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Is the use of a 200 ml vessel suitable for dissolution of low dose drug products?

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Abstract

This work evaluated the use of a commercially available 200 ml vessel for dissolution of five drug products with various solubilities. Each of the five drug products (four with USP monographs and one proprietary tablet formulation) was run at four different conditions (USP 25 monograph, six dosage units in single 1 l vessel, 200 ml at the USP Monograph speed, and 200 ml at calculated paddle speed which matches the hydrodynamics of the USP vessel). Six dosage units in a single vessel were used as a comparison to increase the drug concentration for dissolution testing. Due to the different dissolution hydrodynamics, drug dissolution from the dosage forms was slower using the 200 ml conversion kit than when the USP method with a 1 l vessel was used. However, use of the 200 ml vessel at higher paddle speeds calculated by the power/volume equation, yielded similar results as the monograph method. Thus, it appears that using the power/volume ratio calculation to obtain comparable hydrodynamics lends utility to the 200 ml vessel as a means for characterizing the dissolution profile of low dose solid oral drug products. The results of the multiple dosage units per vessel also gave similar results to that of the USP monograph method.

Keywords: Dissolution; 200 ml vessel; Low dose; Hydrodynamics

1. Introduction

Dissolution is defined as the taking up of a substance by a liquid, with the formation of a homogeneous solution (Walker, 1995). In the pharmaceutical industry, dissolution is used to ensure acceptable in vivo performance as well as to ensure that each batch conforms to product specifications throughout the shelf-life of the dosage form (Cammarn and Sakr, 2000). The requirements for dissolution testing for established products are clearly defined by the USP 25 (USP, 2002) and many monographs exist for commercial products. Typically, dissolution is conducted using Apparatus 1 or 2 with between 500 and 900 ml of aqueous media. In recent years, pharmaceutical companies have developed compounds that are highly potent which results in a very low concentration of drug in the 500–900 ml of dissolution media. With the discovery of compounds that are potent at such low levels, the appropriateness of Apparatus 1 and 2 is being revisited.

Typically, the first dissolution apparatus that is evaluated for a new drug in the solid dosage forms is Apparatus 2, which consists of the following: a covered vessel made of glass or other inert, transparent material; a motor; a metallic drive shaft; and a paddle

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formed from a blade and a shaft (used as the stirring element). The paddle conforms to the specifications in the USP 25 (USP, 2002).

It has been our experience that Apparatus 2 is suitable for evaluating the dissolution characteristics of most drugs from solid dosage forms. In developing a dissolution method for a new proprietary tablet containing 200 μg active, the early dissolution time points could not be quantitated using our current assay method. In order to increase the drug concentration, several options were considered. The first was to use multiple tablets in a single vessel using either 500 or 900 ml of media (Reisman, 1999). The problem with this approach is that it is not recognized in the USP and it does not provide dissolution data on individual units. Another option was to use a 200 ml conversion vessel offered by Van-Kel Technologies, Inc. which can be used with the standard Apparatus 2 dissolution apparatus (VanKel Technology Group, 2000). Again, there is no precedence in the USP and there is no guidance as to what type of calibrator tablets would be required (Dissolution Discussion Group, 1999). The conversion kit is designed to use a 200 ml vessel to help overcome the problem of low drug concentrations. The manufacturer indicates that the kit is ideal for tests where a smaller volume is required. The kit consists of a 200 ml glass vessel (203 cm long with a 42 mm diameter) and a Teflon-coated mini-paddle (381 cm long, 29.8 mm paddle diameter, with a 63.5 mm shaft). The conversion kit is a scaled down model of the traditional 1000 ml vessels and paddles as shown in Fig. 1.

The objective of this work was to explore alternative dissolution conditions to characterize the dissolution rate of our low dose active pharmaceutical ingredient (API). In addition, four other marketed products were chosen to represent the first five levels of solubility as defined by the USP 25 (USP, 2002).

2. Materials and methods

2.1. Materials

The source of the four commercially available drug products were as follows:

Fig. 1. Comparison of the USP Apparatus 2 vessel and paddle and the 200 ml conversion kit manufactured by VanKel Technologies, Inc.

