (Fig. 5).

Advantages of this technique are permanent sink conditions and reduced influence of diffusion during dissolution testing. In most published cases, however, filter holders were used as dissolution cells. Their flat geometry potentially generate a high fluid velocity at the centre but decreasing flow gradient towards the periphery causing diffusion effects and non sink conditions to occur locally. The API concentration in the collected fractions should be checked to confirm that sink conditions have been achieved. For example, a final extracted concentration as high as 50% of the solubility limit has been observed (20). Another issue due to the geometry is air entrapment in the system, which can prevent wetting and dissolution. Some attempts have been made to design flow-through cells more similar to USP 4 cells, with a better internal flow profile to avoid diffusion but still limiting the dead volume to decrease the initial amount of air (26).

Mainly Diffusion-Controlled Cell Apparatus

To perform a dissolution test using this apparatus, a membrane filter with the deposited drug particles on the surface is placed into modified Franz cell or Transwell® system (Figs. 6 and 7 and Table II). The volume of dissolution medium in the donor compartment is normally low, while the volume in the acceptor compartment can range from a few milliliters to 1 L.

This approach aims to better represent the *in vivo* situation with an agitated (*e.g.*, Franz cell) or nonagitated system (*e.g.*, Transwell®). However, it is very difficult to distinguish between diffusion effects through the membrane and the dissolution rate. Therefore, in order to compare dissolution rates, the diffusion coefficient, its reproducibility, and the affinity of the compound to the membranes should be determined prior to each dissolution experiment. For hydrophobic compounds that are highly permeable *in vivo*, the systemic circulation can act as a sink even when the entire respired dose is not soluble in the limited lung fluid volume. In order to mimic this situation *in vitro* and to avoid an unrepresentative nonsink condition, a high diffusion coefficient through the membrane and low retention is required.

In order to better represent *in vivo* dissolution and permeation processes in combination, alternative techniques that deposit the drug particles onto respiratory cell monolayers may provide a more realistic *in vitro* model (27,28) but are outside the scope of this review.

Comparison of Techniques

A small number of comparative evaluations of techniques for dissolution testing of OIPs have been published. Salama *et al.* (29) compared the three classes of dissolution methods, ensuring maximum similarity between the set-ups. The dissolution medium, temperature, volume, drug load, and samples tested were kept constant across the range of experiments. In this study, however, only spray-dried powders designed for modified release rather than collected aerosols were analyzed. USP 2 dissolution apparatus without a powder holder and flow-through dissolution were too fast to discriminate between formulations, although in the case of the former, this may have been due to the filter pore size being similar to that of the undissolved particles. The diffusion Franz cell apparatus provided a more discriminative profile with slower release times. In all these instances, the dissolution media are the same, but the dissolution processes are different, leading to different results.

Further studies have been published comparing these dissolution methods for aerosolized particles (30,31). All of the techniques were able to discriminate between amorphous and crystalline APIs in the formulations, but the dissolution profile was very dependent on the method used.

A significant drawback of many of the techniques is that the dissolution profile shows a dependence on drug loading for poorly soluble drug substances. The extent of this issue can depend on the drug, the dissolution medium, and, most significantly, the aerosol particle collection method. For example, collection of the aerosol on a membrane filter below the air jets of an impactor stage can result in an accumulation of particles as *in situ* agglomerates, which do not wet sufficiently. This effect can give rise to an apparent decrease in dissolution rate and often incomplete dissolution when the mass of drug particles collected on the filters is increased. It is unlikely that these effects have *in vivo* relevance, as they reflect the

Table I. Examples of Dissolution Media Used for Inhaled Product Dissolution Testing

Buffer/Electrolyte	Surfactant	Reference
0.05 M phosphate-buffered saline (PBS) pH 7.4	None	Salama *et al.* (29)
0.2 M phosphate-buffered saline (PBS) pH 7.4	0.02% *w/v* dipalmitoylphosphatidylcholine (DPPC) or polysorbate 80	Son *et al.* (18)
20 mM piperazine-1,4-bis(2-ethanesulfonic) PIPES pH 6.8 134 mM sodium chloride	Sodium dodecyl sulfate (SDS)	Cooper *et al.* (22)
Magnesium chloride, hexahydrate, sodium chloride, potassium chloride, sodium phosphate dibasic anhydrous, calcium chloride dihydrate, sodium acetate trihydrate, sodium bicarbonate, sodium citrate dihydrate pH 7.3–7.4	0.01–0.05% *w/v* Dipalmitoylphosphatidylcholine (DPPC)	Davies and Feddah (20) and Riley *et al.* (21)
Survanta™ beractant - as phospholipids (Abbott Nutrition, Columbus, OH)—a bovine native lung extract (published use for solubility determination only)	Beractant—a natural pulmonary surfactant	Wiedmann *et al.* (26)

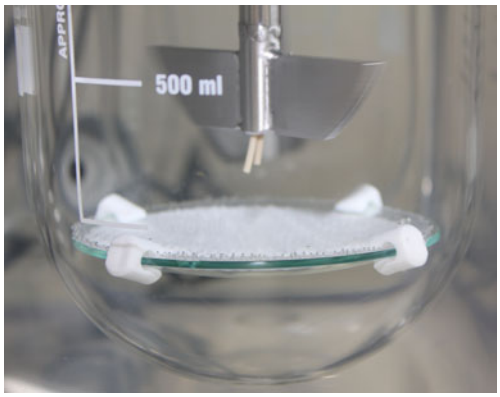

Fig. 4. USP 2 paddle dissolution apparatus. Reproduced with permission from Jensen *et al.* (30)

necessarily very small surface area (relative to that of the lung) on which the respirable fraction is collected *in vitro*.

