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Feasibility studies of utilizing disk intrinsic dissolution rate to classify drugs

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Abstract

The purpose of this report was to investigate the feasibility of using disk intrinsic dissolution rate (DIDR) to determine solubility class membership. We employed a VanKel dissolution apparatus fitted with a Wood's intrinsic dissolution die. To test the robustness of the method, variations of DIDR with compression force, dissolution volume, distance of the drug disk from the bottom of the dissolution vessel, and drug disk rotation speed were studied using furosemide and metoprolol in pH 4.5 acetate buffer as a model system. The DIDRs of six low solubility and nine high solubility model drugs were then determined at pH 1.2, 4.5, and 6.8 and compared to their BCS solubility class membership. It was found that the compression force, dissolution medium volume, and die position had no significant effect on DIDR for the system studied. The proposed compression force, dissolution volume, die position, and rotation speed are 2000 psi, 900 ml, 0.5 in., and 100 rpm, respectively. The test results obtained from 15 model BCS drugs show a good relationship between the DIDR and BCS solubility classification with 0.1 mg/min/cm^2 as a class boundary unless the dose is either extremely low or high where discrepancies may exist between the solubility and DIDR methods. Therefore, more scientific research and debates are needed before considered for regulatory purpose.

Keywords: Disk intrinsic dissolution rate; Biopharmaceutics classification system; Dissolution; Solubility

1. Introduction

Disk intrinsic dissolution rate (DIDR) has been used for many years to characterize solid drugs (Amidon et al., 1982; Yu and Amidon, 1999). Determination of thermodynamic parameters associated with crystalline phase transitions, investigation of mass transfer phenomena during the dissolution process, determination of pH-dissolution rate profiles, the study of surfactant and pH effects on the solubilization of poorly soluble drugs, and understanding of the relationship between the dissolution rate and crystalline form are a few examples of using DIDR determinations (Wadke and Reier, 1972; Dahlan et al., 1987; Jinno et al., 2000; Chan and Grant, 1989).

DIDR is a rate phenomenon instead of an equilibrium phenomenon, so it might be expected to correlate more closely with in vivo drug dissolution dynamics than solubility. Therefore, it has been suggested that DIDR be used to classify drugs instead of solubility. According to the biopharmaceutics classification system (BCS), a drug substance is considered

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highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range 1.0–7.5 (Amidon et al., 1995; Yu et al., 2002). BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability (Amidon et al., 1995). Classifying drugs according to the BCS has resulted in an improved SUPAC-IR guidance, a dissolution guidance, and an FDA guidance on waiver of in vivo bioequivalence studies for BCS Class I drugs in rapid dissolution immediate-release (IR) solid oral dosage forms (CDER/FDA, 1995; 1997; 2000).

We wished to evaluate the feasibility of using DIDR to determine a drug's classification. To establish the robustness of the DIDR measurement procedure, we studied the dependence of the observed DIDR with changes in various experimental variables. Finally, we compared the DIDRs of model BCS compounds with their solubility classification.

2. Materials and methods

2.1. Materials

Atenolol, carbamazepine, cimetidine, furosemide, hydrochlorothiazide, ketoprofen, labetolol hydrochloride, (±)-metoprolol (+)-tartrate, nadolol, naproxen (acid), nortriptyline hydrochloride, piroxicam, propranolol, and ranitidine hydrochloride were obtained from Sigma Chemical Co. (St. Louis, MO, USA). Griseofulvin was obtained from Acros Organics, Geel, Belgium. All chemicals were used as received. Buffers were prepared as described in the US Pharmacopeia 2000.

2.2. Procedure description

Since DIDR is a rate measurement rather than an absolute measurement of drug solubility, the surface area from which dissolution takes place must be known and remain constant. This is achieved by compressing the pure drug in a die with a hole of known diameter to produce a drug disk of known surface area. The resulting disk, if sufficiently compressed, will not disintegrate in the dissolution medium. The die containing the drug disk is then mounted in a holder and the assembly is rotated at constant speed in the buffered dissolution medium that is held at constant temperature. The volume of the dissolution medium is sufficient to maintain sink conditions. The literature describes the dies and assembly used to measure DIDR (Wood and Syarto, 1965).

Disk intrinsic dissolution values in this report were obtained using a modified Wood Apparatus with a 0.5 cm^2 surface area in a VanKel VK7000 dissolution testing station (VanKel Technology, Cary, NC, USA). Drugs were compressed into disks for dissolution measurement using a Carver® Laboratory Press (Carver Inc., Wabash, IL, USA). Absorbances were determined using a Beckman DU-7400 UV-Vis spectrophotometer (Beckman Instruments, Fullerton, CA, USA) at the absorption wavelengths listed in Table 2.