Table 1
Summary of the USP 25 (USP, 2002) dissolution methods

Active pharmaceutical ingredient	Trade name	USP solubility	Volume of dissolution media (ml)	Rotation speed (rpm)	*Q*
Pseudophedrine HCl	Sudafed (tablet)	Very soluble	900	50	75% 45 min
Dipenhydramine HCl	Benadryl allergy (capsule)	Freely soluble	500	100	80% 30 min
P&GP Proprietary API	Tablet	Soluble	500	50	80% 30 min
Guaifenesin	Organidin NR (tablet)	Sparingly soluble	900	50	75% 45 min
Cimetidine	Tagamet (tablet)	Slightly soluble	900	100	75% 15 min

1. Sudafed Nasal Decongestant tablets (30 mg) manufactured by Pfizer Inc., Warner Lambert Healthcare.
2. Benadryl Allergy Ultratab capsules (25 mg) manufactured by Pfizer Inc., Warner Lambert Healthcare.
3. Organidin NR (newly reformulated) tablets (guaifenesin) (200 mg) manufactured by Wallace Laboratories.
4. Tagamet Cimetidine tablets (300 mg) manufactured by SmithKline Beecham.
5. The P&GP proprietary tablet was manufactured in-house.

2.2. Methods

2.2.1. USP methods (USP 25/NF 20)

Dissolution on the commercial drug products was run according to the specified USP method. The media specified for each drug product was water with the exception of our proprietary API which was run in 0.01N HCl. All samples were run on USP Apparatus 2 consisting of a VK7000 dissolution station and a VK8000 dissolution sampling station (Vankel Technologies, Inc., Cary, North Carolina), with a paddle speed of either 50 or 100 rpm as specified in the monograph (see Table 1 for details).

2.2.1.1. Analytical methods. HPLC assay was performed on a Waters Corporation, Milford, Massachusetts, HPLC system consisting of a 717 Autosampler, a 486 Tuneable Absorbance Detector, and a 600F pump. The percent drug dissolved was determined by filtering a portion of the solution under test using the USP method specified in comparison with a known concentration of reference standard in the same medium. UV-Vis methods were performed using an Agilent Technologies, Inc., Palo Alto, California, HP8453 UV-Vis spectrophotometer. The standard curve of absorbance versus concentration was used to determine percent drug dissolved in the dissolution experiments (see Table 2 for details).

Table 2
Summary of HPLC/UV-Vis methods

Active pharmaceutical ingredient	Analytical method	Analytical column	Mobile phase	Detection wavelength (nm)	Injection volume (μl)	Run time (min)
Pseudophedrine HCl	HPLC	Phenomenex, Torrance, California Luna (5 μm Silica (2) 4.6 mm × 25 cm)	17:3 Alcolhol:0.40% ammonium acetate solution	214	10	25
Dipenhydramine HCl	HPLC	Phenomenex, Torrance, California Luna (5 μm CN 4.6 mm × 25 cm)	CN:H_2O:triethylamine (50:50:0.5); pH 6.5 with glacial acetic acid	254	10	10
P&GP Proprietary API	HPLC	Waters, Milford, Massachusetts, Symmetry Shield R_p18 (3.5 μm 4.6 mm × 100 mm)	0.075 M Ammonium acetate solution; pH 5 with glacial acetic acid	270	50	6
Guaifenesin	UV	N/A	N/A	274	N/A	N/A
Cimetidine	UV	N/A	N/A	218	N/A	N/A

2.2.1.2. Power/volume calculations comparing the 1000 ml vessel to that of the 200 ml vessel. In general, two of the important elements needed for a proper scale up or scale down of low viscosity mixing systems are maintaining geometric similarity and maintaining constant power/volume ratio.

Geometric similarity: Although geometric similarity is highly recommended whenever scaling a mixing system up or down, it is not a critical parameter in this application since the fluid flow is turbulent (water like viscosity). For higher viscosity fluids, geometric similarity is usually recommended; for non-Newtonian fluids, geometric similarity is a critical parameter or variable.

A feature that is geometrically similar between the 200 and 1000 ml systems is the ratio of the impeller diameter to the beaker diameter. In the 200 ml beaker, the 29.8 mm impeller is 71% of the beaker diameter, while in the 1000 ml system, the 75 mm impeller is 75% of the beaker diameter. Two ratios that are not geometrically similar between the 200 and 1000 ml systems are the height of the fluid/tank diameter and the position of the impeller relative to the bottom of the beaker/impeller diameter.