Similarly, saturation of the limited volume of dissolution medium used in diffusion cells can also cause decreased dissolution and permeation rates at higher drug loading (16). The *in vivo* significance of such drug loading effects is questionable, as the semipermeable membranes used *in vitro* are unlikely to be representative of the lung epithelial wall where active transportation mechanisms may dominate. To enable a robust comparison of the dissolution profiles of different formulations, it may, therefore, be preferable to use a combination of sample collection and dissolution methods that maintain sink conditions for the drug substance being analyzed.

APPLICATIONS OF DISSOLUTION TESTING TO INHALED PRODUCTS

Within the published literature to date, a variety of developmental and commercial products for inhalation have been tested using the available techniques, and a number of factors affecting dissolution rate have been discussed. These published studies are listed in Table III.

Effect of Solubility on Dissolution Rate

As Table III illustrates, a wide range of drug solubility has been explored in published applications, ranging from freely soluble molecules such as albuterol sulfate to very poorly soluble corticosteroids such as beclomethasone dipropionate (BDP) and fluticasone propionate (FP). Optimization of the dissolution medium is required to achieve a reasonable dissolution rate according to drug solubility. One possibility for the least -soluble drugs is to use a surfactant-containing media, although there is a publication (18) that illustrates poor diffusion of DPPC into the filters. A number of authors (16,20,21) have directly compared dissolution rates of different drugs within the same medium and shown that dissolution rate increases with increasing drug solubility, as expected from theory (*e.g.*, Noyes–Whitney equation) and exemplified in Fig. 8.

Effect of Particle Size and Mass

It is also to be expected from theory that dissolution rates should increase with decreasing drug particle size. It may be important to distinguish, particularly in carrier-based dry

Table II. Examples of Dissolution Techniques Used for Inhaled Product Dissolution Testing

Dissolution apparatus	Aerosol particle collector (filter/filter holder)	Paddle speed/flow rate	Comments	Reference
Paddle apparatus (USP 2)	Stainless steel filter	50 rpm	Dissolution rate dependant on drug loading/filter orientation	Mees *et al.* (22)
	Removable impaction insert with polycarbonate membrane (0.05 and 1 μm) as porous retainer	50–100 rpm	Dissolution rate dependant on drug loading	Son *et al.* (19)
	Regenerated cellulose membrane (0.45 μm)	140 rpm	Orientation of filter influences dissolution rate	Jensen *et al.* (30)
Flow-through cell apparatus	Fiber filter between membrane filters in stainless steel holder	0.5–1.5 ml/min	Linear dependence of dissolution rate with flow rate	Davies and Feddah (20)
	Fiber filter with a membrane filter behind it in stainless steel holder	1 ml/min	Zero order dissolution profiles	Riley *et al.* (21)
	Regenerated cellulose membrane (0.45 μm) between a membrane filter and metal sieve in plastic holder	1 ml/min	First order dissolution profiles	Jensen *et al.* (30)
	0.45 μm nitrocellulose membrane between a second membrane filter an metal mesh screens	0.5 ml/min	Closed system with 1 L reservoir Formulated particles rather than aerosol particles analyzed	Salama *et al.* (32)
Transwell® system apparatus	0.22 μm polyvinylidene difluoride PVDF membrane filter	N/A	Dissolution rate dependent on filter loading	Arora *et al.* (16)
Franz cell apparatus	0.45 μm nitrocellulose membrane	N/A	Receptor cell connected to 1 L heated vessel	Salama *et al.* (29,32)
	0.45 μm regenerated cellulose	100 rpm	Lower dissolution rate compared to other techniques	Jensen *et al.* (30)

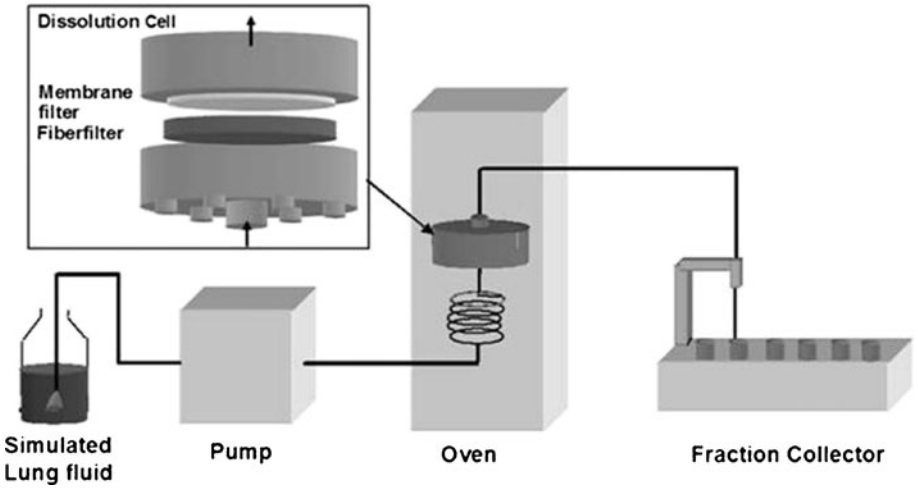

Fig. 5. Schematic representation of flow-through cell dissolution apparatus. Reproduced with permission from Riley *et al.* (21)

