Comparative Dissolution of Diltiazem Immediate and Extended Release Products Using Conventional USP and Innovative Dissolution Paddles

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Abstract: Drug dissolution studies are commonly conducted using compendial methods employing USP Paddle and Basket apparatuses. In many cases, dissolution studies can be of limited benefit especially for product-dependent dissolution procedures like in extended release (ER) formulations. The high variability in dissolution testing, that is not product-related, emphasizes the need for developing new methods for dissolution testing that can address the artifacts found with the current USP dissolution methods. A crescent shaped spindle was suggested as a solution to overcome drawbacks associated with conventional dissolution methods. Diltiazem immediate- and extended-release tablets and capsules were used to evaluate the crescent-shaped spindle and compare it to the USP paddle system. Appropriate dissolution rates were obtained using crescent-shaped spindle at 25 rpm compared to higher rotation speeds of 75/100 rpm with the USP Paddle. Similarity factor (F_2) and dissolution efficiency (DE) parameters were used to evaluate dissolution profiles. Statistical analysis using student t-test and P-value was used to compare the results under various test conditions. For the immediate release (IR) products, only one product out of four had similar dissolution profile in the USP paddle and Crescent shaped spindles. Two products out of five ER products were found similar based on the F_2 value. In general, Crescent shaped spindle provided better evaluation for the dissolution of IR and ER products without any evidence of harsh stirring environment or crushing.

Keywords: Dissolution, Similarity factor, Dissolution efficiency, t-student test, Crescent shaped spindle.

1. INTRODUCTION

Drug absorption from a solid dosage form after oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract. *In vitro* dissolution is often applied to predict the *in vivo* product's performance especially in cases of poorly soluble drugs and extended release formulations [1]. In bioequivalence studies, comparative dissolution studies with the originator are required. Dissolution outcome/profile of the product may be evaluated by several means such as DE and F_2. However, such comparative studies may produce false results due to a number of reasons such as the choice of the dissolution testing method (apparatus and/or experimental conditions). In addition to that, dissolution tests may lack reproducibility, or have poor interpretation of results and poor relevance to *in vivo* characteristics. One of the potential causes of such drawbacks has been linked to be the poor hydrodynamics within the dissolution vessel in the USP Paddle and Basket systems [2-8]. Variability in the interaction between the product and dissolution medium produces highly variable dissolution results [9]. Accumulation of disintegrated materials at the bottom of the dissolution vessel, usually known as cone formation, may lead to a factitious release pattern of the tested products. For example, the dissolution of IR products may appear as an ER profile. Qureshi [9] reported that maintaining a laminar flow in the dissolution vessel would result in a highly variable flow in the curved portion of the vessel especially at the bottom of the vessel. In order to reduce variability in current dissolution tests, Qureshi [10] proposed a new spindle, known as crescent-shaped.

Comparison of various dissolution profiles is analyzed using several special measures including the dissolution efficiency (DE %) and the similarity factor (F_2) [11, 12]. The DE% enables the comparison of several formulations simultaneously and can be theoretically related to the mean plasma concentration-time curve obtained after deconvolution of the *in vivo* data [13-15]. The similarity factor is used to determine whether the test product is similar to the reference products. A F_2 value higher than 50% means that the average difference between both dissolution profiles is less than 10% at all sampling points indicating similarity of the two products [12].

In current work, the crescent-shaped spindle is compared to the USP Paddle method to further evaluate its reported potential benefits. Dissolution efficiency and similarity factor were used to compare the potential parameters and evaluate the dissolution profiles of different products.

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2. EXPERIMENTAL

2.1. Materials and Methods

2.1.2. Pharmaceutical Products

Immediate release diltiazem tablets (IR) 30 and 60 mg and extended release (ER) tablets of 90 &120 mg were purchased from different local Jordanian suppliers. Products were marked as Ai to Di representing immediate release formulations and products marked as Ae to De represented ER products.

All other chemicals and solvents were of analytical grade.

2.2.2. Instrumentation

The dissolution tests were conducted using a VanKel system (VK 700) comprising a bath with six vessels and meeting the physical and mechanical specifications as required by the USP chapter<711> [16].The instrument was mechanically calibrated using a paddle according to the USP requirements. The crescent-shaped spindle was mounted and used as previously described [9] at rotation speed of 25 rpm. The dissolution tests using conventional USP spindles were conducted at 75 and 100 rpm for IR and ER products, respectively.

