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Improved drug dissolution and product characterization using a crescent-shaped spindle

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Abstract

Drug release characteristics of two amoxicillin capsule products, 250 and 500 mg strength each, have been described using USP Paddle and crescent-shaped spindles. Using the same spindles, dissolution experiments were conducted with USP disintegrating (prednisone) and non-disintegrating (salicylic acid) calibrator tablets. Dissolution tests were conducted at 50 and 25 rev min^{-1} using USP Paddle and crescent-shaped spindles, respectively. In all cases, even with the higher 50 rev min^{-1}, lower percent drug release results were observed with the Paddle spindle than with the crescent-shaped spindle, which was operated at 25 rev min^{-1}. The observed lower dissolution for amoxicillin capsule products (< 36 vs > 87% at 30 min) and USP prednisone calibrator tablets (45.5 vs 99.8% at 30 min) with Paddle spindles appeared to occur because of the accumulation of the disintegrated material (cone formation) at the bottom, thus restricting product–medium interaction. Crescent-shaped spindles did not allow any accumulation of the product and provided improved interaction by mixing and stirring, and thus appeared to provide true drug dissolution characteristics of the products. On the other hand, in the case of non-disintegrating USP salicylic acid tablets (18.5 vs 24.4% at 30 min), lower results with Paddle spindles appeared to be because of stagnation of the tablets, which provided poor product–medium interaction for the surface touching the vessel surface. In this case, the crescent-shaped spindles moved the tablets at the base of the vessel, providing improved and efficient product–medium interaction, thus appearing to reflect truer dissolution characteristics of the tablets. The results highlight the possible artifacts of the USP Paddle spindle, which could lead to inaccurate characterization of drug release properties of test products. As reported previously, the artifacts of high variability in results and lack of relevance to product properties appeared to be related to poor mixing and variable hydrodynamics within a dissolution vessel. Results from this study provide further evidence that these artifacts might be addressed adequately using the crescent-shaped spindle, thus resulting in improved drug release as well as better product characterization.

Introduction

At the present time, most drug dissolution studies are conducted using the United States Pharmacopeia (USP) Paddle and Basket apparatuses, using a variety of experimental conditions, such as spindle rotation speeds and dissolution media (USP 2004a). Although pharmacopoeias, such as the USP, recognize other variations of apparatus e.g. Reciprocating Baskets and Flow-through, these are not widely used. The Paddle and Basket apparatuses are preferred because of their simplicity and widespread availability, even though these present difficulties in reproducibility and in general lack of relevance either to results obtained with bioavailability studies or product and/or formulation attributes (McCormick 1995, Qureshi & McGilveray 1995, 1999).

Various reasons have been attributed towards such a lack of reproducibility and relevance of dissolution results. These have included limited training of analysts, substandard apparatus, de-aeration of dissolution media, vibration induced by the environment and complexity of biological system vs simplicity of an in-vitro environment in dissolution apparatus (Gray et al 1994; Meyer et al 1998; Repta 1999; Mirza et al 2000). However, there are limited experimental data available to support these assumptions.

Recently there has been increased attention given to the limitations of the stirring and mixing environment in a dissolution vessel (commonly referred to as

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'poor hydrodynamics') as a potential source of high variability and unpredictability of drug dissolution results (Cox et al 1982; Qureshi & Shabnam 2001; McCarthy et al 2003). Furthermore, it has been reported that poor hydrodynamics may be responsible, in part, for the general lack of bio-relevant dissolution results (Qureshi & Shabnam 2003).

The Paddle and the Basket apparatuses share the same equipment design, except for the spindles, which include a fixed paddle or an attached basket. They, therefore, face the similar artifacts due to poor hydrodynamics within the vessel. It was considered that a modification of the apparatuses might improve the hydrodynamics and mixing within dissolution vessels. This would not only improve the dissolution testing, but the modification could be of economic benefit by saving the current investment in the equipment in use.

With this in mind a new spindle was suggested by Qureshi & Shanbam (2003), that appeared to address the artifacts of the current dissolution apparatus and provided improved dissolution results. This study describes further applications of the new crescent-shaped spindle in comparison with the USP Paddle spindle, using the USP calibrator tablets and multi-vendor amoxicillin capsules as test products.