powder formulations, between primary drug particle size, which is most likely in principle to drive dissolution processes, and the aerodynamic particle size, which drives particle deposition, the latter being a function of drug-carrier agglomerate size, density, and aerodynamic properties. In practice, effects of both primary API size and aerodynamic size have been demonstrated, perhaps reflecting a tendency of the two size metrics to be related within a given product. An effect of primary API particle size on dissolution rate was demonstrated by Mees *et al.* (22), who carried out dissolution on the fine particle fraction of a range of developmental formulations containing differing ingoing APIs (Fig. 9). While in this work, the entire fine particle fraction was collected as a single sample, other authors have demonstrated an effect of aerodynamic size on dissolution rate by collecting multiple size fractions from individual impactor stages, for both carrier-free and lactose based powder formulations (16,18,19) exemplified in Fig. 10. Arora *et al.* (16) demonstrated that the increase in dissolution rate with decreasing aerodynamic size in a carrier-free budesonide product (Pulmicort Turbuhaler®) was in line with the change in calculated surface area. They also identified an influence of particle mass on dissolution rate.

Product Comparisons

Limited information is currently available concerning the ability of dissolution testing of the fine particle fraction to distinguish between different presentations of the same active ingredient. The only published report is that of Arora *et al.* (16), who compared dissolution rates between DPI and MDI presentations of FP and between suspension and solution MDI presentations of BDP in a diffusion cell system.

In the case of FP, no difference in dissolution rate was observed, although the discriminating ability of the method was arguably low. Zero-order kinetics was observed reflecting membrane permeation rate from a rapidly saturated donor cell.

As shown in Fig. 11, some discrimination between the BDP presentations was observed, with a faster initial dissolution rate obtained from the solution MDI product (QVAR®) than the suspension product (Vanceril®). This is to be expected, considering that the drug produced from a formulation containing ethanol as a cosolvent may have a different particle size (relative to a suspension formulation) or be partially dissolved or amorphous upon reaching the lung. Both BDP products showed a faster dissolution/permeation rate than the FP products, despite the similarity in reported aqueous solubility (approximately 0.1 μg/ml) of the two drugs. Several explanations may be offered for these dissolution results. For example, neither of the BDP products may have

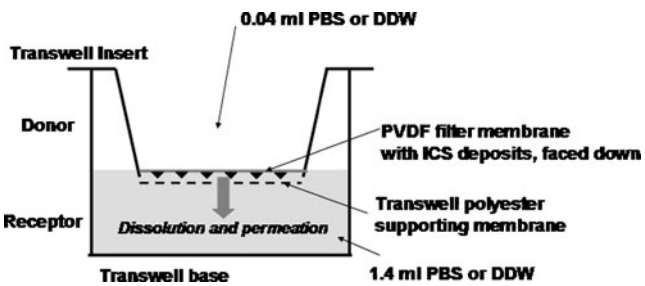

Fig. 6. Transwell® diffusion cell apparatus. Reproduced with permission from Arora *et al.* (16)

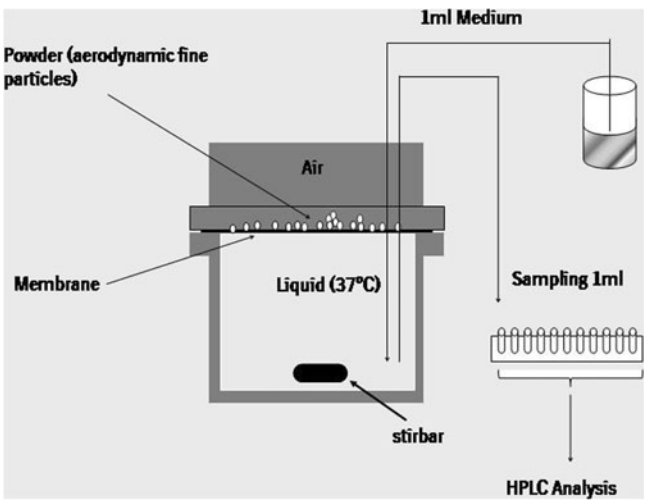

Fig. 7. Franz diffusion cell apparatus. Reproduced with permission from Reiners *et al.* (31)

Table III. Published Applications of Dissolution Testing of the Respirable Fraction of Products for Inhalation