DIDR was determined using a rotating disk of pure drug, usually compressed at 2000 psi, and immersed in a dissolution medium maintained at 37.4 °C. Dissolution media employed were 0.1 N HCl, 0.2 M acetate buffer, pH 4.5; and 0.2 M phosphate buffer, pH 6.8. Samples of the media (4 ml) were withdrawn at regular intervals and a plot of absorbance versus time constructed. Using a series of standard solutions of the drug prepared in the same medium as the DIDR study and chosen to produce the same range of absorbances found in the study, a standard curve of absorbance versus concentration was plotted. DIDRs (j), are easily calculated by

$$j = \frac{V}{\mathrm{d}t}\frac{\mathrm{d}c}{A} \quad (1)$$

where j is the disk intrinsic dissolution rate, V is the volume of the dissolution medium, c is the concentration, A is the area of the drug disk, and t is the time.

2.3. Procedure evaluation

To establish the robustness of the DIDR measurement procedure, we studied the dependence of the observed DIDR with changes in various experimental variables. The variables of interest were: compression force, dissolution volume, distance of the compressed drug disk from the bottom of the dissolution vessel, and the speed at which the drug disk was rotated. The drug powder was compressed at pressures ranging from 600 to 5000 psi. The dissolution medium used for procedure evaluation was pH 4.5 buffer and the volume was varied from 225 to

900 ml. The rotational speed was varied from 15 to 250 rpm. The distance of intrinsic die from the bottom of vessel, which determines the position of the disk of compressed drugs, was varied from 0.25 to 1.5 in.

2.4. Application to BCS compounds

The DIDRs of a total of 15 model compounds were measured. These compounds, consisting of six poorly soluble and nine highly soluble compounds, are tabulated in Table 1. Approximately 500 mg were compressed in the die at 2000 psi for 1 min, except for piroxicam that was compressed at 1000 psi. We found that compression of piroxicam at pressures higher than 1000 psi resulted in a disk that broke apart soon after placing it in the dissolution medium. Metoprolol tended to stick to the metal base-plate, on which the drug is compressed, resulting in fragmenting of the disk when the die was lifted from it. Compressing the drug against a piece of glassine weighing paper placed on the base-plate prevented this from happening.

For most drugs tested, 900 ml of dissolution medium was added to the dissolution vessel and the temperature brought up to 37.4 °C. For slightly soluble drugs, 225 ml of medium was used in order to obtain sufficient concentrations for accurate absorbance measurements. When 225 ml of dissolution medium was used, the withdrawn sample volume (4 ml) was replaced with an equal volume of fresh dissolution medium maintained at 37.4 °C. Withdrawn volumes were not replaced when 900 ml of medium was used.

The die containing the compressed disk of drug was mounted in the dissolution apparatus 0.5 in. from the vessel bottom and rotated at 100 rpm in the dissolution medium maintained at 37.4 °C. Samples were withdrawn every 2 min for highly soluble drugs and every 30 min for slightly soluble drugs until 5–10 data points had been collected. For a few highly soluble drugs, it was necessary to withdraw a known aliquot of the medium and make a volumetric dilution before determining absorbances. All absorbances were determined in duplicate and the average used to plot the curves. The wavelengths at which the absorbances

Table 1
Disk intrinsic dissolution rate of model BCS drugs as a function of pH

Drug	pK_a[a]	Intrinsic dissolution ($n = 3$) (mg/min/cm^2)		
		pH 1.2	pH 4.5	pH 6.8
Low solubility[b]				
Carbamazepine	N/A	0.025 ± 0.002	0.024 ± 0.001	0.029 ± 0.002
Furosemide	3.9	0.0017 ± 0.0001	0.018 ± 0.002	0.502 ± 0.017
Griseofulvin	N/A	0.0026 ± 0.0001	0.0019 ± 0.0000	0.0022 ± 0.0002
Ketoprofen	3.5	0.016 ± 0.001	0.062 ± 0.001	0.567 ± 0.025
Naproxen	4.2	0.0035 ± 0.0001	0.012 ± 0.001	0.264 ± 0.017
Piroxicam	5.1	0.022 ± 0.001	0.0043 ± 0.0006	0.088 ± 0.002
High solubility[b]				
Atenolol	9.6	5.60 ± 0.40	3.74 ± 0.09	2.56 ± 0.13
Cimetidine	6.8	7.30 ± 0.32	2.90 ± 0.19	1.07 ± 0.04
Hydrochlorothiazide	7.9	0.119 ± 0.007	0.124 ± 0.002	0.113 ± 0.009
Labetalol	7.4	1.03 ± 0.04	2.88 ± 0.04	0.76 ± 0.03
Metoprolol	9.7	23.7 ± 2.0	22.4 ± 0.81	21.4 ± 1.1
Nadolol	9.7	8.04 ± 0.081	2.47 ± 0.07	1.44 ± 0.04
Nortriptyline·HCl	10.0	0.895 ± 0.014	7.81 ± 0.35	6.45 ± 0.18
Propranolol	9.5	10.3 ± 0.45	13.3 ± 0.47	14.6 ± 0.32
Ranitidine	N/A	46.1 ± 1.8	47.9 ± 3.1	43.1 ± 0.058

