Journal of Pharmaceutical Sciences xxx (2016) 1–9

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Interlaboratory Validation of Small-Scale Solubility and Dissolution Measurements of Poorly Water-Soluble Drugs

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ARTICLE INFO

Article history:
Received 9 February 2016
Revised 8 March 2016
Accepted 8 March 2016

Keywords:
dissolution
intrinsic dissolution rate
apparent solubility
preformulation
poorly water-soluble drug
small scale

ABSTRACT

The purpose of this study was to investigate the interlaboratory variability in determination of apparent solubility (S_{app}) and intrinsic dissolution rate (IDR) using a miniaturized dissolution instrument. Three poorly water-soluble compounds were selected as reference compounds and measured at multiple laboratories using the same experimental protocol. Dissolution was studied in fasted-state simulated intestinal fluid and phosphate buffer (pH 6.5). An additional 6 compounds were used for the development of an IDR measurement guide, which was then validated with 5 compounds. The results clearly showed a need for a standardized protocol including both the experimental assay and the data analysis. Standardization at both these levels decreased the interlaboratory variability. The results also illustrated the difficulties in performing disc IDR on poorly water-soluble drugs because the concentrations reached are typically below the limit of detection. The following guidelines were established: for compounds with $S_{app} > 1$ mg/mL, the disc method is recommended. For compounds with $S_{app} < 100$ μg/mL, IDR is recommended to be performed using powder dissolution. Compounds in the interval 100 μg/mL to 1 mg/mL can be analyzed with either of these methods.

Introduction

High-throughput screening technologies used during the last decades have increased the number of drug candidates with high potency. At the same time, physicochemical challenges associated with these candidates, such as high lipophilicity and poor aqueous solubility, have also increased. Therefore, water solubility and dissolution rate often need to be determined early in the development process, when the quantity of the compound is limited. Evaluation of these properties can help to obtain early information on whether the compound is expected to have a dissolution rate–limited or solubility-limited absorption, determine the pharmaceutical risk of the project, and define the initial formulation strategy.[1,2] This is particularly relevant for poorly water-soluble biopharmaceutics classification system class 2 and 4 compounds,[3] where salt selection and formulation strategies, such as amorphization and solubilization, may significantly improve the absorption profiles.[4]

This article contains supplementary material available from the authors by request or via the Internet at http://dx.doi.org/10.1016/j.xphs.2016.03.010.

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http://dx.doi.org/10.1016/j.xphs.2016.03.010
0022-3549/

Dissolution studies during the preformulation stage are usually performed using powder-based assays or compressed discs, whereas dissolution studies of formulations typically are performed from tablets.[5-7] In recent years, a small-scale apparatus, the μDISS Profiler (Pion Inc., Billerica, MA), has been developed.[8,9] This apparatus can determine the dissolution rate from either powder or disc using minimal amount of material. It uses fiber optic dip probes to read concentration over time *in situ*, scanning absorbance between 200 and 700 nm. The fiber optic dip probes have interchangeable tips with a path length in the range of 1-20 mm suited for various concentrations in the solution. Powder-based assays facilitate the determination of the dissolution rate through higher concentration of drug, compared with a disc assay, due to the increased surface area of the material that is in contact with the dissolution medium.[10,11] However, the advantage of discs is that they have an exact and constant surface area, which is produced by compressing the powder into a compact disc with a fixed diameter. The intrinsic dissolution rate (IDR) is the surface-specific dissolution rate, which can be calculated if the surface area of the solid material is known. In disc dissolution, the IDR is calculated according to the following equation:

$$\mathrm{IDR_{disc}} = \frac{\mathrm{d}m}{\mathrm{d}t} \times \frac{1}{A_{\mathrm{disc}}} = V\frac{\mathrm{d}c}{\mathrm{d}t} \times \frac{1}{A_{\mathrm{disc}}} \quad (1)$$

where m is the mass (μg), t is the time (min), A_{disc} is the disc surface area ($\mathrm{cm^2}$), V is the volume of the medium (mL), and $\mathrm{d}c/\mathrm{d}t$ is the slope of the straight line from dissolution (μg/(min × mL)). The unit of $\mathrm{IDR_{disc}}$ is, therefore, μg/min/$\mathrm{cm^2}$.[8,9] The advantage with the μDISS Profiler is that it requires only 5-10 mg of compound in comparison with the traditional Wood's apparatus,[12] where material up to ~500 mg is required to compress a disc.[13]

