Comparison of Miniaturized Intrinsic Dissolution Rate Measurement to Traditional Wood's Apparatus

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INTRODUCTION

In the present study, we explored a new miniaturized disk intrinsic dissolution rate (IDR) method applied to 14 model drug compounds, using as little as 5 mg to make compacted disks of 0.071 cm² exposed surface area, rotated in buffer media of as little as 10 mL volume. Drug concentration was measured by an *in situ* fiber optic UV method. All of the low-soluble and many of the high-soluble model drugs considered by Yu et al.[1] along with some other compounds with available IDR data obtained by traditional means were included in the comparison.

The main objective of the study was to demonstrate that the miniaturized disk IDR apparatus and method can produce results of comparable reliability as those obtained by traditional Wood's apparatus methods, without the need for any scaling adjustments, and that the miniaturized apparatus can be potentially useful in BCS classification of solubility, applied at a much earlier time in the development cycle.

MATERIALS AND METHODS

The Mini-IDR compression system (Heath Scientific, UK) in Fig. 1b was used to make miniaturized pellets. As little as 5 mg of the API powder is loaded into the cylindrical hole of a passivated stainless steel die and compressed (1 min at 120 bar) to a uniform, flat surface, with an exposed area of ~ 0.071 cm² (Fig. 2a). The die can accommodate larger weights of API, if needed. Once compressed, the sample die is inserted into a cylindrical Teflon rotating disk carrier containing an embedded magnetic stir bar at its base (Fig. 2b). A black dot on the side of the cup (Fig. 2c) allows for independent rotation speed verification. The stirrer-die assembly is placed in a flat-bottomed glass vial ready for dissolution analysis, as shown in Fig. 2c.

The µDISS Profiler*PLUS* instrument (*p*ION INC), Fig. 1a, used in the dissolution measurements employs eight fiber optic dip probes each with its own dedicated photodiode array (PDA) spectrophotometer. The probes are center-positioned in the vial holding the rotating disk carrier in 10 mL media at 37° ± 0.5° C (Fig. 2c) at stirring speed 100 ± 2 RPM. Some of the challenges of traditional dissolution testing methods that use external sampling of the test solutions were avoided by the use of the *in situ* fiber optic-dip probe UV apparatus, allowing the concentration measurements to be made directly in the dissolution media and the processed results to be plotted in "real time." Interference due to background turbidity is minimized by a spectral second derivative method. The full spectral scanning of all 8 channels takes less than one second. The baseline noise is ±0.0002 absorbance units.

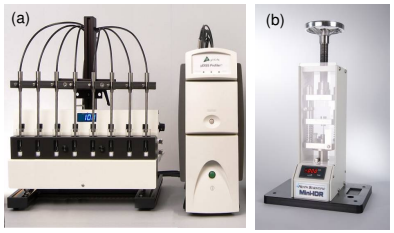


Fig. 1 µDISS Profiler PLUS™ from *p*ION INC (a) uses 8 integrated diode array spectrometers to collect full UV spectra as often as once per second. The Mini-IDR™ apparatus from Heath Scientific, UK (b) can be used to make pellets with 5 - 10 mg of API, instead of the "traditional" 100 – 700 mg.

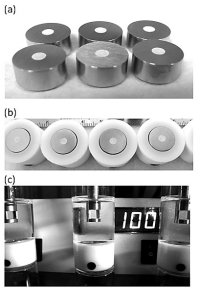


Fig. 2 Miniaturized rotating disk intrinsic dissolution rate sample holder: (a) stainless steel dies with compound pellets; (b) dies inserted into Teflon holders; (c) Teflon holder assembly in 10 mL media, with fiber optic probes inserted.

RESULTS AND DISCUSSION

Dissolution Profiles

During drug product development, investigative dissolution studies are often carried out with rotating disks of compacted powder of the API immersed in dissolution test media (Wood's method). The IDR values are determined according to the Noyes-Whitney equation: IDR = $(dm/dt)_{max}/A$, where the units of IDR are mg min^{-1} cm^{-2}, A is the area of the compound disk (cm²), 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.

Traditionally, an amount of about 150 – 700 mg of pure API is compressed in a punch and die to produce a pellet with an exposed surface area typically from 0.5 to 1.3 cm². Usually, samples are extracted from the media using some kind of filtering and at certain time intervals as the compound is dissolved. UV absorption data are externally measured at a particular wavelength to calculate the concentration of API as a function of time.

The new *in situ* fiber optic dip-probe method use 30 – 100 times less API and requires neither filtration nor extraction of dissolution media.[2,3] Fig. 3 combines dissolution profiles of 13 model drugs with IDR values spanning 6 order of magnitudes.