[a] Data from: Singh, Dalby, Hollenbeck; Drug Solubility Monographs, Version 2 (November 1995) and C. Brownell (personal communication).

[b] A drug substance is considered highly soluble when the highest dose strength is soluble in ≤250 ml of aqueous media over the pH range 1.0–7.5.

Table 2
Wavelengths (nm) at which disk intrinsic dissolution rates were measured

Drug	pH 1.2	pH 4.5	pH 6.8
Low solubility			
Carbamazepine	286	286	300
Furosemide	278	274	274
Griseofulvin	296	296	292
Ketoprofen	259	260	261
Naproxen	223	236	275
Piroxicam	336	361	207
High solubility			
Atenolol	225	235	225
Cimetidine	219	227	220
Hydrochlorothiazide	275	276	273
Labetolol	208	223	210
Metoprolol	275	274	275
Nadolol	205	226	205
Nortriptyline·HCl	240	240	212
Propranolol	289	234	289
Ranitidine	226	313	228

were measured are tabulated in Table 2. All DIDR determinations were done in triplicate in dissolution media at the three physiologically significant pHs previously mentioned: pH 1.2 (0.1 N hydrochloric acid), pH 4.5 (0.2 M acetate buffer), and pH 6.8 (0.2 M phosphate buffer).

3. Results and discussion

3.1. Procedure evaluation

Fig. 1 shows a typical plot of concentration versus time for the model drug furosemide at pH 1.2, 4.5, and 6.8. The small errors among the three runs using three disks in three dissolution vessels indicate excellent reproducibility (CV generally less than 10%). Linearity was also good with a correlation coefficient of 0.99.

Table 3 shows the effect of compression force on intrinsic dissolution of the model drugs metoprolol, a BCS high solubility drug, and furosemide, a BCS low solubility drug. Table 3 shows that the DIDRs of both metoprolol and furosemide do not vary significantly with the compression force, demonstrating the robustness of the method. Such robustness is important since DIDR studies done in industry have used widely varying compression forces, e.g. from 500 to 22,000 psi (Huang, personal communication).

The compression force used depends upon the diameter of the die. In general, the larger the diameter of the die, the higher the necessary compression forces to keep disk hardness constant. However, it was observed that higher compression forces sometimes result in fragile disks that fragment in the dissolution

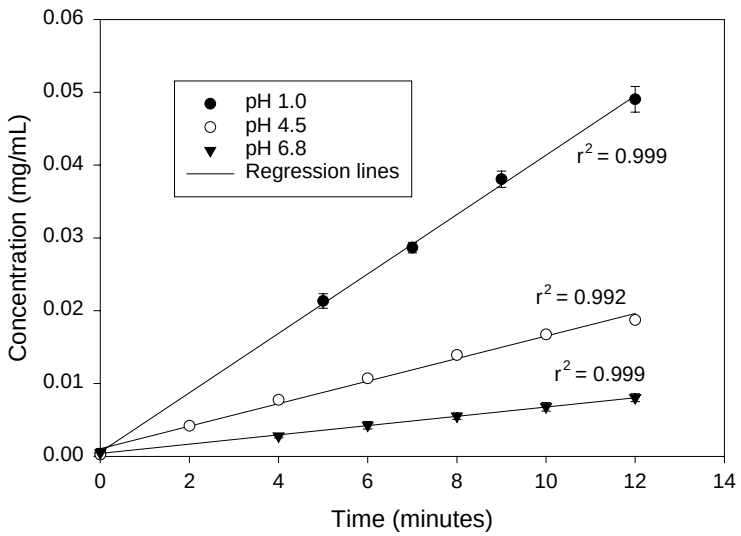

Fig. 1. Concentration–time profile for the model drug cimetidine at pH 1.0, 4.5 and 6.8 ($n = 3$).