API	Aqueous solubility (with a reference where absent from the primary reference)	Product	Technique	Reference
Salbutamol (albuterol) sulfate	100–1,000 mg/ml (33)	Ventolin® HFA MDI	Paddle over disk	Son *et al.* (18)
Hydrocortisone	100 μg/ml–1 mg/ml (33)	Development DPI	Paddle over disk	Son *et al.* (19)
Development LABA	300 μg/ml	Development MDI	Flow-through	Riley *et al.* (21)
Flunisolide	140 μg/ml	Aerobid® MDI	Diffusion Cell	Arora *et al.* (16)
Triamcinolone acetonide	21–26 μg/ml	Azmacort® MDI	Diffusion Cell	Arora *et al.* (16)
Triamcinolone acetonide	21–26 μg/ml	Azmacort® MDI	Flow-through	Davies and Feddah (20)
Budesonide	14–21 μg/ml	Pulmicort Turbuhaler® DPI	Diffusion Cell	Arora *et al.* (16)
Budesonide	14–21 μg/ml	Pulmicort Turbuhaler® DPI	Flow-through	Davies & Feddah (20)
Budesonide	14–21 μg/ml	Pulmicort Flexhaler® DPI	Paddle over disk	Son *et al.* (18)
Development ICS	<5	Development MDI	Flow-through	Riley *et al.* (21)
Beclomethasone dipropionate	0.1 μg/ml	QVAR® solution MDI	Diffusion Cell	Arora *et al.* (16)
Beclomethasone dipropionate	0.1 μg/ml	Vanceril® MDI	Diffusion Cell	Arora *et al.* (16)
Fluticasone propionate	0.1 μg/ml	Flovent Diskus® DPI	Diffusion Cell	Arora *et al.* (16)
Fluticasone propionate	0.1 μg/ml	Flovent® HFA MDI	Diffusion Cell	Arora *et al.* (16)
Fluticasone propionate	0.1 μg/ml	Flixotide® Accuhaler® DPI	Flow-through	Davies and Feddah (20)
Development API	<0.1 μg/ml	Development DPI	Paddle over disk	Mees *et al.* (22)

contained the fully crystalline form used to determine the solubility value nor the solubilities may have been determined using different methods or media.

Although in principle, the fine particle fraction of suspensions aerosolized by nebulization could also be analyzed using these dissolution techniques, to date there are no examples of this reported in the literature.

Modified Release Applications

Applications of dissolution testing in the development of particles or formulations engineered to achieve modified release have been reported (34–37). Testing has focused on API or blend powder without separation of the respirable fraction, typically using conventional USP dissolution apparatus. These reports demonstrate that it is possible to achieve significant changes in *in vitro* release rate with coated particles engineered for this purpose. For example, as shown in Fig. 12, Coowanitwong *et al.* (36) achieved substantial retardation of release of rifampin by coating with poly(lactic acid). In this case, a relationship with *in vivo* pharmacokinetics in rats was demonstrated (Fig. 13), with poly(lactic acid)-coated modified release particles giving substantially longer t_{max} and lower C_{max} than unmodified rifampin particles.

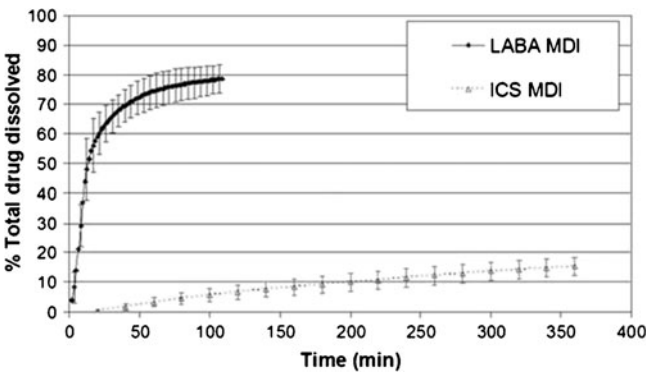

Fig. 8. Dissolution profiles of ICS and LABA aerosolized particles of differing solubilities. Data shown as mean±SD (n=3). Reproduced with permission from Riley *et al.* (21)

STATISTICAL ANALYSIS OF DISSOLUTION PROFILES

Application of Statistics to Dissolution Data

When analyzing data from dissolution experiments, statistical techniques can in principle be used for either modeling the dissolution profiles (*i.e.*, describing the profiles in mathematical terms) or for comparing profiles (*i.e.*, aiming to make statements about similarity or dissimilarity of dissolution profiles). These two distinctly different goals require different statistical techniques and considerations. Although statistics are quite often included in many of the published OIP dissolution papers (mostly for describing the curves), actual details of the statistical methodology and the structure of data are not always clearly stated, hampering a thorough review and discussion of the outcomes of statistical analysis.

Modeling of Dissolution Profiles

In general, profiles can be described using statistical models based either on release kinetic functions or on mathematical curves. These approaches model individual profiles but do not provide a directly quantifiable comparison of profiles.

