Powder Intrinsic Dissolution Rate Measurement: When is it Possible?

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INTRODUCTION

This research investigated the applicability and limitations of a novel approach for measuring intrinsic dissolution rates (IDR) of very small quantities of compounds introduced as powders to buffered solutions and comparing these results to disk IDR obtained using the traditional Wood's apparatus[1] and miniaturized disk IDR approach[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) spectrometer. 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 and 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.

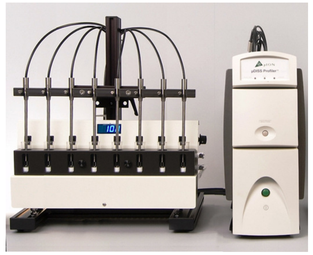


Fig. 1. µDISS Profiler PLUS™ from *p*ION INC uses a temperature controlled Mini-Bath and 8 integrated diode array spectrometers to collect full UV spectra as often as once per one second.

Relationship between Disk IDR and Powder Dissolution

Investigative dissolution studies are often carried out with rotating discs[1,2] where compacted powder of the API with known exposed area is immersed in dissolution test media. By definition, $\mathrm{IDR_{disk}} = (dm/dt)_{max}/A_{disk}$, where the units of IDR are mg min^{-1} cm^{-2}, A_{disk} is the area of the drug disc (cm^2), m is the mass (mg), t is the time (min), and $(dm/dt)_{max}$ is the maximum slope of the dissolution curve, evaluated at the start of the dissolution process. According to the Noyes-Whitney equation, for diffusion controlled dissolution process, $\mathrm{IDR_{disk}}$ is proportional to solubility at the solid-liquid interface (c_s) and inversely proportional to the thickness of the diffusion boundary layer h (Eq. 1). At the same time the *initial* dissolution rate of the powder, $\mathrm{DR_{pwd}}(t\to 0)$, can be expressed as (Eq. 2) :

$$\mathrm{IDR_{disk}} = \frac{dm}{dt}\cdot\frac{1}{A_{\mathrm{disk}}} = \frac{D}{h_{\mathrm{disk}}}\cdot c_s \qquad (1)$$

$$\mathrm{DR_{pwd}}(t\to 0) = \frac{dm}{dt_{t\to 0}} = D\cdot\frac{A_{\mathrm{pwd}}}{h_{\mathrm{pwd}}}\cdot c_s \qquad (2)$$

Substituting the product of diffusivity (D) and c_s from (Eq. 2) into (Eq. 1), $\mathrm{IDR_{disk}}$ can be expressed in terms of $\mathrm{DR_{pwd}}$:

$$\mathrm{IDR_{disk}} = \mathrm{DR_{pwd}}(t\to 0)\cdot\frac{h_{\mathrm{pwd}}}{A_{\mathrm{pwd}}}\cdot\frac{1}{h_{\mathrm{disk}}} \qquad (3)$$

Initial dissolution rate of the powder can be directly obtained from the dissolution experiment and h_{disk} can be calculated for known rotation speed and viscosity[3]. For low soluble compounds when change in the area can be neglected, the integrated Noyes-Whitney equation (2) may be used to fit the experimental dissolution data

$$c(t) = c_s\left\{1-\exp\left[-\left(\frac{D}{V}\right)\left(\frac{A_{\mathrm{pwd}}}{h_{\mathrm{pwd}}}\right)(t-t_{LAG})\right]\right\} \qquad (4)$$

where the ratio of powder area and effective diffusion boundary layer A_{pwd}/h_{pwd} is determined as one of the fitting parameters along with c_s and a (wetting) lag time (t_{LAG}).

RESULTS AND DISCUSSION

The consideration described above opens the possibility of deriving $\mathrm{IDR_{disk}}$ values from the powder dissolution experiments by using by using eqs. (3) and (4). We'll call such powder dissolution-derived IDR as $\mathrm{IDR_{disk}}$, to avoid confusion with *disk* IDR values obtained using the traditional[1] or miniaturized IDR approaches[2].

The Case of a Practically Insoluble Compound: Glibenclamide

Fig. 2 shows dissolution profiles of 1.4 mg (a) and 2.9 mg (b) of glibenclamide in 20 mL of phosphate buffer at pH 6.5. Although initial dissolution rates are different for these two profiles due to difference of the exposed area, both replicates produce virtually identical *powder* IDR : 0.19 µg min^{-1} cm^{-2} (a) and 0.21 µg min^{-1} cm^{-2} (b).

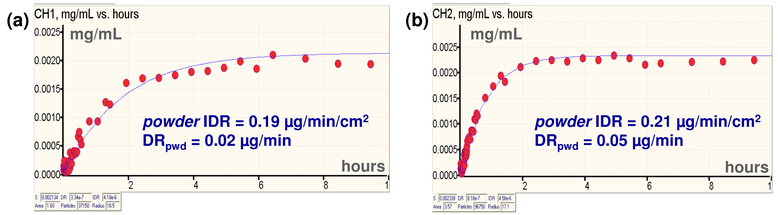


Fig. 2. Screen shot from the µDISS Profiler*PLUS* Command Software showing concentration versus time profile for glibenclamide at pH 6.5. The blue curve is the "real-time" fit of the dissolution profile with equation (4).

Projected IDR values from powder dissolution measurements are in good agreement with results obtained using the Mini-IDR apparatus, see Fig. 3: IDR = 0.18 (±0.02) µg min^{-1} cm^{-2}. It should be noted that in case of the powder dissolution experiment, less than 3% of the initial material was dissolved. This means that saturation was reached and equilibrium solubility could therefore also be determined at the end of the assay.