Constant power/volume: For the dissolution of solids into liquids, the rate of dissolution is a function of the ratio of power/volume being put into the fluid. Specifically, if the ratio of power/volume increases upon scale-up, there may be a corresponding increase in the rate of dissolution. Thus, maintaining a constant power/volume ratio is important in order to achieve similar results. The amount of power delivered to the fluid is calculated via the following equation (Perry and Green, 1999) Eq. (1):

$$\text{Power} = \rho \times N_p \times N^3 \times D^5 \quad (1)$$

where, ρ = fluid density (kg/m^3—assumed 1 for water); N_p = power number (a characteristic of the type of impeller being used—dimensionless); N = rotational speed of impeller (revolutions/s); D = impeller diameter (m); power (W).

From preliminary experiments, it was found that the dissolution rate of the 200 μg proprietary tablet formulation in the 200 ml vessel (when operated at

Table 3
Conditions of the experiment

Drug product	Dissolution method	Sampling time intervals (min)
Pseudophedrine HCl	1. USP: 900 ml; 50 rpm 2. Multiple dose units: 900 ml; 50 rpm 3. 200 ml (USP paddle speed): 200 ml; 50 rpm 4. 200 ml (calculated paddle speed): 200 ml; 137 rpm	15, 30, 45
Dipenhydramine HCl	1. USP: 500 ml; 100 rpm 2. Multiple dose units: 500 ml; 100 rpm 3. 200 ml (USP paddle speed): 200 ml; 100 rpm 4. 200 ml (calculated paddle speed): 200 ml; 255 rpm	10, 20, 30
P&GP Proprietary API	1. USP: 500 ml; 50 rpm 2. Multiple dose units: 500 ml; 50 rpm 3. 200 ml (USP paddle speed): 200 ml; 50 rpm 4. 200 ml (calculated paddle speed): 200 ml; 137 rpm[a]	10, 20, 30
Guaifenesin	1. Multiple dose units: 900 ml; 50 rpm 2. USP: 900 ml; 50 rpm 3. 200 ml (USP paddle speed): 200 ml; 50 rpm 4. 200 ml (calculated paddle speed): 200 ml; 137 rpm	15, 30, 45
Cimetidine	1. USP: 900 ml; 100 rpm 2. Multiple dose units: 900 ml; 100 rpm 3. 200 ml (USP paddle speed): 200 ml; 100 rpm 4. 200 ml (calculated paddle speed): 200 ml; 255 rpm	5, 10, 15

[a] The original analysis of speed calculations (based on 900 ml) was used to run all the tests. For the P&GP Proprietary API run at 500 ml, paddle speed 50 rpm, Eq. (1) yielded a paddle speed of 167 rpm. Due to lack of drug to re-run the P&GP Proprietary API at 167 rpm, it was decided that if it passed the acceptance criteria at 137 rpm, then it would follow that it would also pass at 167 rpm.

50 rpm) is slower than the dissolution rate when the experiment is conducted in the 1000 ml vessel (again at 50 rpm). The reason for the different dissolution rate was traced to the different ratio of power/volume between the two systems. Specifically, the ratio of power/volume is 0.0002 kW/m^3 for the 200 ml system, while it is 0.004 kW/m^3 for the 1000 ml system. Thus, the challenge was to determine the operating conditions (speed of impeller) needed in the 200 ml system in order to match the ratio of power/volume of the 1000 ml system. It was determined from Eq. (1) that 137 rpm was needed in the 200 ml system to replicate the ratio of power/volume that is delivered by running the 1000 ml system at 50 rpm (0.004 kW/m^3). However, if the 1000 ml system is run at 100 rpm, delivering a ratio of power/volume of 0.032 kW/m^3, then the 200 ml system needs to be operated at 273 rpm to match the ratio of power/volume. In order to match the ratio of power/volume in the system with 500 ml and 50 rpm, using the 200 ml vessels a speed of 167 rpm is required and those with 500 ml of media and 100 rpm would require a speed of 332 rpm for the 200 ml system. The paddle speed is mechanically limited to 255 rpm, so all of the calculation results that indicate running at a speed greater than 255, were run at 255.

2.2.2. Dissolution procedures

The following four dissolution conditions were used (see Table 3—conditions of the experiment):

1. One dosage unit of the drug was put into each of the six vessels and the dissolution test was run according to the condition specified in the USP monograph.
2. Six dosage units of the drug were put into each of the six vessels and the dissolution test was run according to the condition specified in the USP monograph.
3. One dosage unit of the drug was put into each of the 200 ml conversion vessels and the dissolution test was run according to the condition specified in the USP monograph.
4. One dosage unit of the drug was put into each of the 200 ml conversion vessels and the dissolution test was run according to the condition determined from the power/volume ratio calculation.

