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Intrinsic Drug Dissolution Testing Using the Stationary Disk System

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Introduction

The intrinsic dissolution rate is defined as the rate of dissolution of a pure pharmaceutical active when conditions such as surface area, temperature, agitation-stirring speed and pH and ionic strength of the dissolution medium are kept constant. The determination of this parameter allows for screening of drug candidates and in understanding their solution behavior under different bio-physiological conditions (1).

The implementation of "sameness" analysis has been presented and applied in a number of scientific guidelines for demonstrating formulation equivalencies among semi-solids, immediate release solid oral and extended release solid oral dosage forms. Test methods for these analyses involve the use of vertical diffusion cells, enhancer cells and the USP apparatus one and two (2). The evaluation of the intrinsic dissolution of active pharmaceutical ingredients (API) is a means to demonstrate chemical purity and equivalency. The need to demonstrate "sameness" among APIs has risen due to changes in the bulk active synthesis, the final crystallization steps, particle size and surface area, polymorphism and scale-up issues regarding batch-size and manufacturing site. This report describes the new stationary disk system from Distek, Inc., and points out its features, advantages and applications in drug dissolution testing. A comparison is made with the rotating disk system (Wood apparatus from VanKel Industries, Cary, NC).

Description of the apparatus

Stationary Disk System (Distek, Inc.). The stationary pellet or disk system is a new apparatus from Distek Inc., North Brunswick, NJ (Figure 1). The apparatus consists of a steel punch, die and a base plate. The die base has three holes for the attachment of the base plate. The three fixed screws on the base plate are inserted through the three holes on the die and then fastened with the three supplied washer and nuts. Test material is placed in the 0.8-cm (0.315-inch) diameter die cavity. The punch is then inserted into the cavity and compressed, with the aid of a bench top Carver™ press, for 4 -5 minutes at 2000 PSI. The base plate is then disconnected from the die to expose a smooth compact pellet of 0.5-cm^2 surface area. A Viton™ gasket is placed around the threaded shoulder of the die and a polypropylene cap is then screwed on to the threaded shoulder of the die. The assembly is next immersed, pellet side up, into the bottom of the dissolution vessel (flat bottom) containing 900mL dissolution medium at 37°C. The use of a pair of forceps facilitates this operation and allows for a placement of 6 dies within 30 seconds. The dimensions of the flat portion at the bottom of the dissolution vessel permits the die assembly to settle in a perfectly horizontal position, and without shifting during the stirring of the dissolution medium. The USP apparatus 2 paddle provides the stirring mechanism for the dissolution apparatus. The recommended operational speed is between 10 to 100 rpm. The distance of the bottom of the stirring paddle from the die face is 1-inch.

Rotating disk system (USP Wood apparatus). The rotating pellet or disk system is the Wood appa-

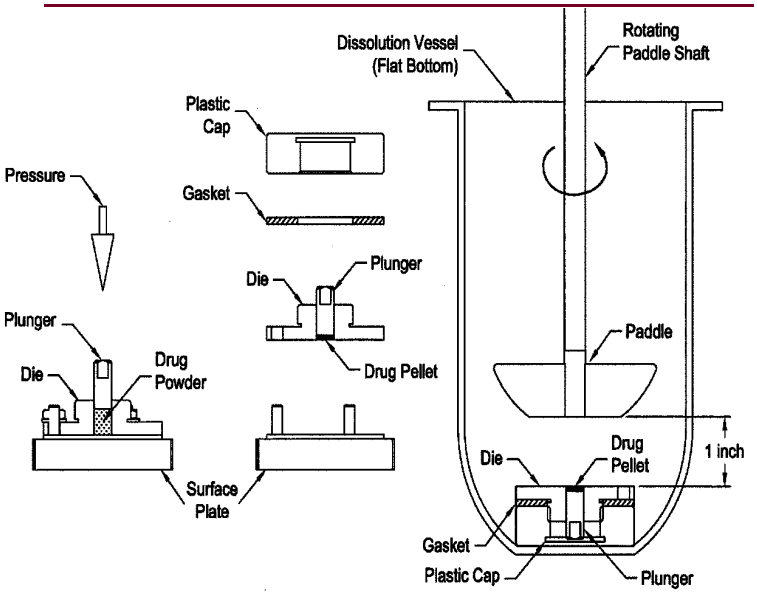

Figure 1: Stationary Disk System (Distek Inc.)

Stationary Disk System … *continued*

ratus from VanKel Industries, Inc., Cary, NC. The description of the apparatus can be found in the manufacturer's manual (3) and the United States Pharmacopoeia (USP) supplement (4). Table 1 compares the two types of apparatus and points out their key features, strengths and weaknesses.