Materials and Methods

Materials

Two conventional (immediate, fast)-release amoxicillin capsule (250 and 500 mg) products were purchased from the local Canadian market. The brands of these products are identified as A and B. All these products are interchangeably prescribed based on the bioequivalence of the products of respective strengths (Ministry of Health 2003).

USP calibrator tablets (prednisone tablets, Lot N and salicylic acid tablets, Lot O) were obtained from USP (Rockville, MD). All other chemicals and solvents were of analytical grade and used as obtained from the vendors.

Stirring/mixing spindle

The crescent-shaped spindle (US Patent 6,676,285) can be described as being designed to fit into the currently used dissolution vessels, as a substitute for the currently employed paddle (or basket) spindle. The agitator has a stem part and the lower half is curved to conform to the shape of the vessel, in which it is rotated, but having no direct contact with the surface of the vessel.

The end of stem, conforming to the shape of the bottom part of the vessel, has filamentary elements filling the gap between the stem and the bottom part of the vessel (Qureshi & Shabnam 2003). Therefore, when the device attached to the vertical shaft rotates, the brush-type agitator will sweep through the bottom and sides of the vessel accomplishing the spreading and mixing of the disintegrating material and thereby avoiding accumulation (coning).

Methods

The dissolution tests were conducted using a Vankel system (VK 700), which comprised a bath with six vessels and met the physical and mechanical specifications as required by the USP (USP 2004a). The dissolution tests were conducted using the USP Paddle and crescent-shaped spindles at rotation speeds of 50 and 25 rev min^{-1}, respectively. Before use, the dissolution media were equilibrated at 37°C overnight to de-aerate the medium to minimize bubble formation, which could be caused by escape of dissolved gases during the test.

The dissolution tests for amoxicillin products were conducted using 900 mL 0.05 M phosphate buffer solution (pH 6.8). For each vessel, the amount of amoxicillin dissolved was determined at 10, 20, 30, 60, 90 120 and 180 min. As recommended in the USP, a wire helix was wrapped around the capsule before dropping it into the vessels, to ensure it sank to the bottom. The quantitation (USP 2004b) was carried out using HPLC using a 5 μm C_{18} column with a mobile phase consisting of a mixture of phosphate buffer (0.05 M, pH 5.0) and acetonitrile (96:4). The flow rate was set at 1 mL min^{-1} and quantitation was performed at 230 nm.

For USP calibrator tablets, dissolution tests were conducted according to the procedures described in the sheets that accompanied the calibrator tablets.

Data analysis

The data were collated and analysed using SAS software (SAS Institute, Cary, NC). 95% Confidence intervals (CI) around the mean for individual amoxicillin capsules were calculated from analysis of variance results as follows. The error term from analysis of variance results considered within-run component of variance (s^2_w). The between run variance (s^2_b) component was calculated from the Mean Squares (MS) term from the analysis of variance as follows: (MS-s^2_w)/6. The total variance for an individual result was thus obtained as the sum of within and between laboratory variance components i.e. $s^2_T = s^2_w + s^2_b$ (Miller & Miller 1988). This total variance was used for calculating 95% CI. Variability in results were reported as percent relative standard deviation (%r.s.d = (s.d./mean) × 100).

Results

Drug release profiles for amoxicillin capsule products using USP Paddle and crescent-shaped spindles are shown in Figures 1 and 2, respectively. Both products showed significant cone formation with the USP Paddle spindle, which was associated with a reduced dissolution rate. However, no cone formation, attributed to improved stirring and mixing, was observed using the crescent-shaped spindle and resulted in much higher drug release rates, even at 25 rev min^{-1}.

Figure 3 shows drug dissolution of USP prednisone calibrator tablets using Paddle and crescent-shaped spindles at 50 and 25 rev min^{-1}, respectively. The mean (± s.d.)