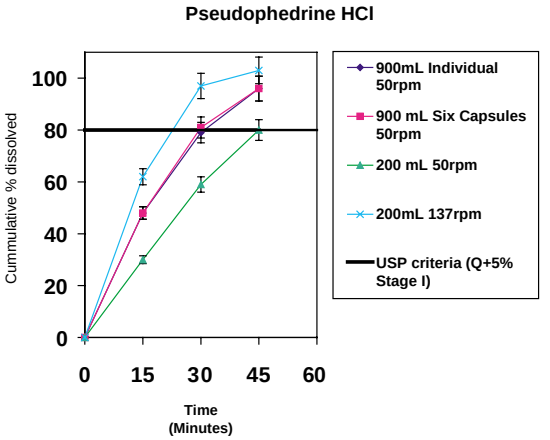

Fig. 2. Mean dissolution profile of Pseudophedrine HCl tablets (30 mg) at the various experimental conditions.

3. Results and discussion

3.1. USP monograph method versus 200 ml

Table 4 shows the mean dissolution results for the five drug products and Figs. 2–6 show the mean dissolution profiles. The USP method passed all monographed dosage units after Stage 1. The 200 ml vessels using the paddle speed as indicated by the USP method shows a lower percent of drug dissolved with all of the drug substances except for the Dipenhydramine HCl. The most significant difference was seen with Guaifenesin tablets (14% versus 88% at 45 min). Using the 200 ml conversion kit increases the drug

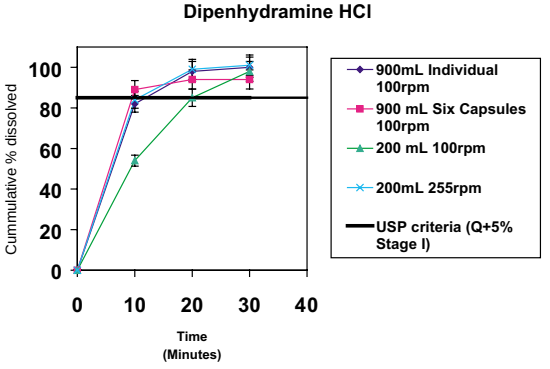

Fig. 3. Mean dissolution profile of Dipenhydramine HCl capsules (25 mg) at the various experimental conditions.

Table 4
Results of the dissolution testing that were obtained through experimentation

Drug product	Q	Dissolution condition	Rotation speed (rpm)	Mean percent dissolved	S.D.	USP stage 1 criteria[a]
Pseudophedrine HCl	75% 45 min	900 ml-individual	50	96	3.27	Yes
		900 ml-(6 dose units/vessel)	50	96	1.37	Yes
		200 ml	50	80	4.34	Stage 2 required[a]
		200 ml	137	103	3.17	Yes
Dipenhydramine HCl	80% 30 min	500 ml-individual	100	100	2.04	Yes
		500 ml-(6 dose units/vessel)	100	94	0.63	Yes
		200 ml	100	98	3.38	Yes
		200 ml	255	101	1.46	Yes
P&GP Proprietary API	80% 30 min (internal specification set by P&GP)	500 ml-individual	50	99	2.92	Yes
		500 ml-(6 dose units/vessel)	50	103	2.40	Yes
		200 ml	50	83	5.42	Stage 2 required[a]
		200 ml	137	103	1.66	Yes
Guaifenesin	75% 45 min	900 ml-individual	50	88	5.01	Yes
		900 ml-(6 dose units/vessel)	50	85	7.55	Stage 2 required[a]
		200 ml	50	14	4.79	No (fails Stage 3[a])
		200 ml	137	102	0.91	Yes
Cimetidine	75% 15 min	900 ml-individual	100	99	4.08	Yes
		900 ml-(6 dose units/vessel)	100	98	4.28	Yes
		200 ml	100	82	9.32	Stage 2 required[a]
		200 ml	255	97	1.70	Yes

[a] Acceptance criteria—Stage 1: each unit is not less than $Q + 5\%$. Stage 2: average of 12 units ($S_1 + S_2$) is equal to or greater than Q and no unit is less than $Q - 15\%$. Stage 3: average of 24 units ($S_1 + S_2 + S_3$) is equal to or greater than Q, not more than two units are less than $Q - 15\%$ and no unit is less than $Q - 25\%$.