2.2.3. Dissolution Conditions

The tests were conducted using 900 mL of medium maintained at 37 ± 0.5 C^0. The amount of diltiazem, dissolved in the medium, was determined by collecting samples at predetermined intervals and up to three hours for the IR products and 24 hours for the ER product. Briefly, 5 mL sample was withdrawn for analysis and immediately replaced with an equal volume of fresh medium maintained at the same temperature. Samples were filtered using 0.45 μm syringe filters and then analyzed for diltiazem content using UV-spectrophotometry at 240 nm (SpectroScan 80D, SpectroScan, USA). Diltiazem concentration was calculated using linear calibration plots. The dissolution test for each product was performed in six replicates/vessels and mean values as well as standard deviations were calculated. Before adding diltiazem products, dissolution media in each vessel was sonicated at 37 ± 0.5 °C for 30 minutes to de-aerate the medium. Further, the medium was kept in the vessels for 10 more minutes within the dissolution apparatus to equilibrate with the water bath temperature.

2.2.4. Data Analysis

A model-independent technique was used to compare the dissolution profiles of the products. The model, based on similarity factor F_2, was described by Moore *et al.* using the following equation [17].

$$f_2 = 50\log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}\left(R_t - T_t\right)^2\right]^{-0.5}\times 100\right\}$$

Where R_t and T_t are the reference and test product results at time point t, respectively, and "n" is the number of sampling points. F_2 data were calculated using mean values of percentage dissolved at the various sampling times. The dissolution profiles from the USP spindle and the Crescent shaped for the same product were used to calculate the similarity factor F_2. The official USP paddle was used as a reference and the crescent shaped spindle was the test. Values of $F_2 \geq 50$ indicate similarity of two profiles under the assumption of a maximum allowable difference of 10% [1].

The dissolution efficiency (DE) was used to evaluate the dissolution performance of the products under different test conditions. DE was calculated as follows: $DE = \int y\frac{dt}{100t}$ where y is the percentage of drug dissolved at time t [18].

DE was determined at 30, 60, 90 and 180 minutes for the IR products and at 3, 6 and 24 hours for the ER products. DE values were statistically analyzed using the student t-test with a significance level of p-value ≤0.05.

3. RESULTS AND DISCUSSION

Linearity of diltiazem standard calibration curve was obtained with a correlation coefficient (r^2) over (0.999) and then used to calculate the amount of the drug dissolved in each sample. For appropriate comparison of the DE values obtained from the two spindles, the experimental setup was based on the same apparatus, medium and the tested product.

Drug release profile of IR diltiazem tablets from different manufacturers are shown in Figs. (**1** and **2**). The corresponding DE data and F_2 are presented in Tables **1** and **2**. For product A_i (60 mg tablets), the dissolution profiles obtained from the two spindles were similar with a F_2 value of 64.14. While the DE value for the total dissolution time of 180 minutes showed no significant statistical difference, the DE value at 60 minutes was more significant in the crescent shaped spindle compared to the official USP one.

For product B_i (60 mg tablets), the F_2 value (33.47) indicated that the two spindles resulted in different dissolution profiles. The DE value for the total time profile of 180 minute indicated higher dissolution efficiency for the crescent shaped spindle compared to the official USP one. In addition, the DE value at 30 and 90 minutes were also higher for the crescent shaped spindle compared to the official USP one.

Further, F_2 (38.27) for product C_i (60 mg tablets) showed difference in the dissolution profiles between the two spindles. The difference between DE values at 180 minutes was statistically significant ($P<0.05$). The DE_{30} value for the crescent shaped spindle was lower than that of the USP spindle.

The DE for diltiazem (30 mg tablets) value for the total time of 180 min showed a significant difference between the two spindles. While the DE value at 30 minutes indicated no difference, the DE_{60} & DE_{90} showed significant difference in the dissolution between the two spindles. Further, the dissolution profiles for the product using the two spindles (Fig. **2**) were not similar, F_2 value (33.23).

