Miniaturization of Powder Dissolution Measurement and Estimation of Particle Size

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INTRODUCTION

It has been shown[1], that disk intrinsic dissolution rate (IDR) can be determined from powder dissolution experiments for BCS class II and IV (low soluble) compounds. This research investigated the applicability of a novel approach for estimating particle size from powder dissolution experiments of very small quantities of compounds. Five model compounds were selected for the study: hydrochlorothiazide, phenazopyridine, 2-naphthoic acid, indomethacin, and dipyridamole (span in solubility 5-911 µg/mL).[2]

MATERIALS AND METHODS

The µDISS Profiler*PLUS*™ instrument (*p*ION INC), Fig. 1, used in the dissolution measurements employs eight fiber optic dip probes, each with its own dedicated photodiode array (PDA) spectrophotometer. Each probe is positioned centered in the vial holding a magnetic stirrer in 1-3 mL media at 37° ±0.5° C maintaining a stirring speed of 100 ±2 RPM. Some of the challenges of traditional dissolution testing methods that use external sampling of the test solutions are avoided by using in situ fiber optic dip probes, since the concentration measurements are performed directly in the dissolution media, allowing the processed results to be plotted in "real time." Interference due to background turbidity is minimized by a spectral second derivative method. Full spectral scans of all channels takes less than one second. The baseline noise is ±0.0002 absorbance units.

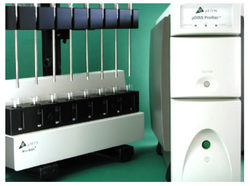

Fig. 1. µDISS Profiler PLUS™ from *p*ION INC uses a temperature controlled Mini-Bath and 8 integrated diode array spectrometers to collect full UV spectra as often as once per one second.

In Situ Dissolution in 96-well Microtitre Plate

A new prototype instrument (*p*ION INC, to be released in 2010) allowing *in situ* concentration monitoring in 96-well microtitre plate format was used to evaluate if powder dissolution/solubility experiments could be done in 0.1-0.2 mL of buffer with uninterrupted stirring and real time concentration detection, eliminating the filtration step. Compounds were introduces as slurries or DMSO stock solutions and their concentration in the plate was monitored every 2 minutes by collecting full UV spectrum (200 – 720 nm).

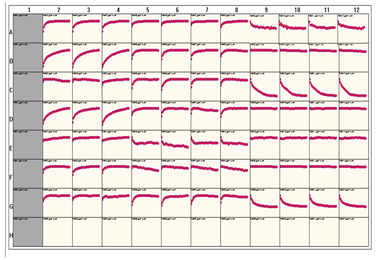

Fig. 2 Print screen of dissolution/precipitation profiles in 96-well microtitre plate.

Theoretical Framework

Under several simplifying assumptions that are expected to hold for low soluble compounds (e.g., dose number >> 1), it was shown[2], that the dissolution of a poly-disperse powder can be described by the following equation:

$$C_{tot}(t) = \sum_{i=0}^{N-1} C_i^{\infty} \cdot \left(1 - \exp\left[-\frac{1}{f_i} \cdot \left(\frac{A^0_{pwd,i}}{V}\right) \cdot P^0_{ABL,i} \cdot t\right]\right) \quad (1)$$

The total concentration, $C_{tot}(t)$, µg/mL, of the dissolved drug, as a function of time, t (min), is equal to the sum of the size group concentrations, where C_i^{∞} is the i^{th} group concentration at t= ∞. $\Sigma f_i = 1$ and $\Sigma C_i^{\infty} = S$, where S (µg mL^{-1}) is solubility. For the rest of the time, $f_i = C_i(t)/C_{tot}(t)$. The total initial powder surface area of i^{th} group is $A^0_{pwd,i}$. The $P^0_{ABL,i}$ is permeability through diffusion layer (ABL) of thickness $h^0_{pwd,i}$ adhering to the particles of i^{th} size. The volume of the medium is V (cm^3).

The dissolution profiles were fitted with eq. (1) under additional assumptions that only two particle sizes dominated and the particles were spherical. The thickness of ABL surrounding i^{th} particle was refined taking into account the spherical particle model[3].

RESULTS AND DISCUSSION

Specific Surface Area (Dry State) and Particle Size Distribution

Figure 3 shows the results of the BET-determination of the powder specific surface area (A_{BET}, cm^{2}mg^{-1}) and displays the Coulter counter particle size distribution (PSD) profiles for hydrochlorothiazide, one of the four model drugs considered. Also indicated is the weighted logarithm-mean particle sizes, d_p. The specific surface area can be used to estimate particle size assuming spherical mono-disperse particles with density ρ = 1.3 g cm^{-3}.

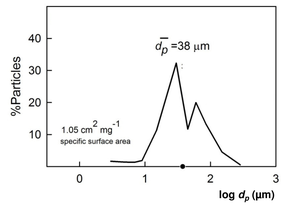

Fig. 3 Measured Coulter counter particle size distributions for hydrochlorothiazide, where d_p is the characteristic size of the particles.[2]

The average calculated particle diameters would be 48, 3.4, 15, and 13 µm for hydrochlorothiazide, phenazopyridine, 2-naphthoic acid, and indomethacin, respectively. These BET-based values, when compared to PSD-based (d_p) values, suggest that phenazopyridine may consist of agglomerated/porous particles in the Coulter suspension, since the calculated spherical particle diameter (3.4 µm) is about five times lower than the d_p value (16 µm) from the Coulter counter assessment.

Powder Dissolution Profiles

Figure 4 shows the powder dissolution profile of hydrochlorothiazide (pH 1.2, 4.5, 6.8). In the selected media, the compounds studied are predominantly uncharged, given the pK_as of the drugs.