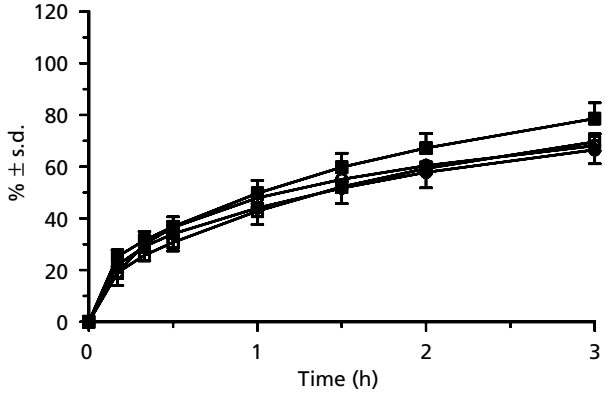

Figure 1 Drug release profiles of two amoxicillin capsule products (250 and 500 mg each) observed with USP Paddle spindle at 50 rev min^{-1}. ■ Brand A, 250 mg; □ brand A, 500 mg; ● brand B, 250 mg; ○ brand B, 500 mg. For details of experimental conditions, see the experimental section.

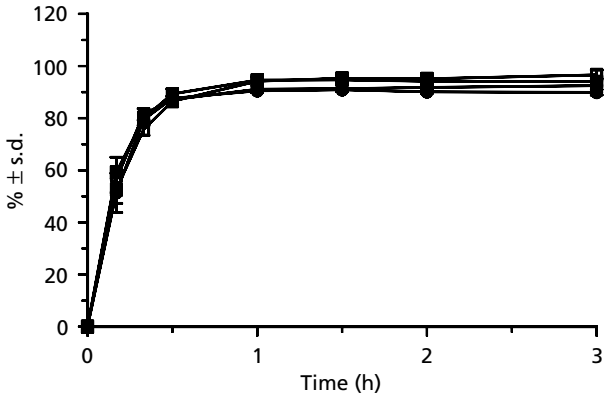

Figure 2 Drug release profiles of two amoxicillin capsule products (250 and 500 mg each) observed with crescent-shaped spindle at 25 rev min^{-1}. ■ Brand A, 250 mg; □ brand A, 500 mg; ● brand B, 250 mg; ○ brand B, 500 mg. For details of experimental conditions, see the experimental section.

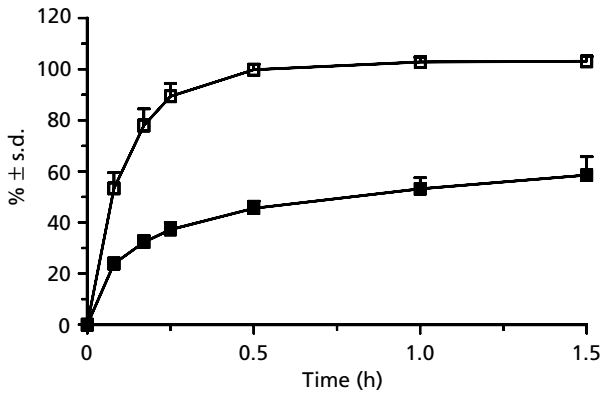

Figure 3 Drug release profiles of USP prednisone (disintegrating) calibrator tablets using USP paddle (■) at 50 rev min^{-1} and crescent-shaped (□) at 25 rev min^{-1}. For details of experimental conditions, see the experimental section.

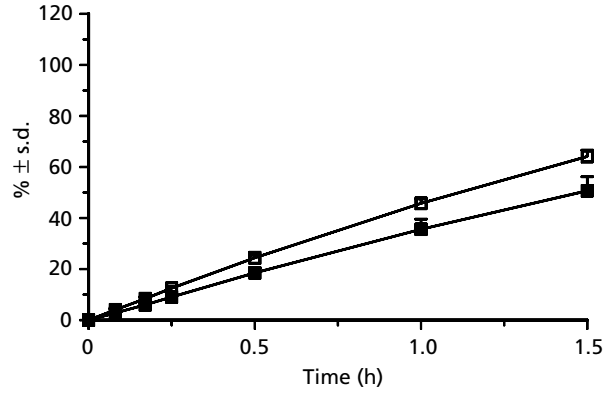

Figure 4 Drug release profiles of USP salicylic acid (non-disintegrating) calibrator tablets using USP paddle (■) at 50 rev min^{-1} and crescent-shaped (□) at 25 rev min^{-1}. For details of experimental conditions, see the experimental section.

percent drug release from prednisone calibrator tablets using the USP Paddle spindle at 30 min was 45.5 ± 2.7 with a minimum and maximum of 42.2 and 49.6, respectively, which is well within the expected range. This demonstrated that the equipment and overall testing conditions were within expected standards. Figure 4 shows corresponding drug release profile of salicylic acid calibrator tablets using USP Paddle and crescent-shaped spindles at 50 and 25 rev min^{-1}, respectively. As expected, drug release was higher with the crescent-shaped spindle than with the Paddle, as interaction of the medium with the tablets was more efficient and thorough using the crescent-shaped spindle.