Table 3
The effect of disk compression force on disk intrinsic dissolution rate[a]

Drug	Compression force (psi)	Intrinsic dissolution (mg/min/cm^2)		
		Mean	S.D.	CV (%)
Metoprolol	600–700	19.9	1.345	6.76
	900–1000	20.3	0.929	4.57
	2000	22.4	0.252	1.12
	3000	22.7	0.608	2.68
	4000	21.6	0.379	1.75
	5000	21.7	0.503	2.32
Furosemide	600–700	0.019	0.0006	2.99
	900–1000	0.020	0.0010	5.00
	2000	0.018	0.0015	8.33
	3000	0.021	0.0006	2.79
	4000	0.019	0.0010	5.26
	5000	0.022	0.0012	5.33

[a] Medium: pH 4.5, 0.2 M acetate buffer, 900 ml, 37.5 °C. Disk rotation speed: 100 rpm. Disk distance from vessel bottom: 0.5 in.

medium. Piroxicam, for example, exhibited such behavior. A compromise compression force, 1000 psi, was therefore found that produced a disk with acceptable mechanical properties. We selected 2000 psi as a standard for other drugs since this is the compression force that is more likely used in tablet compression.

Table 4 shows the effect of dissolution volume on the intrinsic dissolution of metoprolol and furosemide. We evaluated dissolution volumes of 225 and 900 ml. In cases of very low solubility, it was necessary to use the smaller volume to obtain higher and therefore more accurate and precise absorbance values. Table 4 demonstrates that DIDR was not a function of the dissolution volume for the range of volumes studied.

Table 4
The effect of dissolution volume on disk intrinsic dissolution rate[a]

Drug	Dissolution volume (ml)	Intrinsic dissolution (mg/min/cm^2)		
		Mean	S.D.	CV (%)
Metoprolol	225	21.6	0.4510	2.1
	500	20.0	0.6430	3.2
	900	22.4	0.8740	3.9
Furosemide	225	0.016	0.0015	9.5
	500	0.017	0.0012	6.8
	900	0.017	0.0010	5.9

[a] Medium: pH 4.5, 0.2 M acetate buffer, 37.5 °C. Disk rotation speed: 100 rpm. Disk distance from vessel bottom : 0.5 in. Disk compression force: 2000 psi.

Table 5
The effect of disk distance from vessel bottom on disk intrinsic dissolution rate[a]

Drug	Disk distance from vessel bottom (in.)	Intrinsic dissolution (mg/min/cm^2)		
		Mean	S.D.	CV (%)
Metoprolol	0.25	23.4	0.28	1.2
	0.5	22.4	0.81	3.6
	1.0	23.7	0.23	1.0
	1.5	23.3	0.31	1.3
Furosemide	0.25	0.017	0.0017	10.2
	0.5	0.017	0.00097	5.8
	1.0	0.017	0.00035	2.0
	1.5	0.018	0.0023	12.9

[a] Medium: pH 4.5, 0.2 M acetate buffer, 37.5 °C. Disk rotation speed: 100 rpm. Disk distance from vessel bottom: 0.5 in. Disk compression force: 2000 psi.

Disk position might affect the mixing of the solution, so we studied the effect of disk distance from the bottom of the vessel using metoprolol and furosemide as model compounds. Our results, shown in Table 5, suggest that the solution in the vessel is well mixed and that disk position does not affect DIDR. The effect of rotation speed on DIDR is shown in Fig. 2. The increase in DIDR was directly proportional to the square root of the rotational speed as predicted by theory (Yu and Amidon, 1999).

In summary, disk compression pressure, dissolution medium volume, and die position were found to have no significant effect on DIDR, demonstrating the robustness of the intrinsic dissolution methodology. The proposed compression force, dissolution medium volume, die position, and rotational speed are 2000 psi, 900 ml, 0.5 in., and 100 rpm, respectively.