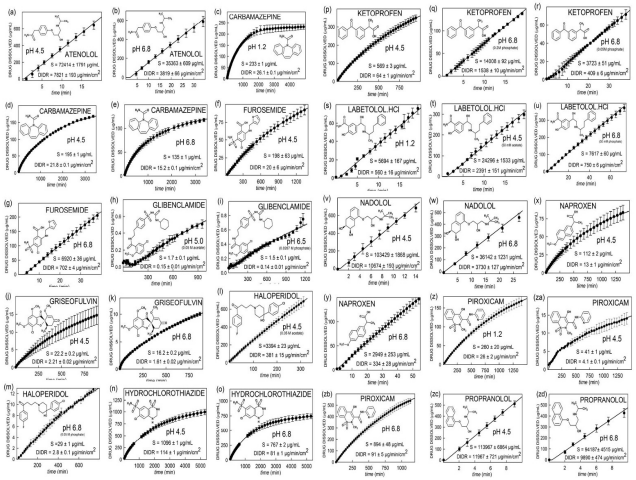


Fig. 3 a-zd Dissolution profiles. DIDR = disk IDR.

Sensitivity of the Method

The majority of compounds included in the study and shown in Fig. 3 were selected to match the ones investigated by Yu *et al.*[1] for comparison reason. Glibenclamide was selected to demonstrate the sensitivity of the UV *in situ* method. As evident from Fig. 4, concentrations below 0.5 µg/mL can be confidently determined. The blue line approximates the collected data with the exponential solution of the Noyes-Whitney equation and allows estimation of solubility at the liquid-solid interface from the slope of the dissolution profile.

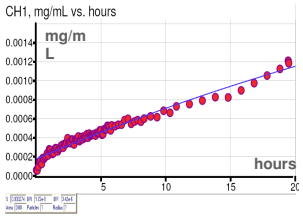
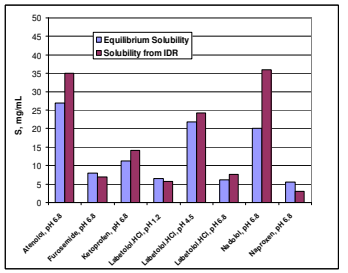


Fig. 4. Screen shot from the µDISS Profiler Command Software showing concentration versus time profile for glibenclamide at pH 6.5.

Dissolution and Solubility

If complicating effects (e.g., polymorphic changes during dissolution) are neglected then IDR is proportional to the solubility of the drug at the solid-liquid interface[1-3]. Thus, in some cases the compound solubility can be determined from the slope of the dissolution curve even if saturation is not reached and long before the solution equilibrates. Fig. 5 shows comparison of solubility estimated from the dissolution profile with equilibrium solubility measured at liquid-surface interface by the method described in Ref. 4.



Despite the fact, that compounds were completely dissolved at the end of the IDR experiment, solubility determined from the initial slope of the dissolution profile correlates well with equilibrium solubility measured independently.

Fig. 5. Solubility determined by Sarajuddin and Jarowski method[4] at the liquid-surface interface (blue bars) and solubility estimated from the slope of dissolution curve (brown bars). Thickness of the diffusion boundary layer was calculated based on Levich's equation.

It is important to note, that depending on buffer concentration, pH at the surface of the ionizable solid API may be significantly different from the bulk pH of the dissolution media and that solubility at surface pH (not bulk pH) is the driving force behind the dissolution process.

Correlation between mini IDR and traditional IDR Methods

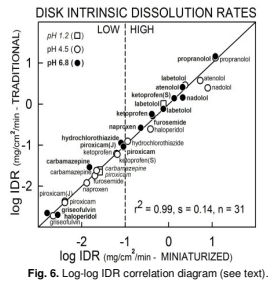


Fig. 6. Log-log IDR correlation diagram (see text).

Fig. 6 is the resultant correlation log-log plot between IDR values determined in the study (Fig. 3) and data collected with traditional method (mostly from ref. 1). A very high correlation was achieved in the study, with r^2 = 0.99 over more than 4 orders of magnitude in IDR values. The vertical line in Fig. 6 is a suggested dividing line between LOW and HIGH-soluble compounds if IDR were to be used for the purpose of BCS classification of solubility[1].

CONCLUSIONS

Miniaturized IDR results correlated extremely well with published IDR data with no additional adjustments. Use of the Mini-IDR apparatus in conjunction with the µDISS Profiler*PLUS* dissolution system reduces the amount of API needed 20-100 times enabling reliable IDR studies much earlier in the drug discovery and development process.

Solubility values at the solid-liquid interface obtained from the initial slope of dissolution curves correlated well with equilibrium solubility determined independently. This study supports the usage of IDR as a surrogate for solubility classification in BCS.

REFERENCES

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