concentration. Four out of the five drug products tested would still require Stage 2 testing to meet the USP criteria for dissolution because Stage 1 (each of six individual units is not less than $Q + 5\%$) criteria was not met. Stage 2 testing requires that the average of 12 units is equal to or greater than Q and no unit is less than $Q - 15\%$. Using the 200 ml conversion kit with a higher paddle speed as determined by the ratio of power/volume equation appears to give a similar dissolution rate when compared with the dissolution rate

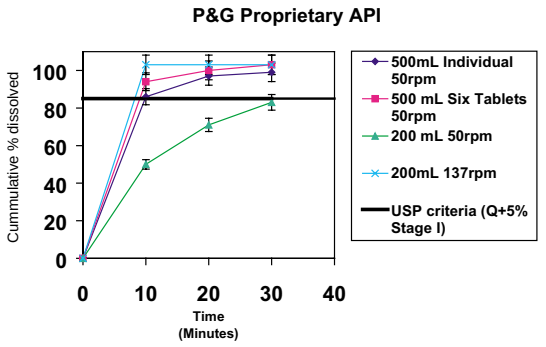

Fig. 4. Mean dissolution profile of P&GP Proprietary API tablets (200 μg) at the various experimental conditions.

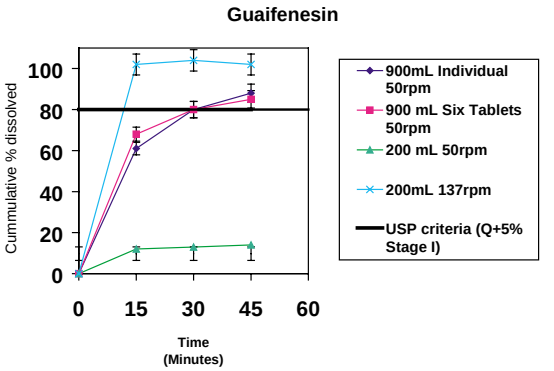

Fig. 5. Mean dissolution profile of Guaifenesin tablets (200 mg) at the various experimental conditions.

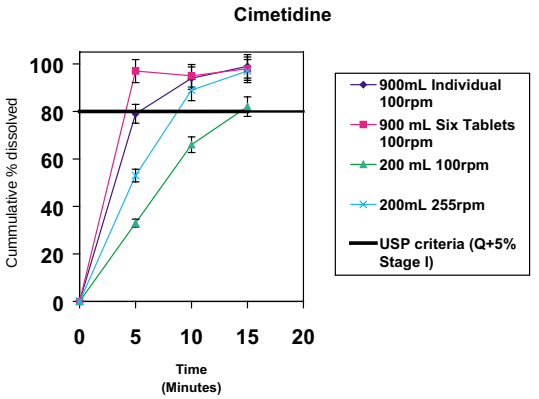

Fig. 6. Mean dissolution profile of Cimetidine tablets (300 mg) at the various experimental conditions.

seen when using the 1 l vessel according to the USP monograph. Each drug product met Stage 1 criteria.

3.1.1. USP monograph method versus multiple tablets

In all cases, the drug products passed the Stage 1 criteria set forth in the USP for testing using either the individual or the multiple dosage units. The use of multiple tablets increases the drug concentration, however, there is no precedence for this approach and dissolution on an individual dosage unit is the preferred method. It was expected that placing six dosage units in one single vessel would form a cone of insoluble excipients on the bottom of the vessel further decreasing the rate of dissolution. This coning phenomenon was not observed and had no affect on the dissolution results.

4. Conclusion

The USP criteria for Stage 1 dissolution (USP, 2002) were met by using multiple dose units in a single vessel. Although the use of multiple dose units per vessel increases the drug concentration, there is no USP precedence for using this approach. Using the commercially available 200 ml vessels with the paddle speed as specified by the USP monograph resulted in slower dissolution rates and required Stage 2 testing for four of the five drug products tested. The slower dissolution is attributed to the different hydrodynamics between the 200 and the 1000 ml vessels. If the hydrodynamics in the 200 ml vessel are comparable to that in the USP 1000 ml vessel as determined by matching the power/volume ratio to determine paddle speed, similar dissolution conditions can be achieved.

Thus, use of the power/volume ratio calculation appears to be a suitable means of obtaining comparable hydrodynamics. Thus, it appears the 200 ml vessel has utility for characterizing the dissolution profile of low dose solid oral drug products.

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