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Technical Note: Miniaturized Intrinsic Dissolution Rate (Mini-IDR™) Measurement of Griseofulvin and Carbamazepine

Cynthia M. Berger[1,3], Oksana Tsinman[1], Dmytro Voloboy[1], Dana Lipp[1], Steven Stones[2], and Alex Avdeef[1]

e-mail: Cberger@pion-inc.com

[1]*pION INC, 5 Constitution Way, Woburn, MA 01801, USA.*

[2]*Heath Scientific Co Ltd., 1 North House, Bond Avenue, Bletchley, MK1 1SW, UK.*

ABSTRACT

Griseofulvin and carbamazepine were selected as model drugs to compare measurements of disk intrinsic dissolution rate (IDR) by a traditional (Wood apparatus) USP method (500-mg pellet, 900 mL media) and a new miniaturized method (5-mg pellet, 15 mL media) at 37 °C and 100 rpm. An in situ fiber optic UV instrument was used to collect dissolution data, with IDR calculated and displayed in real time. The IDR values from the present study and those reported by an FDA group (*1*) agree well, suggesting that the scale-down of hydrodynamics may be a reliable option for early development studies, where quantities of API are often highly limited.

INTRODUCTION

The classical disk intrinsic dissolution rate (IDR) (i.e., the rotating disk method) is a useful tool for mechanistic dissolution studies because of its well characterized fluid hydrodynamics. IDR measurements have been used to characterize solid oral dosage forms of drugs, including studies of dissolution–pH rate profiles in the presence of buffers, complexing agents, and various formulation excipients (*2–6*). It is currently debated at the FDA whether the IDR method can be used to determine solubility class membership in the Biopharmaceutics Classification System, with encouraging early indications (*1*).

In the classical method, a pure drug is compressed in a die with a hole of known diameter to produce a pellet of known exposed surface area (*7*). It is assumed that during the dissolution period, the exposed area of the pellet remains constant.

Thermostated baths are used, accommodating 500 or 900 mL dissolution vessel volumes, with temperature maintained constant at 37 °C (but in research settings, it is not uncommon to use 25 °C). About 100–700 mg of pure drug substance are needed to make the pellet. The typical surface area ranges from 0.5 to 1.3 cm^2. Typical pressures used are about 2000 lbs/in^2 (138 bar), applied for about one minute.

The IDR value is typically calculated from the equation

$$IDR = V/A\ dc/dt \qquad (1)$$

where the units of IDR are $mg/min{\cdot}cm^2$, V is the volume (mL), A is the area of the drug disk (cm^2), c is the concentration (mg/mL), and t is the time (min).

However, in early pharmaceutical development, usually the amount of drug (active pharmaceutical ingredient–API) available for testing is very limited, and the above classical method cannot be applied because of the large requirement of compound. The long standing concern that the hydrodynamic conditions may not scale down to small dimensions has stalled most groups from looking at small-volume dissolution substantially below 50–200 mL. In the present study, we compare a traditional USP approach with a new miniaturized API-sparing (5 mg) and media-sparing (15 mL) method for disk IDR measurement.

EXPERIMENTAL

Griseofulvin and carbamazepine were obtained from Sigma Aldrich. Griseofulvin was used as received. However, since carbamazepine was observed to undergo polymorphic transformation during preliminary studies, the compound was recrystallized from water at 37 °C before final use. A new miniaturized press apparatus, Mini-IDR™ (Heath Scientific), produced pellets that require only about 5 mg of API. The powder material was compressed inside stainless steel die cylinders to an exposed surface pellet with nominal surface area of 0.13 cm^2. The stainless steel dies were inserted into plastic holders containing embedded magnets and were placed into glass vials. The vials were then inserted into the µDISS Profiler™ (*p*ION INC) constant temperature chamber (37 °C) adapted with in situ fiber optic (FO) probes (*8*, *9*). The FO UV probes (5-mm pathlength) were lowered into each vial, and 15 mL of dissolution media (0.2 M phosphate buffer, pH 6.8) was pipetted directly into each vial. The disks were magnetically stirred at 100 rpm. The stirring speed was verified by an external control. The UV detection system consisted of a bank of six integrated

[3]*Corresponding author.*

diode array spectrophotometers, which can follow the concentration of the API release in situ as a function of time without having to filter the solutions. Conditions of the miniaturized IDR experiments are compared to the disk IDR in Table 1.

RESULTS AND DISCUSSION

Griseofulvin is a nonionizable molecule and is only slightly soluble in water. The drug solubility has been determined by the µDISS Profiler™ to be 17 ± 2 µg/mL (n = 4) at 37 °C, compared to an in-house solubility value of 25 ± 14 µg/mL (n = 221) at 25 °C using a miniaturized shake-flask instrument (µSOL Evolution™, *p*ION INC) in solutions containing 1% (v/v) DMSO. The in situ monitoring of the concentration-versus-time profile was collected as shown in Figure 1.