Product B_e showed dissolution efficiency values of the crescent spindle that are not significantly different from that in the paddle one. However, the other two products A_e and C_e showed differences in dissolution efficiency between the two spindles. In addition, all DE values for product C_e were significantly different for the dissolution profiles of the official USP and crescent shaped spindles. The drug release behavior of diltiazem ER tablets (90 and 120 mg) and capsules

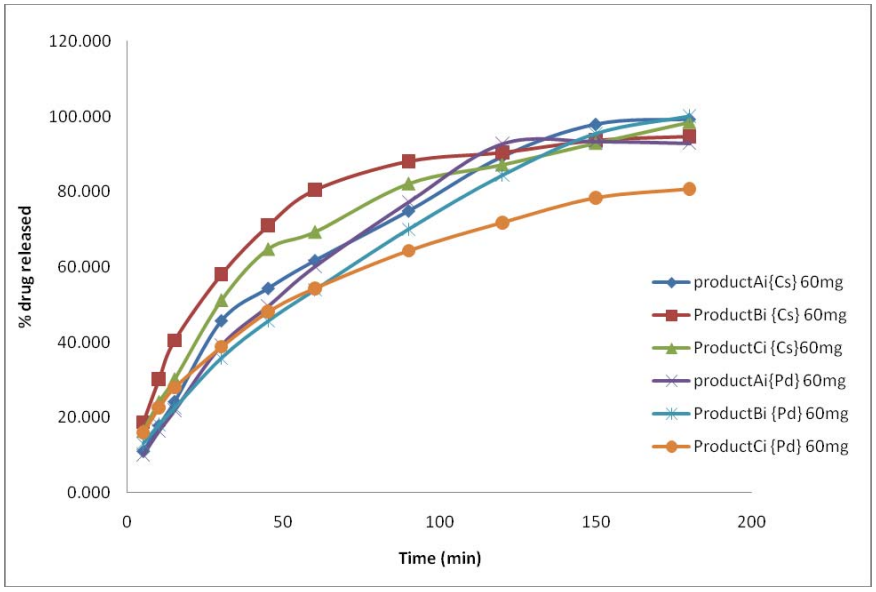

Fig. (1). Comparative dissolution profiles of diltiazem (60mg) Immediate release tablets (n=6) with the crescent- shaped spindle {Cs} at 25rpm and the USP paddle spindle {Pd} at 75rpm.

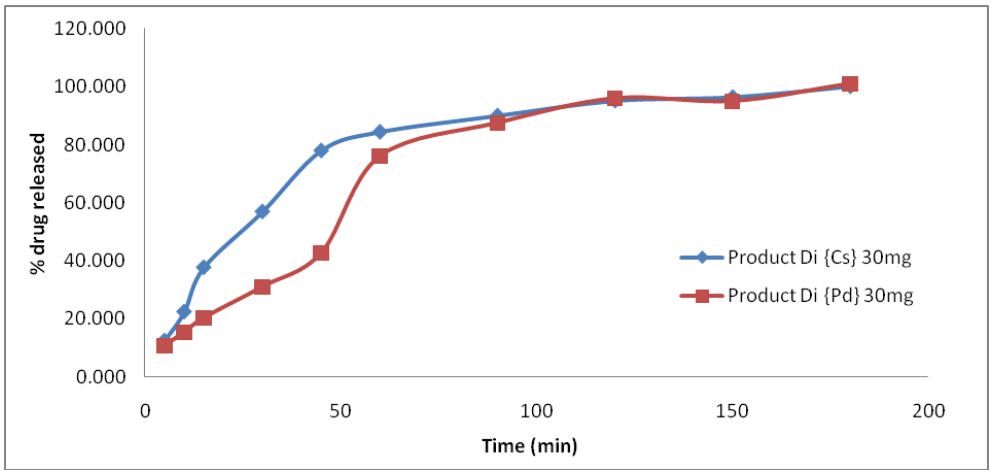

Fig. (2). Comparative dissolution profiles of diltiazem (30mg) Immediate release tablets (n=6) with the crescent- shaped spindle {Cs} at 25rpm and the USP paddle spindle {Pd} at 75rpm.

(120 mg) are shown in Figs. (**3**, **4**, and **5**), respectively. Table **3** shows the dissolution efficiency and similarity factor values for the dissolution profiles of product A_e, B_e, and C_e.

While product B_e (90 mg retard tablets) had similarity factor F_2 above 50 for the two spindles, product A_e and C_e were not similar (Data not shown in the table). It is worth to mention that product A_e and C_e released almost 85% of diltiazem at 3 hours of starting the dissolution test using either spindle. Product B_e was the only retard product which showed some sustained release pattern by released only 35% at 3 hours. Product A_e and C_e reached plateau at 6 hours while product B_e reached 72% at the same time.