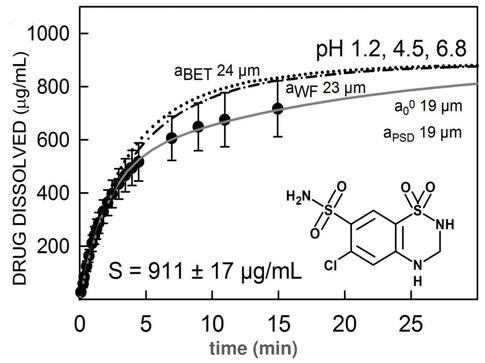

Fig. 4. Powder dissolution curve for hydrochlorothiazide with experimental points fitted with various models.

The dot and dash-dot curves were simulated using the Wang-Flanagan[3] diminishing diameter spherical particle non-sink equation incorporated into the microspeciation program, µDISS-X.[1,2] The appropriate intrinsic solubility values, stirring conditions, temperature and USP buffer concentrations were used as parameters. Specifically, the dot curves were simulated using the dry-state spherical particle radius (µm), a_{BET} = 30 / (A_{BET} ρ). In the dash-dot curves, the spherical particle radii, a_{WF}, were adjusted (using µDISS-X) to best match the measured powder dissolution profiles. The solid curves were the outcome of the biexponential spherical particle equation analysis (eq. 1, N = 2). Table 1 contains the determined size parameters for all of the model compounds studied.

Table 1. Spherical Particle Radii from Various Models.

COMPOUND	A_{BET} [a] (cm^2/mg)	a_{BET} [b] (µm)	a_{PSD} [c] (µm)	a_0^0 (µm)[d]	pct[e]	a_1^0 (µm)[d]	a_{WF} [f] (µm)
hydrochlorothiazide, pH1.2,4.5,6.8	1.1	24	19	19 ± 1	65%	115 ± 10	23
phenazopyridine.HCl, pH 1.2	13.1	1.7	7.9	16 ± 1	80%	24 ± 7	14
2-naphthoic acid, pH 4.5	3.4	7.3	11	68 ± 1	95%	402 ± 25	60
indomethacin, pH 4.5	3.9	6.4	5.1	16 ± 1	85%	94 ± 7	19
dipyridamole, pH 6.8 (stable polymorph)	--	--	--	10 ± 1	84%	35 ± 30	11

[a]Dry-state specific surface area by the BET surface adsorption method. [b]Calculated dry-state radius, assuming A_{BET} represents a monodisperse population of spherical particles. [c] Weighted log-mean particle distribution radius, $a_{PSD} = d_p / 2$. [d] a_0^0, a_1^0 are the primary and secondary particle radii from eq. 1 analysis. [e] Percentage of the smaller particles from eq. 1 analysis. [f] Radius from fitting powder dissolution curve to the Wang-Flanagan monodisperse spherical particle non-sink equation, using µDISS-X program.

Microtitre Plate Dissolution Data

The powder dissolution profiles of hydrochlorothiazide (pH 4.5) introduced as DI water slurry were also collected in the microtitre plate dissolution experiment (Fig. 2). Three replicates were averaged (blue symbols in Fig. 5) and the data were fitted (dashed line in Fig. 5) using eq. 1 and assuming N = 1. As evident from Fig. 5, the model described the experimental points very well and particle size analysis indicated effective particle radius to be 27.5 µm - good agreement with BET data (24 µm) and primary particle radius (19 µm) resulted from analysis of powder dissolution data presented in Fig. 4, a. The specific surface area estimation (0.84 cm^2 mg^{-1}) is within 20% from one measured by Coulter method (1.05 cm^2 mg^{-1}).

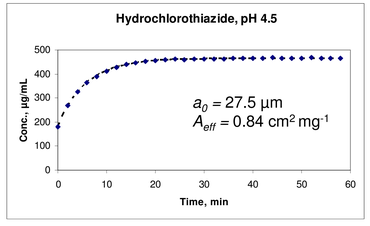

Fig. 5. Dissolution profile of hydrochlorothiazide from 96-well dissolution experiment (0.22 mg in 0.2 mL of USP pH 4.5 buffer, 25℃). Points represent averages over 3 replicates with errors (not shown) within 10 – 15%.

CONCLUSIONS

Our study suggests that the non-USP miniaturized apparatus can be used to approximate particle size from the powder dissolution data.

For the drugs studied, the simplified poly disperse particles (two dominant radii) dissolution model explained data equally well or better than Wang-Flanagan spherical particle non-sink equation[3] and determined particle sizes agreed reasonably with those independently measured by the Coulter counter method.

By substantiating that the quantity of API used in traditional dissolution studies could be reduced by 10,000-fold without sacrificing the quality of the measurement, here and in our preceding works,[1,2] we are confident that the opportunity to consider investigative dissolution studies earlier in drug development is feasible, in projects where only a few mg of API may be available for evaluation.

The study suggests that further miniaturization of the dissolution apparatus, to the level of the 96-well microtitre plate, may be possible.

REFERENCES

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(2) Avdeef, A; Tsinman, K; Tsinman, O; Sun, N; Voloboy, D. Miniaturization of Powder Dissolution Measurement and Estimation of Particle Size. *Chem. Biodiversity* **2009**, in press.

(3) Wang, J.; Flanagan, D. R. General Solution for Diffusion-Controlled Dissolution of Spherical Particles. 1. Theory. *J. Pharm. Sci.* **1999**, *88*, 731-738; 2. Evaluation of Experimental Data. *J. Pharm. Sci.* **2002**, *91*, 534-542.