In all cases, lower percent drug release results were observed with the Paddle spindle than with crescent-shaped spindle. The observed lower dissolution for amoxicillin capsule products (<36 vs $>87\%$ at 30 min) and USP prednisone calibrator tablets (45.5 vs 99.8% at 30 min) with Paddle spindles appeared to occur because of accumulation of the disintegrated material (cone formation) at the bottom, due to limited product–medium interaction. As the crescent-shaped spindles did not allow accumulation of the product and provided improved interaction by mixing and stirring, they appeared to provide higher drug dissolution results. On the other hand, for non-disintegrating USP salicylic acid tablets (18.5 vs 24.4% at 30 min) lower results with Paddle spindles appeared to be due to stagnation of the tablets, which provided poor product–medium interaction for the surface touching the vessel surface. In this case, the crescent-shaped spindles moved the tablets at the base of the vessel, providing improved and efficient product–medium interaction, thus appearing to provide higher dissolution results.

Discussion

It has been shown that high variability and unpredictability in dissolution results using the USP Paddle spindle occurred because of vortex-type hydrodynamics, which

create an un-stirred zone at the bottom-centre of the vessel (Haystead 2003: McCarthy et al 2003; Qureshi & Shabnam 2001). Furthermore, by its nature, the vortex-type hydrodynamics force accumulation of disintegrated material in this zone thus retarding efficient product–dissolution medium interaction and mixing. Due to this lack of efficient mixing, some tested products do not exhibit their true drug release properties (i.e. slow release is an artifact of the technique). Therefore, generally, observed dissolution will be slower and less than expected for most of the products.

This cone formation, due to the vortex hydrodynamics effect, resulting in poor product–medium interaction was also reported as one of the possible causes of the generally reported lack of relevance of dissolution results to observed drug release in-vivo (Beckett et al 1996; Qureshi & Shabnam 2003). In contrast with the in-vitro (dissolution) environment with the USP paddle spindle, where disintegrated product accumulated, in-vivo (GI tract) physiology forces the product to spread and mix (Levy 1963; Wilding et al 1991; Ganong 2003). Thus, if using the USP Paddle spindle with a round-bottomed vessel, the dissolution results should not be expected to relate to in-vivo results, at least in many cases.

To address these artifacts the crescent-shaped spindle has been proposed, which not only avoids the accumulation of the product but facilitates spreading and mixing of the material in the dissolution vessel as one would anticipate in the GI tract. Therefore, in many cases the expected dissolution characteristics would be more relevant to the physiological situation than with the currently used paddle spindle.

Figures 1 and 2 illustrate this behaviour with amoxicillin capsule products using the USP Paddle and crescent-shaped spindles, respectively. A significant difference in release characteristics was observed depending on the type of spindle employed. With the Paddle spindle, once the capsule shells were dissolved, the contents accumulated at the bottom. This resulted in poor dissolution. However, using the crescent-shaped spindle, the accumulation of material was avoided and appropriate higher dissolution results were obtained due to the improved product–medium interaction.

Intuitively, results obtained using the USP Paddle spindle did not reflect accurately the release attributes of the products. The products were immediate (fast) release, however results obtained made it appear to have more dissolution characteristic of a slow-release product. Thus, products with disintegrated material, which settle at the bottom of the vessel, might not be accurately characterized using the USP spindle method. From a bio-relevancy point of view, the slower (decreased % dissolved) results obtained using the Paddle spindle would be less likely to correlate with the in-vivo dissolution, as from a bio-study this product is reflected as a fast release. The use of the crescent-shaped spindle appeared to address this artifact of the Paddle spindle and provided improved interaction and higher dissolution rate, reflecting the fast-release characteristics of the product, even with the lower 25 rev min^{-1} vs 50 rev min^{-1}.