3.2. DIDRs for the BCS compounds

Table 1 shows the DIDR results obtained on six randomly selected low solubility and nine high solubility BCS model compounds. It can be seen that there is a good qualitative correlation between the solubility classification and DIDR values. Table 1 suggests

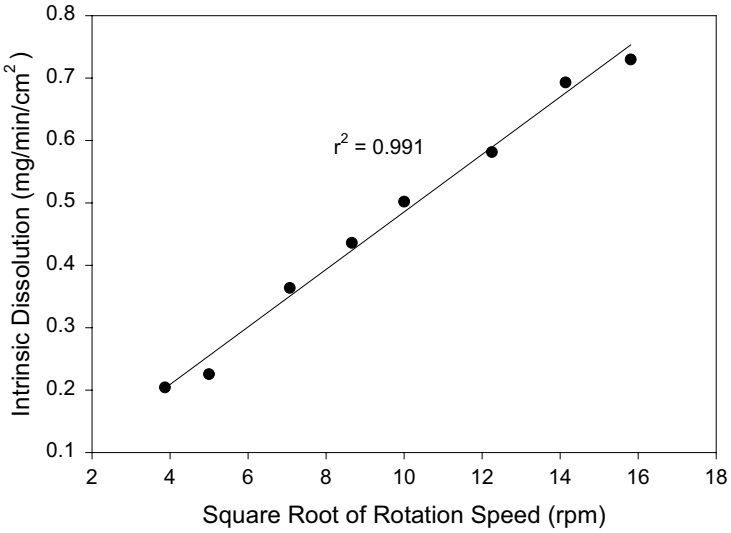

Fig. 2. Variation of intrinsic dissolution with disk rotation speed for the model drug furosemide at pH 6.8. The DIDR increases as the square root of rotation speed as predicted by Eq. (1).

the cut-off value of 0.1 mg/min/cm^2 for classifying high/low DIDR, in line with solubility classification.

Based on the Levich equation (Levich, 1962), DIDR may be calculated by

$$j = 0.62\left(\frac{D^{2/3}\omega^{1/2}}{\nu^{1/6}}\right)c_s \quad (2)$$

where c_s is the saturated concentration or solubility, D is the diffusion coefficient, ω is the angular velocity of the rotating disk, and ν is the kinematic viscosity of the dissolution medium. This model assumes equilibrium at the interface of solid and liquid, and the liquid at the interface is the same as the liquid in bulk dissolution. In many cases, these assumptions may not be met due to poor wetting, pH changes, and others, and the relationship between DIDR and solubility is not always present. Nevertheless, DIDR is a good way to probe the relative solubility of drugs. For example, the actual solubility of a drug may not be determined due to potential changes in solvates and hydrates, polymorphs, and salt forms during the solubility experiments. DIDR might be then used to determine its solubility before the changes actually occur.

The determination of DIDR is a relatively simple procedure, especially if an automatic dissolution apparatus is employed. However, compression could induce polymorphic form change, resulting in incorrect measurement (Yu et al., 2002). DIDR along with permeability is a rate phenomenon instead of an equilibrium phenomenon. Therefore, it might be expected to correlate more closely with in vivo drug dissolution dynamics than solubility. It should be noted that dose is considered in the classification of solubility while intrinsic dissolution does not consider the effect of dose. Thus, when the dose is either extremely high or extremely low, a discrepancy between the current solubility classification and the DIDR may occur. For example, a compound with the solubility of 1 μg/ml may be classified as a high solubility compound if the dose is 0.25 mg or less based on the solubility classification while it is likely classified a low solubility compound if directly based on DIDR. On the other hand, a compound with the solubility of 4 mg/ml may be classified as a low solubility compound if the dose is 1000 mg or more based on the solubility classification while it is likely classified a high solubility compound if directly based on DIDR. Further, when the dose is extremely high, the in vivo absorption may be solubility limited (Yu, 1999). While such discrepancies may not be an issue for purpose of drug discovery and development, it could create confusion. Therefore, when the dose is extremely low, say 1 mg or less, or extremely high, say 1000 mg or higher, precautions must be taken. It seems

that more scientific research and debates are needed in this area before adopted for regulatory purpose.

4. Conclusions

We have shown DIDR to be a convenient, simple method to classify drugs. The variables in producing the drug disk, e.g. compression pressure, dissolution medium volume, and die position have no significant effect on DIDR, demonstrating the robustness of the intrinsic dissolution methodology. We propose a compression force of 2000 psi, unless the disk fragments in solution in which case a lower force needs to be employed. Dissolution medium volume is the standard 900 ml unless higher concentrations are needed for low solubility drugs where 225 ml can be used. The die position and rotational speed are 0.5 in. and 100 rpm, respectively. DIDR generally correlates with the BCS solubility classification with 0.1 mg/min/cm^2 as a class boundary unless the dose is either extremely low or high where a discrepancy may exist between the solubility and DIDR methods. We wish to emphasize, however, that our proposal of 0.1 mg/min/cm^2 as a class boundary is based solely on the results from the 15 compounds we studied; studies on additional compounds may lead us to revise the class boundary. Therefore, more scientific research and discussion will be needed to resolve this problem before DIDR can be implemented for regulatory purposes.

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