Model-dependent release kinetic functions can be used to describe dissolution curves based on the kinetics of drug release and the discernment of the release mechanisms, such as zero-order, first-order, Higuchi, Hixon–Crowell, and Peppas models. For example, the Higuchi model is:

$$f_t = K_H\sqrt{t}$$

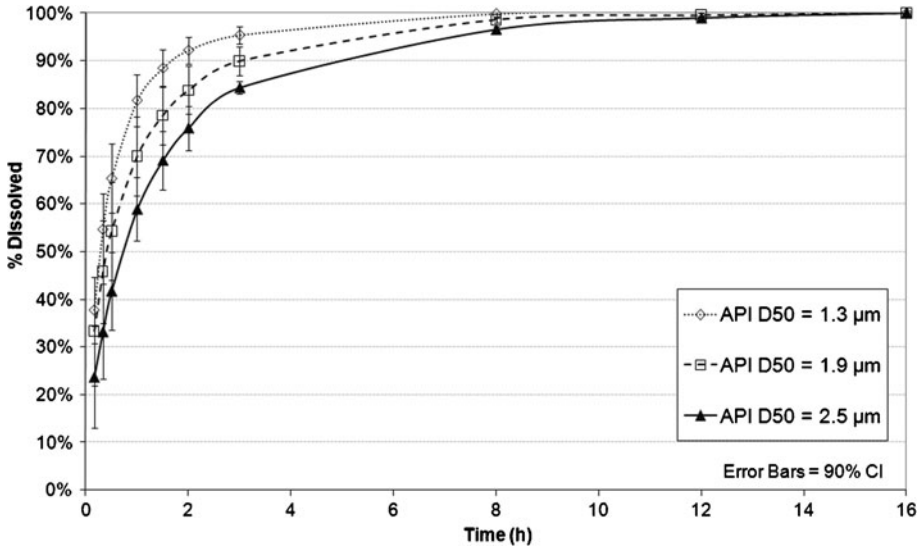

Fig. 9. Effect of API particle size on dissolution rate of a low-solubility drug in a dry powder inhaler formulation. Data shown as mean±90% confidence intervals (number of replicates not stated). Reproduced with permission from Mees *et al.* (22)

where K_H is the Higuchi dissolution constant reflecting formulation characteristics, and f_t is the amount of drug release as a diffusion process based on Fick's law, which is square root time (t) dependent.

Model-dependent release kinetic functions are most easily applied to well-characterized systems (*e.g.*, products containing monodispersed particles). Their application to inhaled products containing polydispersed API particles is more challenging.

Dissolution profiles can also be described by model-dependent mathematical models, such as Weibull, logistic, and Gompertz, which are not necessarily directly related to physicochemical aspects of the dissolution process. An example of the Weibull model, which, according to the literature, seems to be describing OIP dissolution profiles (f_t) reasonably well, is given below (where a and b are scale and shape parameters, respectively):

$$f_t = 1 - \exp\left[\frac{-(t - T_i)^b}{a}\right]$$

Costa and Lobo (38) criticized the use of this Weibull model for characterizing dissolution profiles because of a lack of kinetic basis and the fact that no single parameter was directly related to the intrinsic dissolution rate of the drug. Papadopoulou *et al.* (39) showed that a constrained Weibull could be related to kinetic processes. Papadopoulou's argument, however, is applied to a matrix-controlled release product (*i.e.*, where release is diffusion-controlled) and, therefore, has an underlying conformance to the Higuchi model. This situation may not be applicable for inhaled products. In particle-size controlled systems, both Weibull parameters vary when the particle size distribution shifts (*i.e.*, no single parameter is directly related to intrinsic dissolution rate).

Davies *et al.* (20) modeled OIP dissolution profiles using logarithmic, Weibull, or linear functions depending on the drug and dissolution medium. Some of the papers, for example, Salama *et al.* (32), used minimum R^2 to determine the best overall mathematical model to fit the data, without considering whether a particular model could be better justified based on the drug's physicochemical properties.

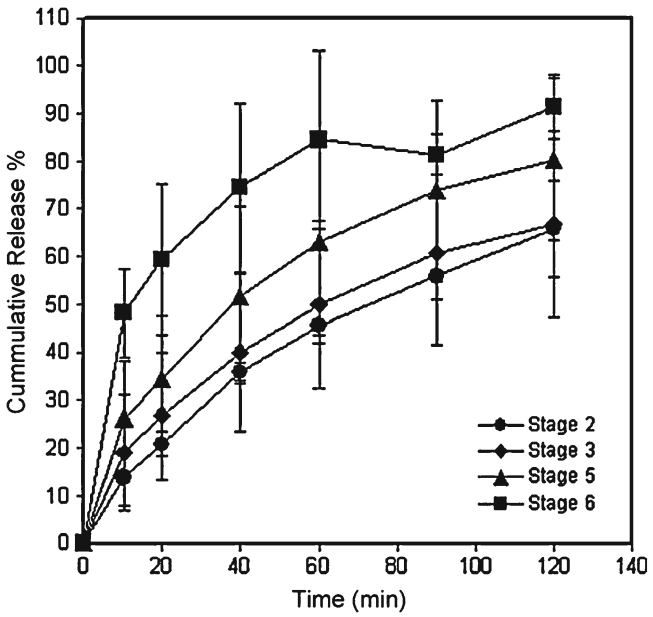

Fig. 10. Dissolution of hydrocortisone aerodynamic particle size fractions collected from NGI stages 2–5. Data shown as mean±SD (n=3). Reproduced with permission from Son *et al.* (19)

Methods for Comparing Dissolution Profiles

Several approaches to compare dissolution profiles are used routinely for solid oral dosage forms. The profiles being compared are customarily referred to as test (T) and reference (R), although the comparison need not necessarily be conducted for bioequivalence purposes.