As reported previously (Qureshi & Shabnam 2001), the placing and landing of a product in relation to the un-stirred area will create higher variability in results. This expected higher variability was also evident from the summary of results reported in Table 1. Percent drug release values using the USP Paddle spindle were smaller with wider 95% CI compared with corresponding results with the crescent-shaped spindle.

Table 1 Overall means and 95% confidence intervals (CI) for amoxicillin capsule products using different spindles. Values in parentheses represent expected variability values (%r.s.d.) for a single unit in a run of six units

Spindle	Sample time (min)	Mean	95% CI (%r.s.d.)
Crescent	10	54.9	39.8–70.1 (13.8)
	20	79.1	69.5–88.7 (6.1)
	30	87.6	83.0–92.3 (2.7)
	60	92.6	87.9–97.3 (2.5)
	90	93.0	87.9–98.1 (2.7)
	120	92.8	87.7–97.9 (2.8)
	180	93.2	87.1–99.3 (3.3)
USP Paddle	10	21.3	12.8–29.7 (19.9)
	20	29.1	20.7–37.5 (14.4)
	30	34.5	24.9–44.1 (13.9)
	60	46.1	36.0–56.3 (11.0)
	90	54.7	43.9–65.5 (9.9)
	120	61.1	49.5–72.8 (9.5)
	180	70.7	57.2–84.2 (9.6)

It is important to note that the 95% CI were calculated using pooled data from both products and strengths. Such an approach would be expected to provide the widest variability in results, including from product-to-product and strength-to-strength (which will include lot-to-lot variability as well) and should help in setting improved tolerances for product characterization. Analysing and setting strength and/or product-dependent tolerances may artificially provide narrow variability and interval. However, such different tolerances may not be justified for products that are expected to have similar drug release characteristics and are interchangeably prescribed to patients, as in the case of the amoxicillin products tested in this study.

A similar example of slow dissolution due to poor mixing and product–medium interaction is seen with the USP prednisone calibrator tablets. This product was developed based on formulation attributes of a product tested extensively in one of the US FDA laboratories and identified as NCDA#2 tablets (Moore & Cox 1997a). The reported characteristics of this formulation was that after disintegration, the particles were settled as a pointed mound (cone) at the bottom centre of the vessel. Thus, after cone formation, the observed drug release was influenced by poor interaction with medium, not characteristic of the product itself. The cone acted as a barrier for the drug trapped inside, inhibiting interaction with the dissolution medium. Thus, the undesired and unexpected slow drug release from an actual fast-release product was a result of the artifact of the technique. Furthermore, for this particular product, the sensitivity of the accumulated material to any disturbance

was so high that it was reported (Moore & Cox 1997b) that, even if the medium was not sufficiently de-aerated, the dissolved gases made the accumulated particles bounce and provide higher and more variable drug release results. This might be assumed, mistakenly, to be related to other factors such as apparatus, the product itself and/or the analysts.

Therefore, to reduce the variability in dissolution results, it is recommended that dissolution testing of the USP calibrator tablets, or any other product which shows sensitivity to such medium based buoyancy, should be conducted with a de-aerated medium (Moore & Cox 1997b; USP 2004a). This means that to reduce the particle buoyancy the medium is de-aerated, which in turn will further reduce the drug release from the cone, unrelated to the actual drug release attributes of the product. In essence, in such cases the current practice of dissolution testing using the USP Paddle spindle with de-aerated medium, in fact, provides dissolution characteristics unrelated to meaningful product attributes.

To summarize this concept, the drug release from USP calibrator tablets is retarded (reduced) because of cone formation and is not reflective of the true product release characteristics. For improved drug release characterization, the drug must not accumulate at the vessel bottom and should be mixed adequately. The proposed spindle provides such an advantage, which is reflected by faster drug release from the product.