Experiment

Test compounds were selected based on their solubility in water, simulated gastric fluid (0.1N HCl acid) and simulated intestinal medium (pH 7.2 buffer). All the dissolution experiments were performed with the Distek Model 2100B dissolution system and the Distek Model 2230 autosampler. The operational speed was 50 rpm. At appropriate time intervals, an automated sample collector removed aliquots from the dissolution medium. The analysis of each test compound (Table 2) was carried out using an ultraviolet-visible spectrophotometer and 1-cm quartz cells. Reference standard solutions for

Table 1: Comparison of the Rotating and Stationary Disk Systems

	Rotating Disk System	**Stationary Disk System**
Operation	Rotating or forced shear-like dissolution operation. Similar to USP procedure 1. Dissolution is achieved by shear like motion of the pellet in the dissolution medium. Pellet faces down.	Static or solvent shear-like dissolution operation. Similar to USP procedure 2 Dissolution is achieved by moving a volume of dissolution medium over the pellet. Pellet faces up.
Dissolution Testing Station	Designed for apparatus similar to the VanKel VK7000 module	Used with USP 2 paddles on any dissolution module
Dissolution vessel	Standard curved bottom one-liter beaker	Flat bottom one-liter beaker The flat surface diameter is 5.38 cm (2.12 inches)
Shaft design	Stainless steel rod with hollow die holder	Uses standard paddle from USP apparatus 2. Die holder acts as a plastic screw cap and base.
Introduction of compact pellet into the dissolution medium	Pellet and die assembly is introduced into the dissolution medium all at once, when the dissolution drive mechanism is lowered.	Pellet and die assembly is introduced into the dissolution medium one at a time with the aid of a pair of forceps
Die weight	≈ 515 g	≈ 144 g
Die height	≈ 3.54 cm	≈ 1.27 cm
Die diameter	≈ 5.38 cm	≈ 5.38cm
Die cavity diameter / Area	0.8 cm / 0.5 cm^2	0.8 cm / 0.5 cm^2
Recommended speed	50 rpm	50 and 100 rpm
Miscellaneous	Formation of air bubbles can interfere with dissolution rate. Small drop in temperature of dissolution medium (≈ 2° C) when the device is first lowered into the vessel. Heat transfer out of the vessel through the shaft.	No air bubbles formed on the pellet surface. No change in temperature since the device is small and is totally submerged into the dissolution medium.

each drug were prepared in the dissolution medium of choice in order to generate an absorbance versus concentration standard curve. The absorbance of the sample aliquots was used to determine the amount of drug recovered at each time point.

The apparatus was also used to determine the intrinsic dissolution rate of a test compound, peldesine (CAS 133432-71-0), from pellets containing two types of hydroxypropyl methylcellulose (HPMC) i.e. USP grade 2208 and 2190 (type K4M and E4M from Dow Chemicals, Midland, MI). The pellets were made from powder blends that contained by weight 30% drug, 30% HPMC, 34% microcrystalline cellulose, 5% pre-gelatinized starch and 1% of lubricant and glidant. The dissolution of drug was performed for 12 hours at 50 rpm and in 0.1N hydrochloric acid. Sample aliquots were taken as before and assayed for drug concentration.

Comparison of dissolution profiles

The cumulative amount of drug substance dissolved at any time point is the product of the drug concentration in the sample and the volume of media. Intrinsic dissolution takes into account the correction factor for reduced volume, where the amount of drug substance contained in each sample volume is added back to the cumulative amount, at subsequent time points (5).

The amount of drug dissolved per unit area (mg/cm^2) is plotted against time (min). The slope of the line is the intrinsic dissolution rate in $mg/cm^2/min$. The USP recommends that the earlier time points be used in the calculation of slope. Based on our experience, the use of at least 5 points from the earlier segment of the dissolution curve will provide meaningful data.

The similarity factor f_2 compares the dissolution profiles for each compound tested by both apparatus. The equation used in the calculation is

$$f_2 = 50 \cdot \log\{[1+(1/n)\sum_{t=1}^{n}(T_R - T_S)^2]^{-0.5} \cdot 100\}$$

where, T_R and T_S are the cumulative percentage dissolved at each of the selected n time points of the rotary and stationary pellet systems, respectively. If the f_2 value is between 50-100, the intrinsic dissolution profiles are equivalent (6).

Table 2: Intrinsic Dissolution Rates and Similarity factor f_2

Compound	Dissolution medium	Intrinsic Dissolution Rate ($mg/cm^2/min$)		f_2
		Rotating Disk System	Stationary Disk System	
Acetaminophen	Water	1.67	1.81	72
Diclofenac sodium	Water	2.98	3.29	75
Isoniazid	Water	11.98	12.21	81
Dibucaine	0.1 N HCl	4.03	4.51	55
Peldesine (milled 50 to 150 mm)	0.1 N HCl	1.91	2.77	39
Peldesine (micronized 2 to 5mm)	0.1 N HCl	2.78	2.98	63
Ibuprofen	pH 7.2 buffer	0.33	0.37	74

NA: f_2 analysis is not necessary for compounds that are rapidly dissolving.