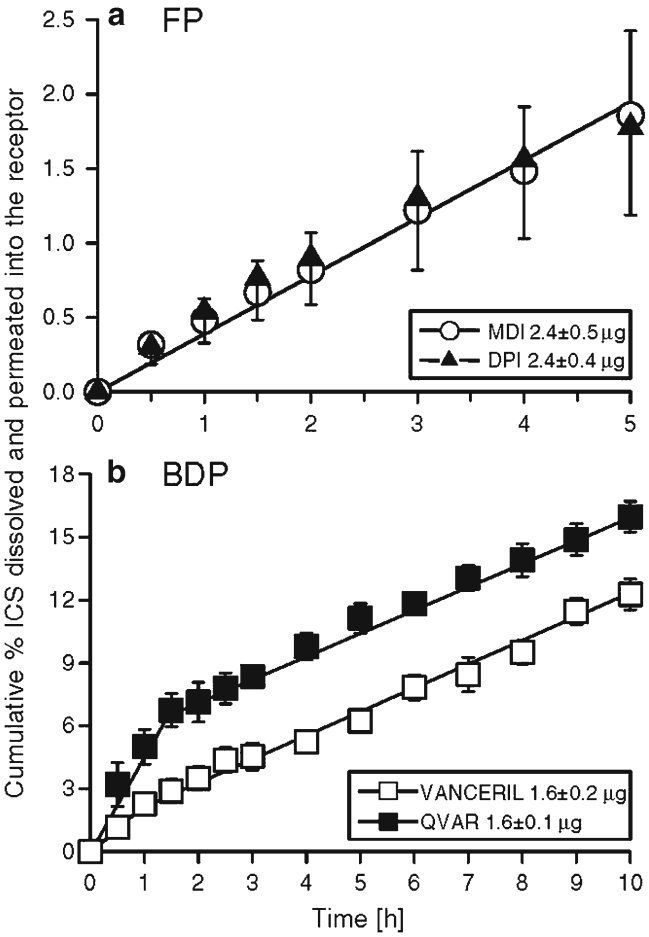

Fig. 11. Comparison of dissolution rates for 2.1–3.3 μm aerodynamic size fractions of fluticasone propionate (FP) and beclomethasone dipropionate (BDP) products. Data shown as mean±SD (n=3). Reproduced with permission from Arora *et al.* (16)

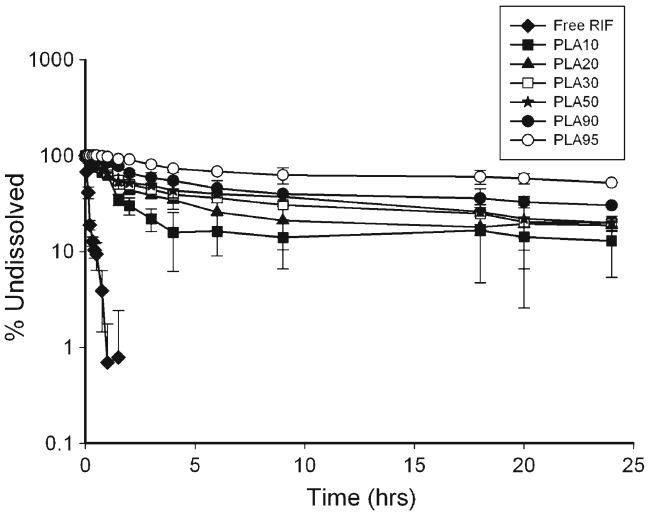

Fig. 12. Release profiles of free rifampin compared to rifampin microspheres containing 10–95% poly(lactic acid). Number of replicates not stated in the original reference. Reproduced with permission from Coowanitwong *et al.* (36)

For a solid oral product, Tsong and Hammerstrom (40) present statistical methods using analysis of variance, based on a single dissolution time point (ANOVA or Student's t test), or for multiple dissolution time points (MANOVA). Other approaches use model-independent methods (f_1 and f_2) or statistical comparison of model parameter estimates. Multivariate approaches (*e.g.*, MANOVA) compare entire profiles, but may not have sufficient statistical power to detect important differences. ANOVA and t test approaches are more statistically powerful, but compare only single dissolution time points or impose multiplicity issues when applied to multiple time points.

Two currently used model-independent approaches for comparison of T and R dissolution profiles are based on a difference factor (f_1) and a similarity factor (f_2):

$$f_1 = \frac{\sum_{j=1}^{n} |R_j - T_j|}{\sum_{j=1}^{n} R_j} \times 100;$$

$$f_2 = 50 \times \log\left\{ \left[1 + (1/n) \sum_{j=1}^{n} |R_j - T_j|^2 \right]^{-0.5} \times 100 \right\}$$

The difference factor, f_1, measures the percent error over all time points to determine if there is evidence of significant difference between the two profiles. By contrast, the similarity factor, f_2, uses an equivalence approach based on mean squared differences to determine if there is sufficient evidence of similarity between the two profiles. Both FDA and EMA suggest the following acceptance criteria for solid oral dosage forms:

- f_1 values lower than 15 (0–15) indicate no difference (*i.e.*, there is no evidence of difference, or cannot see 'signal above noise')
- f_2 values higher than 50 (50–100) indicate similarity (*i.e.*, there is evidence that there is no important difference). In addition, regulators request that the sponsor use at least 12 individual dosage units when comparing dissolution profiles *via* the similarity factor.