It is commonly argued that obtaining faster and higher dissolution is not an objective of dissolution testing and, in cases where a cone is formed, increased spindle speed may be used to diminish the cone formation thereby obtaining higher dissolution results, if so desired. Unfortunately, this appears to be a commonly held opinion and practice (USP 2004c). The consequence of this belief leads to arbitrary choices of spindle speeds to obtain the desired faster results, depending on the nature of formulation/product. There are a number of inherent deficiencies of such an approach of choosing product-dependent spindle speed ($rev\,min^{-1}$). Firstly, dissolution testing procedures and specifications will become product dependent, i.e. one set of procedures and/or tolerances for products with denser material and a second set for lighter material, and yet other tolerances for those in between. This is possibly a major reason why there are multiple procedures and tolerances for pharmacopoeial monographs such as the USP. Not only does this situation create a complex system for tolerances, but also product-to-product comparison will not be possible as different products will be judged by their own standards. Therefore, in many cases, the practice of comparative dissolution testing whether for formulation development, assessing the impact formulation/manufacturing changes, or generic vs innovator product, would not be possible or accurate. Secondly, the product-dependent choice of experimental conditions such as $rev\,min^{-1}$ are intuitively not accurate in terms of the biological relevancy of dissolution testing. The reason being that with the multiple choices of agitation (stirring speed) one would have to assume that human (GI tract) physiology was dependent upon product characteristics. Obviously, this would be an inaccurate assumption. The human physiological aspect remains the same whatever the product, and is independent of its release characteristics. Therefore, any technique which requires multiple experimental conditions, in particular for biologically equivalent products, should be considered limiting and possibly unacceptable, and products should be tested using a technique which, as much as possible, would be free from the artifacts of product–apparatus interactions. Thirdly, another flawed assumption is that a dissolution test is an analytical test to show that a product is capable of adequately releasing the drug with a reasonable agitation and within a reasonable time, and so relevance of the experimental conditions to biological conditions may not be critical. Unfortunately, it appears that this view has emerged because of many unsuccessful attempts to show relevance of dissolution results to their biological responses (pharmacokinetics). However, historically and in reality, the drug dissolution test was conceived as a quality control release test to indicate expected drug release in man and was considered as an in-vitro surrogate for in-vivo release and absorption rate (Wagner 1971; Abdou 1989; McGilveray & Qureshi 1996), although not always successfully. Nonetheless, regulatory agencies throughout the world require that such relationships of in-vitro and in-vivo results be developed or at least attempted and this is confirmed by the fact that, in limited cases, acceptable dissolution results can be considered adequate to waive the requirements of testing in man (FDA 2000). Therefore, a dissolution test should really be considered as a surrogate of in-vivo dissolution and experimental conditions should simulate the physiological environment as much as possible.

With respect to in-vivo/in-vivo correlation (IVIVC) or bio-relevancy aspect of dissolution results, there are a number of approaches suggested in the literature to establish such relationships (USP 2004d). For example, the most commonly used or desired models relate to prediction of expected drug–plasma concentrations from dissolution results or predicting in-vitro dissolution results from plasma–drug concentration results. Generally this is referred to as point-by-point, or level A, correlation and is established using a mathematical technique known as convolution/deconvolution. However, the most basic and fundamental type of bio-relevancy relationship is that if a product shows fast-release characteristics in-vivo, then its in-vitro dissolution results must be reflective of this observation. By choosing such an approach it is not necessary to conduct expensive concurrent in-vivo (bioavailability/bioequivalence) studies to establish bio-relevancy of dissolution results. If a dissolution test shows an uncharacteristic dissolution result, as in this case for amoxicillin products using the Paddle method, where a fast-release product shows apparent slow-release characteristics, there is no need for conducting or developing further elaborate IVIVC predictions, thus saving significant human and financial resources. However, as a crescent-shaped spindle provides bio-relevant results, i.e. a fast-release product showing fast dissolution, if necessary further elaborate IVIVC studies may be conducted with concurrent in-vivo studies for more precise prediction of plasma drug levels.

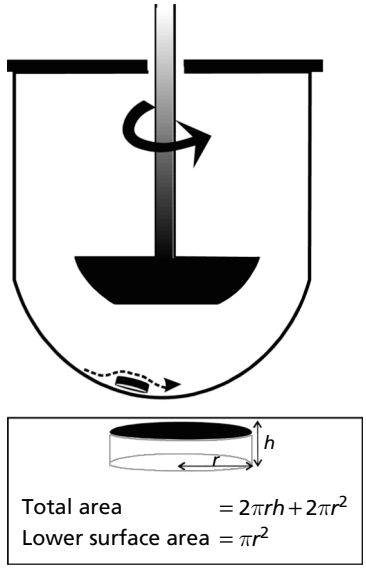

Figure 5 Schematic of medium flow in a dissolution vessel using USP paddle spindle with non-disintegrating product such as USP salicylic acid calibrator tablets.