Disc dissolution studies are limited by the compound solubility and the molar extinction coefficient of the compound. When the solubility is poor, the concentration of compound in the medium dissolved from the disc can be below the detection limit of the probe for a long period. In contrast, powders can dissolve up to 600 times faster than discs.[9] For the powder assay, an excess of compound needs to be used so that the saturated concentration is obtained.[9] To calculate powder IDR, the powder dissolution data are curve fitted with a biexponential equation, as previously suggested by Tinke et al.[14] and used in former studies when establishing the powder dissolution method using the μDISS.[9] Based on the assumption that there may be 2 particle size populations, the following equation is used:

$$C_{\mathrm{tot}}(t) = C_0^{\infty}\left[1 - \mathrm{e}^{-k_0(t-t_{\mathrm{LAG}})}\right] + C_1^{\infty}\left[1 - \mathrm{e}^{-k_1(t-t_{\mathrm{LAG}})}\right] \quad (2)$$

where C_{tot} is the total concentration (μg/mL) of the dissolved drug as a function of time t (min), C_0^{∞} and C_1^{∞} are concentrations at $t = \infty$ of the dissolved particles from each of the 2 particle size populations, k_0 and k_1 (per minute) are rate constants, and t_{LAG} is the lag time occurring due to experimental delays, such as poor wettability. The analysis is made with the assumption that a saturated solution is present at $t = \infty$. The derivative of Equation 2 at the start of dissolution (evaluated at $t = t_{\mathrm{LAG}}$) is set equal to the limiting slope in the Nernst–Brünner equation:

$$\frac{\mathrm{d}C_{\mathrm{tot}}(t_{\mathrm{LAG}})}{\mathrm{d}t} = k_0 C_0^{\infty} + k_1 C_1^{\infty} = \frac{A_{\mathrm{app}}}{V} \times \frac{D}{h_{\mathrm{app}}} \times S \quad (3)$$

where A_{app} is the apparent total surface area ($\mathrm{cm^2}$), h_{app} is the apparent thickness of the aqueous boundary layer, D ($\mathrm{cm^2}$/min) is the diffusivity of the compound in the medium, V ($\mathrm{cm^3}$) is the volume of the medium, and S (μg/mL) is the solubility of the compound. The ratio of A_{app} and h_{app} at the start of the dissolution is defined as:

$$\left(\frac{A_{\mathrm{app}}}{h_{\mathrm{app}}}\right) = \frac{V}{DS}\left(k_0 C_0^{\infty} + k_1 C_1^{\infty}\right) \quad (4)$$

when excess material is present, $S = C_0^{\infty} + C_1^{\infty}$. To determine the 5 constants associated with Equation 2 (C_0^{∞}, k_0, C_1^{∞}, k_1, and t_{LAG}), nonlinear weighted regression analysis is used in the μDISS Profiler. These constants are used to calculate the IDR by making use of standard assumptions for disc IDR calculations:

$$\mathrm{IDR} = 0.0573\frac{\mathrm{DR}_{\mathrm{pwd}}^{\max}}{V} \times \mathrm{MW}^{-0.30} \times \sqrt{\mathrm{RPM}} \times \left(\frac{C_0^{\infty} + C_1^{\infty}}{k_0 C_0^{\infty} + k_1 C_1^{\infty}}\right) \quad (5)$$

where $\mathrm{DR}_{\mathrm{pwd}}^{\max}$ (μg/min) is the maximum slope in the powder dissolution curve, MW is the molecular weight of the drug, and RPM (rev/min) is the rotation speed.[9]

IDR measurements have many scientific and regulatory applications and are used for instance in polymorph identification, formulation assessment, and batch quality control. It is, therefore, important that measurements are reproducible and generate high-quality data. Variability associated with dissolution testing has been reported for the US Pharmacopeial (USP) apparatuses 1 and 2.[7,15] In 1 study, 28 laboratories used the same experimental protocol to measure dissolution of USP calibrator tablets, Food and Drug Administration prednisone tablets, and glibenclamide tablets. A coefficient of variation (CV) of 14%-37% was reported for glibenclamide tablets, the number being dependent on sampling time and method used (basket or paddle). For the USP calibrator tablets and Food and Drug Administration prednisone tablets, the CV was 9%-24% at the 30-min sampling time point, whereas the CVs for glibenclamide tablets were 29.4% and 19.7% for the basket and the paddle method, respectively. This variation could not be associated with the product or compound, but rather to the dissolution testing itself.

In this study, interlaboratory differences of apparent solubility (S_{app}) and IDR measurements were evaluated with the aim to develop guidelines for measuring the IDRs of poorly soluble compounds when only available in limited amounts. Miniature dissolution methods are increasingly used in academic research and industry laboratories,[11,16-24] but, to the best of our knowledge, there are no common, standardized experimental protocols for the μDISS Profiler. Furthermore, the variability between powder and disc IDR measurements has not been described for poorly water-soluble compounds. The standardization and validation of protocols for this miniaturized dissolution method are therefore needed. This study was undertaken as a part of the ORBITO (Oral Biopharmaceutical Tools) consortium within the Innovative Medicine Initiative program. The interlaboratory variability was assessed using 3 structurally diverse and poorly water-soluble reference compounds. The dissolution measurements were performed at multiple laboratories. The same batch of each of the compounds and identical experimental protocols were used at all laboratories, with the purpose to diminish the influence of the drug material itself and the experimental assay on the variability of the IDR. Six additional, structurally diverse compounds with varying protolytic functions were selected to evaluate the established protocols and to produce a guide for whether to use the powder or disc protocol. The established guide was then applied to 5 compounds of past and present Research and Development programs provided by the European Federation of Pharmaceutical Industries and Associations partners to test the applicability of the recommended workflow.