The f_2 metric has been the focus in regulatory guidances where comparison of dissolution profiles is used to support "biowaivers" for process scale-up or formulation changes for solid oral dosage forms. The use of f_2 metric is not, however, mandated. The FDA guidances (41,42) generally allow use of "appropriate statistical testing with justification." The EMA

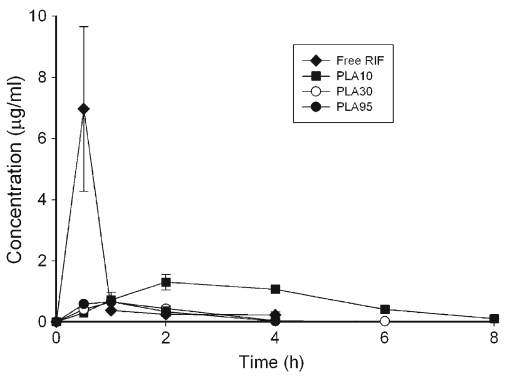

Fig. 13. Plasma concentration *vs* time profiles obtained after intra-tracheal instillation of free rifampin and poly (lactic acid)-coated microspheres in rats. Number of replicates not stated in the original reference. Reproduced with permission from Coowanitwong *et al.* (36)

guideline (43) suggests comparison of individual time points, model parameters, as well as similarity factors. An additional consideration for OIP particles fractionated by cascade impactor is the introduction of multiple acceptance limits for different size ranges (18), which applies as well to other tests besides f1 and f_2.

Figure 14, for a blinded solid oral product, shows the average dissolution profiles (solid lines) and individual dissolution test results at each time point, along with the calculated values for f_1 and f_2. In this example, the two profiles would not be declared significantly different ($f_1<15$), but they do show evidence of similarity ($f_2>50$).

To date, very little substantive quantitative (statistical) comparisons of dissolution profiles of OIPs have been published. In those instances where this was attempted, the metrics and associated acceptance criteria for solid oral dosage forms have been assumed (18).

DISCUSSION

US Pharmacopeial Position

In 2008, an *Ad Hoc* Advisory Panel of the US Pharmacopeia considered the possible development of dissolution testing in association with OIPs, in the light of developments in experimental techniques that might be capable of the robustness necessary for compendial acceptance (14). They concluded with the following position statement:

> A relationship between *in vitro* dissolution and some relevant parameters of bioavailability may be required before one can predict the bio-performance of aerosols. At this time two cases may be possible:
>
> 1. If particle size and thus surface area are the rate-controlling factors for aerosol drug dissolution, manufacturers may need only control particle size and distribution as quality and process control steps during manufacturing and batch release. Such controls may help identify shelf life provided that a relationship between particle size and dissolution has been established.
> 2. In addition to using cascade impactors to characterize aerosolized drug products, manufacturers may need to conduct dissolution tests for these drug products. The dissolution apparatus could be a flow-through cell that may be modified from USP Apparatus 4. GMPs would be required.

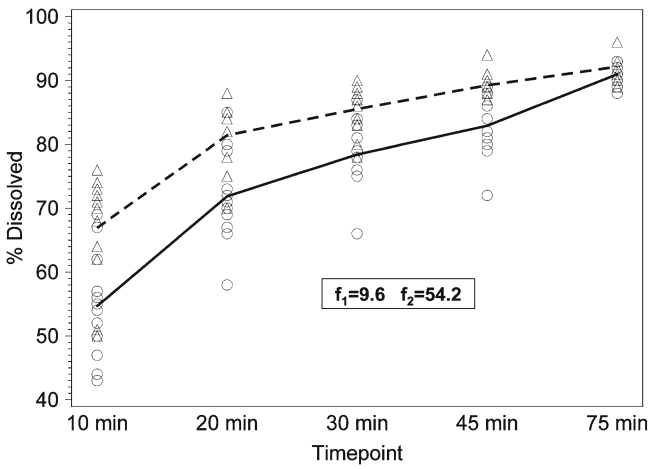

Fig. 14. Example of f_1 and f_2 calculated values for two dissolution profiles for a blinded solid oral product

In spite of the availability of several procedures that might be implemented, after searching several biomedical databases, the USP Panel could not find information suggesting adverse outcomes associated with dissolution in the fluids that line human respiratory tract. However, they made the important qualification that past experience may not be predictive of future developments, such as the creation of novel controlled-release inhaled-based products. Consequently, the Panel's recommendation was that the US Pharmacopeia need not at this juncture be concerned with standards for dissolution of inhalation dosage forms, noting that the importance of dissolution testing may rather be a future consideration if a procedure is developed by/for the industry, or in case of a public health/regulatory concern. In line with its overall conclusion, the USP Panel did not consider specific statistical issues for analysis of dissolution data for OIPs.