Current dissolution apparatus, in particular with the Paddle spindle, provide laminar flow based hydrodynamics in the dissolution vessel, which is not as turbulent as expected in a biological environment. Such laminar flow will provide limited interaction of product with the medium on the surface of the product resting on the vessel (Figure 5). Such a limited interaction will be more visible and pronounced with products that are of a non-disintegrating type, such as the USP salicylic acid calibrator tablets. It has been shown (Morihara et al 2002) that due to limited interaction with the medium on the surface which touches the vessel, reduced dissolution was observed for such products. However, in the body such one-sided interaction would not be observed, as the products will move in the GI tract by tossing and turning. Thus, in-vitro, using the USP Paddle spindle, this phenomenon will not be reflected and therefore the dissolution results will be lower than anticipated in-vivo. However, with the proposed spindle, a test product moves within the vessel and will interact better with the medium thus yielding an improved and higher dissolution rate, as reflected in Figure 4. It should be noted that higher percent drug results are obtained, not because of higher agitation, but because of improved product and medium interaction.

Evidence of available surface area–medium interaction may be demonstrated indirectly, if one correlates ratios of the observed percent drug release by the two methods (Paddle and crescent-shaped) to ratios of the areas available with the two methods (Figure 5). The area available for the crescent-shaped spindle, which is the total surface area of the tablet, may be calculated using the formula given in Figure 5 (Washington 1990). The area for salicylic acid tablets with a mean (n = 6) diameter of 9.58 mm and thickness of 3.22 mm was 240.9 mm^2. The area excluding the surface resting on the vessel (total area – area touching the vessel surface) was 168. 9. The ratio (0.7) corresponded well with the ratios of the dissolution results obtained at the earlier sampling times of 5 and 10 min (Table 2). With the passage of time, size (area) of the tablet would be reduced faster with the crescent-shaped spindle (higher dissolution), this ratio of the dissolution results would increase as well, since the denominator in the ratio would be decreasing faster. Therefore, it may be concluded that faster drug dissolution from all surfaces results in this case, for non-disintegrating tablets, using the crescent-shaped spindle and thus provides a more accurate reflection of product dissolution characteristics than those obtained using the USP Paddle, where dissolution is not observed from all product surfaces.

Table 2 Means (%r.s.d.) and ratios of percent drug release from USP salicylic acid calibrator tablets using different spindles

Time (min)	Percent (%r.s.d.)		Ratio
	USP Paddle	Crescent-shape	
0.0	0.0	0.0	
5.0	2.78 (7.0)	4.02 (12.2)	0.69
10.0	5.97 (8.9)	8.38 (8.8)	0.71
15.0	9.07 (9.6)	12.50 (6.3)	0.73
30.0	18.52 (9.7)	24.43 (4.4)	0.76
60.0	35.58 (11.2)	45.75 (3.4)	0.78
90.0	50.68 (10.8)	64.12 (3.9)	0.79

Another important conclusion drawn from the relationship of surface area ratios to dissolution ratios is that the physical integrity (no breaking or chipping of tablets) may be assumed to be the same or similar with both type of spindles. In fact, this was confirmed during the experiment by the absence of shearing or of the milling effect of the crescent-shaped spindle on the tablets.

Conclusion

For efficient drug dissolution evaluation, the testing environment should be such that the medium hydrodynamics be turbulent and not laminar so that effective mixing and stirring in the vessels can occur. Proper mixing and stirring are critical for the efficient absorption of drugs through the GI tract. The current dissolution testing practice, using the USP Paddle spindle, does not provide such an environment. In fact the opposite occurs (laminar flow vs turbulence and absence of mixing and stirring), which forces the product and its disintegrated aggregate to accumulate at the base of the vessel providing limited medium–product interaction. Therefore, results obtained with such apparatus will be of limited relevance to true product characteristics. The new crescent-shaped spindle created improved hydrodynamics in the vessel, thus providing improved drug dissolution results and potentially improved relevance to in-vivo drug release characteristics.

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