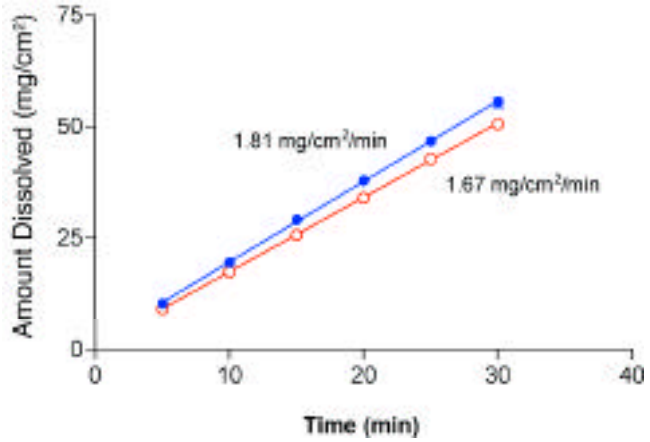

Figure 2: Intrinsic dissolution of acetaminophen, USP (n=6, SD)
Key: (•) Stationary disk and (o) Rotary disk methods

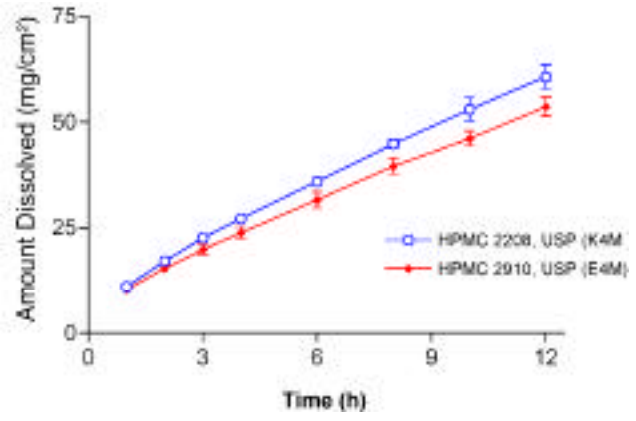

Figure 3: Dissolution of peldesine from tablet blends containing hydroxypropyl methylcellulose, HPMC (n=6, SD)
Key: USP grades of HPMC (o) 2208 and (®) 2910

Stationary Disk System ... *continued*

Results and Discussion

The amount of drug dissolved per unit area when plotted against time produced linear curves with correlation coefficients higher than 0.990 in each case. Figure 2 (page 21), for example, illustrates the dissolution of acetaminophen in deionized water. Table 2 compares the intrinsic dissolution rates of each compound tested using both the rotary and the stationary disk systems. The similarity of both apparatus was compared by the similarity factor analysis, f_2. The performances of both devices were comparable in the case of acetaminophen, diclofenac sodium, isoniazid, dibucaine and ibuprofen (i.e., $f_2 > 50$) which means that the difference in dissolution profiles is less than 10%. Milled peldesine (50 to 150mm particle size) had a f_2 value of 39, suggesting a greater than 10% difference in the two systems. But when peldesine was micronized (2 to 5mm particle size) the difference was less than 10% (i.e., $f_2 = 63$). The differences in f_2 values for the same compound may suggest that prior to intrinsic dissolution testing, the test substance needs to be well characterized especially in terms of particle size distribution. A narrower particle size range would be desirable. As expected, the micronized drug appeared to have a faster dissolution rate than the milled drug.

The number of sampling intervals for each test compound depended on its solubility and the dissolution medium used. Standard deviations were calculated at each time point for n=6 vessels. When the stationary disk system was used, the standard deviation at the later time points (20 to 30min) was approximately 0.2-4.0% when compared to 0.5-2.0 % observed with the rotating disk system. These differences are attributed to the mechanism of dissolution (7, 8). In the case of the rotary operation, the pellet undergoes a shear-like motion over a planar solvent front similar to USP procedure 1. In the case of the stationary disk system, a fixed body (volume) of solvent is stirred over the pellet similar to USP procedure 2 and the enhancer dissolution cell used for semi-solids (VanKel Industries).

The dissolution of peldesine from pellets prepared with two types of drug-HPMC blends was determined using the stationary disk system. The dissolution rate from the type 2208 blend was 4.45 mg/cm2/hr when compared to 3.88 mg/cm2/hr for the type 2910 blend (see Figure 3, page 21). These numbers suggest that tablets prepared with the first blend will release drug at a faster rate than those prepared with the second HPMC type. The drug dissolution rate from one face of a sustained-release pellet allows the formulator to gather information that may be useful in the design of a sustained-release tablet. The desired release characteristics can be predicted from the approximate size and dimensions of the tablet surface area and the drug-polymer composition.

Conclusions

The intrinsic dissolution rate of an API can be reasonably determined in order to describe the rate of dissolution of drug and to determine batch to batch chemical equivalency. The two apparatus used are well designed and are easy-to-use tools that can be used to obtain meaningful answers. A preliminary validation of operating speeds and pellet-to-paddle distances has been previously reported (9) and was not discussed in this article. The USP supplement 1 has listed the Wood apparatus as one of the systems that can be used to measure intrinsic dissolution of an API, but has left the door open for new and improved devices such as the stationary disk system. Some of the advantages of the new system, besides those listed in Table 1, are that it can be used with different dissolution modules including those that require sampling through a port in the stirring paddle and those that use in-situ fiber optic probe analysis.

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