Product A_e (90 mg Retard tablets) had a higher dissolution efficiency using the crescent shaped spindle compared to the official USP spindle. It reached the plateau concentration at 4 hours with the crescent shaped spindle compared to 6 hours using the official USP spindle.

The dissolution profile of product D_e (120 mg Retard tablets) in the crescent shaped spindle showed better dissolution (Table **4**) with DE values at 24 hours and 6 hours significantly higher than those obtained from the USP spindle. The DE values at 3 hours were not significantly different and their value was low compared with the DE value obtained at 6 hours which indicates that the extended release properties were maintained at that time. The two profiles were found similar with F_2 of (57.73).

Dissolution of diltiazem extended release capsules was different from that obtained from the tablets. The hard gelatin capsule contained the sustained release beads. Table **5** shows analysis of dissolution data for the two spindles. The 120 mg capsules showed bi-phasic dissolution characteristics with both spindles. The F_2 value showed that the two dissolution profiles were not similar. However, the DE values over whole time (24 hours) and at 6 hours showed that there was no statistically significant difference between the two

Table 1. Drug Release Profiles of Diltiazem (60mg) Immediate Release Tablets (n=6) with the Crescent- Shaped Spindle at 25rpm and the USP Paddle Spindle at 75rpm. DE: Dissolution Efficiency, t: Time in Minutes

Product A_i	Crescent-shaped	USP spindle	T-test	P-value	F_2 test
DE_{all} (S.D.)	24.3(2.03)	24.19(0.6)	0.1118	0.9132	64.14
DE_{t30} (S.D.)	1.2(1.2)	2.94(2.68)	1.4515	0.1773	
DE_{t60} (S.D.)	12.7(3.1)	8.55(2.51)	2.5485	0.0289	
DE_{t90} (S.D.)	62.8(4.0)	60(1.7)	1.5780	0.1456	
Product B_i					
DE_{all} (S.D.)	33.1(3.13)	21.3(1.3)	8.5282	0.0001	33.47
DE_{t30} (S.D.)	9.91(3.83)	7.4(1.1)	1.5429	0.1539	
DE_{t60} (S.D.)	14.96(5.96)	11(2.5)	1.5008	0.1643	
DE_{t90} (S.D.)	71.37(7.78)	60.8(1.6)	3.2597	0.0086	
Product C_i					
DE_{all} (S.D.)	28.25(1.26)	27(0.3)	2.3640	0.0397	38.27
DE_{t30} (S.D.)	5.18(1.25)	12.2(0.5)	12.7724	0.0001	
DE_{t60} (S.D.)	15.08(3.55)	15.7(1.1)	0.4086	0.6914	
DE_{t90} (S.D.)	67.84(3.01)	67.8(0.4)	0.0323	0.9749	

Table 2. Drug Release Profiles of Diltiazem (30mg) Immediate Release Tablets (n=6) with the Crescent- Shaped Spindle at 25rpm and the USP Paddle Spindle at 75rpm. DE: Dissolution Efficiency, t: Time in Minutes, S: Similarity Factor

Product D_i	Crescent-shaped	USP spindle	T-test	P-value	F2 test
DE_{all} (S.D.)	32.05(3.61)	24.36(1.92)	4.6068	0.0010	33.23
DE_{t30} (S.D.)	5.61(5.12)	7.94(2.6)	0.9939	0.3437	
DE_{t60} (S.D.)	12.17(4.9)	6.5(2.43)	2.5393	0.0294	
DE_{t90} (S.D.)	70.09(6.61)	56.38(2.44)	4.7662	0.0008	