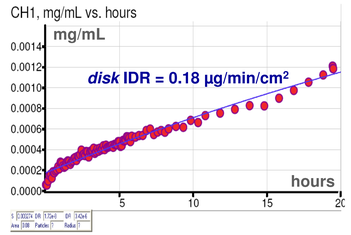


Fig. 3 Example of the dissolution profile of glibenclamide released from a constant exposed pellet area of 0.071 cm^2.

It's interesting to note, that half-time to reach saturation ($t_{1/2}$) was 1 and ½ hour respectively for dissolution profiles in Fig. 2, a, b, while the projected $t_{1/2}$ for the miniaturized IDR experiment was 27 hours.

The Changing Surface Area of a Dissolving Powder

The approximation (Eq. 4) works reasonably well for practically insoluble compounds when the change in exposed area in the beginning and at the end of the dissolution experiment can be neglected. If a substantial amount of compound gets dissolved, the simple exponential curve (Eq. 4) may not fit the experimental data well. For example, the relative change in area of particles with spherical or cubic symmetry versus fraction of material dissolved is shown in Fig. 4. The mathematical model has been further developed to include change of area into the fitting of powder dissolution data.

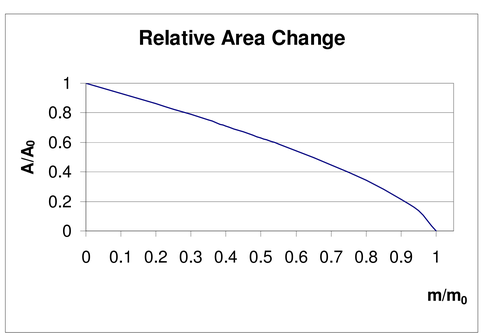
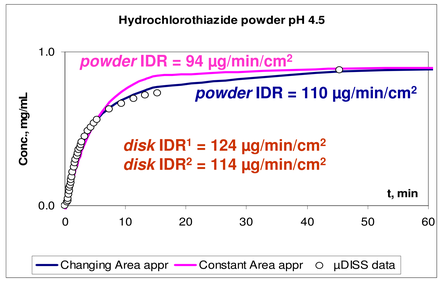


Fig. 4. Relative change in the area for isometric powders when mass m is proportional to $A^{3/2}$ (e.g., spherical and cubic particles)

As an example, Fig. 5 shows the dissolution profile of hydrochlorothiazide when more than 90% of the amount of compound was dissolved.



It is clear that the curve accounting for area shrinkage (blue line) fits the experimental data much better than the curve based on the simpler Eq. 4 (purple line). Also, *powder* IDR determined from the blue curve correlates better with published *disk* IDR[1,2].

Fig. 5. Dissolution data for hydrochlorothiazide fitted with a constant area model (Eq. 4, purple line) and with a model that takes into account the change in powder area during the dissolution experiment.

Further development and validation of the powder dissolution model with changing area is required in order for the *powder* IDR approach to be extended to compounds completely dissolved at the end of the assay.

Correlation between Powder IDR and Traditional IDR Methods

One of the main objectives of this study was to demonstrate that traditional disk IDR measurements requiring from 100 – 700 mg of API (traditional Wood's apparatus[1]) to 5 – 15 mg of API (miniaturized disk IDR[2]) can be effectively substituted by small volume powder dissolution experiments sometimes using 0.05 to 1 mg of compound per mL of medium.

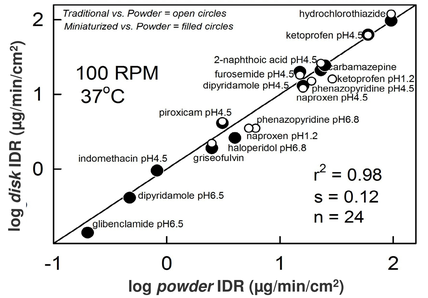


Fig. 6. Log-log *disk* IDR versus *powder* IDR correlation diagram.

Fig. 6 is a correlation log-log plot between $\mathrm{IDR_{disk}}$ values determined in the study (log *powder* IDR) and data collected with either the traditional Wood's method[1] (open circles) or with the miniaturized IDR method[2] (filled circles). A very high correlation (r^2 = 0.98) was achieved in the study, with IDR values spread over 3 orders of magnitude. The study suggests that for low soluble compounds $\mathrm{IDR_{disk}}$ can be reliably determined by analyzing powder dissolution profiles.

CONCLUSIONS

Although powder dissolution research and IDR studies are traditionally done separately, this work demonstrates that at least for the case of *low soluble compounds*, disk IDR numbers can be reliably derived from powder dissolution data.

Powder dissolution IDR results for low soluble compounds correlate extremely well with published disk IDR data.

The use of a small volume powder dissolution apparatus (µDISS Profiler*PLUS*) can reduce the amount of needed API by 10,000-fold compared to traditional methods, enabling IDR studies much earlier in the drug discovery process.

The turn-around time for powder dissolution experiments is much shorter than for traditional IDR studies. *In situ* measurement also yields much higher data density.

Powder dissolution experiments do not require sink conditions to be maintained as the entire detailed dissolution curve is used to derive *powder* IDR values.

Additionally, the effective area of the powder as well as the effective spherical particle size can be estimated by analyzing the powder dissolution profiles[4].

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