Industry Position

In addition to the review of the current state of dissolution techniques presented above, the IPAC-RS Dissolution Working Group has considered the purpose of dissolution testing of inhaled products in light of the published work in the area, including the US Pharmacopeial position statement. Dissolution testing appears to be most promising as a tool supporting development of OIPs, which have been engineered to achieve modified-rate (increased or decreased) release to, or through the lung. This type of evaluation has well-defined *in vitro* release methodologies in place for solid and semisolid dosage forms that have been standardized in the compendial literature. The logic underlying the development of uniform, well understood and robust procedures for such dosage forms is self-evident, given that their delivery to the site of action in the body takes place at some stage by a formulation-controlled process, and that very often, it is the associated drug release kinetics that govern the release of the actual API to the site of action and the consequent physiological effect.

The situation with the delivery of APIs to the site of action from OIPs is somewhat different. Although dissolution in fluids lining the cellular walls of the respiratory tract is involved in the drug delivery process, other factors such as the overall permeability of the lung tissues can also play an important part in the transport of API to the site of action. Furthermore, currently available OIPs generate polydisperse aerosols from which the particles do not deposit uniformly within the respiratory tract. This outcome arises because the deposition process is both particle size and velocity dependent, and both variables change significantly as a function of location within the airways. Furthermore, they are dependent upon the breathing pattern adopted by the patient. Finally, for patients with airways disease, the transport and deposition of airborne particles through the respiratory tract can be influenced by airway patency (openness) that is likely to change with disease progression, particularly if tissue damage or remodeling takes place, as is the situation with emphysema and advanced stages of chronic obstructive pulmonary disease

(COPD). This heterogeneity in respiratory tract deposition profile as well as active transport mechanisms can influence the systemic absorption of the API, complicating the process of interpreting the resulting pharmacokinetic data (44). Furthermore, there is no standard dissolution fluid that can be said to be representative of respiratory tract deposition in the entire lower respiratory tract for OIPs.

There is some evidence that dissolution testing may be able to distinguish between formulations of the same drug. It may therefore prove to have value as a more general development tool, probing the effect of drug or formulation characteristics. However, the published literature does not demonstrate conclusively that dissolution testing provides insight into such effects that could not be achieved by theoretical considerations or simpler measurements.

Fundamental challenges remain in the development of dissolution methodology for inhaled products, exhibited particularly in the published data for the low solubility compounds, which are thought most likely to be subject to dissolution rate-limitation *in vivo*. These arise from the limited surface area on which the respirable dose is necessarily captured *in vitro* and are manifested as mass-dependent dissolution rates and/or permeation-controlled zero-order kinetics in a number of examples (16–18). These effects may impact the discriminating ability of the technique and make quantitative comparison between batches or products challenging. The methodology remains practically challenging, *e.g.*, in terms of dose collection and in the preparation of biorelevant media preferred by many authors.

Considering these challenges, the lack of evidence demonstrating robustness of most published methods, and limited discussion of statistical approaches to data handling, dissolution testing of inhaled products should currently be regarded as a developmental tool, which itself requires further development. There is currently no evidence suggesting a need for dissolution to be considered as a quality control test for inhaled products, and it is clear that current methodology would be incapable of robustly supporting such an application.

To maximize the benefits of dissolution data for OIP development, however, much additional experimental, clinical, and statistical research is needed, especially in the following areas:

- Establishing quantitative *in vitro–in vivo* relationships between dissolution data and PK, PD or clinical data
- Establishing quantitative *in vitro–in vivo* relationships between dissolution data and PK, giving consideration to the appropriate dissolution timescale relative to mucocilary or macrophage particulate clearance mechanisms
- Improving the robustness and validation of the dissolution apparatus, particularly with regards to drug loading effects
- Using a truly predictive dissolution medium that correctly simulates dissolution in the lung
- The use of experimental dissolution data within predictive pharmacokinetic models [*e.g.*, GastroPlus™ Simulations Plus Inc., Lancaster, CA pulmonary module data (45) or the published Hochhaus model data (46)]. Most available models, however, either assume first-order dissolution kinetics or predict dissolution based an assumption of monodispersed particles, while most published dissolution data from polydispersed APIs deviate significantly from first-order kinetics
- Use of dissolution data as a parameter for product development design-of-experiments, selecting an appropriate mathematical/statistical model to reduce the dimensionality of the dissolution data, preferably to a single dimension.

CONCLUSIONS

Building on the 2008 USP *Ad Hoc* Inhalation Advisory Panel's report, the IPAC-RS Dissolution Working Group reviewed all current literature and considered the strengths and limitations of the published procedures for dissolution testing of OIPs. Even though the number of publications has increased since 2008, the fundamental conclusions drawn by the USP Panel (*e.g.*, challenges with the choice of the fluid medium, lack of adverse dissolution-related outcomes that would justify the need for a standardized dissolution test) have not changed. Furthermore, the published methods lack any validation data for various OIP and API types, which would be needed to demonstrate their robustness before being developed into a compendial test. For these reasons, IPAC-RS endorses the recommendation of the USP *Ad Hoc* Inhalation Advisory Panel not to pursue the development of standardized methods for possible compendial use, but will continue to maintain a watching brief on the possible impact of dissolution-related effects associated with potential new forms of OIPs, particularly those involving controlled release.

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