Carbamazepine is also a nonionizable, slightly water soluble molecule. The drug solubility has been determined by the µDISS Profiler™ as 180 ± 4 µg/mL (n = 5) at 37 °C, compared to an in-house solubility value of 116 ± 12 µg/mL (n = 14) at 25 °C using a miniaturized shake flask instrument (µSOL Evolution™). The in situ monitoring of the concentration-versus-time profile was collected as shown in Figure 2.

The dynamic IDR value was estimated by the µDISS Profiler™ during data acquisition according to a nonlinear regression approach, using the equation

$$C(t) = C_o + S\,(1 - e^{-kt}) \qquad (2)$$

where $C(t)$ and C_o are concentration (mg/mL), S is the solubility, k is a parameter (1/min) equal to $P_{ABL}A / V$, A is the area (cm²), t is the time (min), V is the volume (cm³), and P_{ABL} is the permeation of the drug through aqueous boundary layer permeability (cm/min) between the surface of the solid and the bulk solution.

By combining eqs 1 and 2, IDR is calculated as

$$IDR = S\,k\,V/A \qquad (3)$$

In Table 2, the MIDR results are summarized and compared to the values reported by the FDA group (*1*).

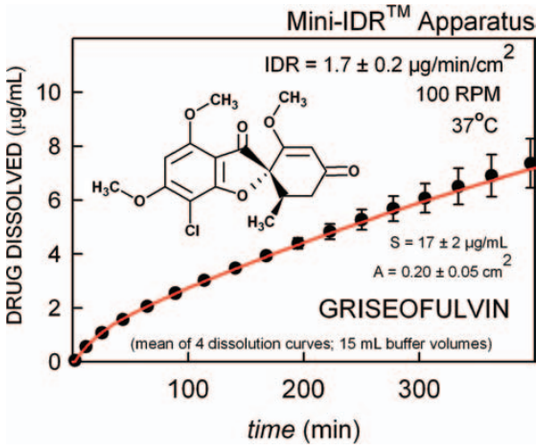

Figure 1. Dissolution curve with error bars for griseofulvin.

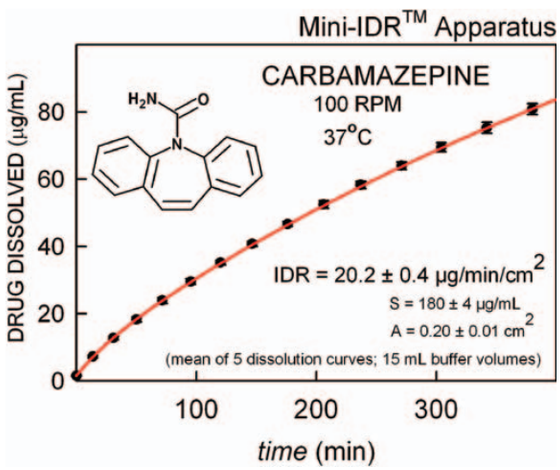

Figure 2. Dissolution curve with error bars for carbamazepine.

Table 1. Comparison of Experimental Conditions between Traditional Disk IDR and Mini-IDR.

	Wood's apparatus (7)	Mini-IDR method
Compression rate	2000 psi	1300–1500 psi
Compression time	1 min	1 min
Stirring speed	100 rpm	100 rpm
Temperature	37 °C	37 °C
Volume	225/900 mL	15 mL
Sample	500 mg	5 mg
Nominal Area	**0.5 cm²**	**0.13 cm²**
Media	pH 6.8, 0.2 M phosphate	pH 6.8, 0.2 M phosphate
Detection	UV, single wavelength	UV, entire wavelength
Sampling	every 30 min	every 2 min
	(5–10 data points)	(120 data points)

Table 2. Results and Comparison of the IDR Measurements.

Intrinsic Dissolution Rate (IDR) in mg/min/cm² units

COMPOUND	IDR	t (°C)	RPM	A (cm²)	Vol (mL)	Ref
carbamazepine	0.029	37	100	0.5	900	Yu et al. (*1*)
	0.020	37	100	0.2	15	this work
griseofulvin	0.0022	37	100	0.5	900	Yu et al. (*1*)
	0.0017	37	100	0.2	15	this work

CONCLUSIONS

The Mini-IDR values from the present study and the traditional disk IDR values reported by an FDA group (*1*) agree well, suggesting that the scale-down of hydrodynamics may be a reliable option for early development studies, where quantities of API are often highly limited.

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