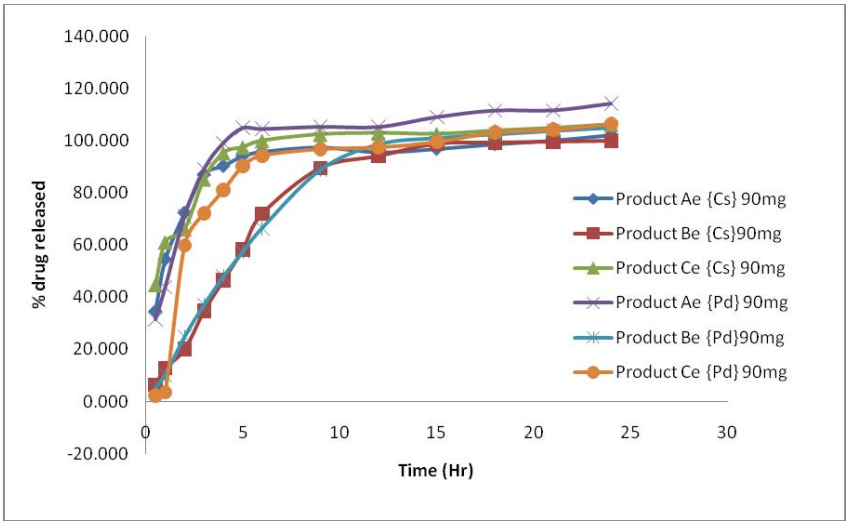

Fig. (3). Comparative dissolution profiles of diltiazem (120mg) Extended release tablets (n=6) with the crescent- shaped spindle {Cs} at 25rpm and the USP paddle spindle {Pd} at 100rpm.

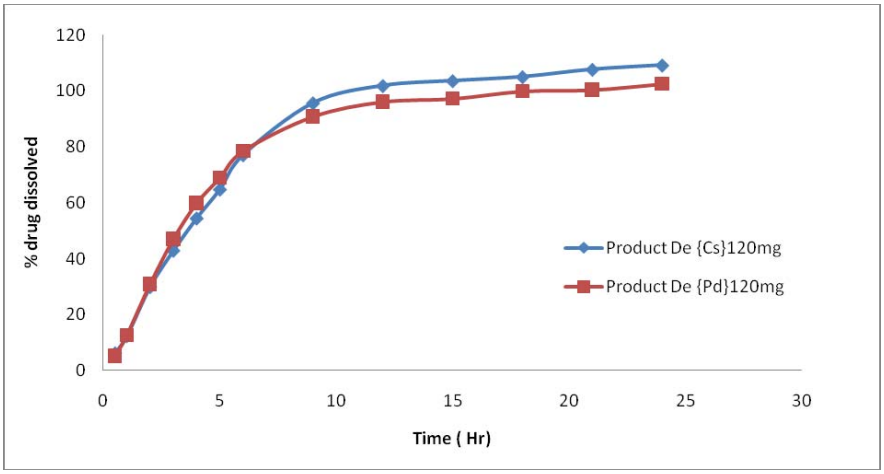

Fig. (4). Comparative dissolution profiles of diltiazem (120mg) extended release Capsules (n=6) with the crescent- shaped spindle {Cs} at 25rpm and the USP paddle spindle {Pd} at 100rpm.

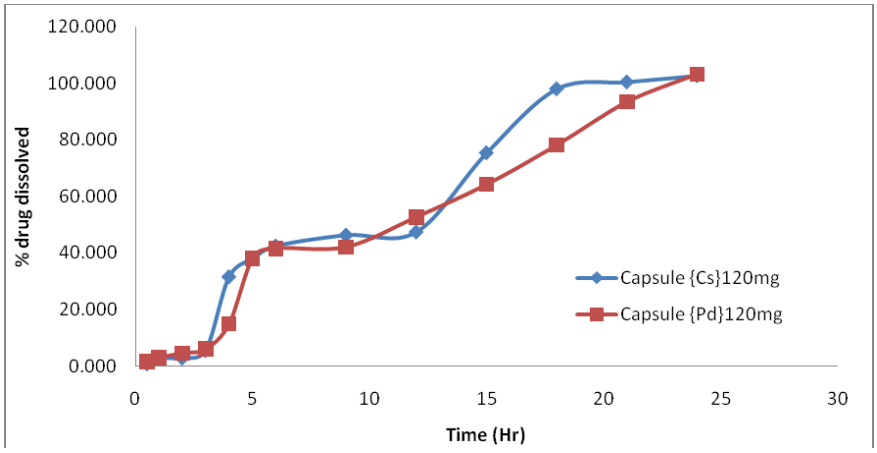

Fig. (5). Comparative dissolution profiles diltiazem (90mg) extended release tablets (n=6) with the crescent- shaped spindle {Cs} at 25rpm and the USP paddle spindle {Pd} at 100rpm.

Table 3. Drug Release Profiles of Diltiazem (90mg) Extended Release Tablets (n=6) with the Crescent- Shaped Spindle at 25rpm and the USP Paddle Spindle at 100 rpm. DE: Dissolution Efficiency, t: Time in Hours

Product A_e	Crescent-shaped	USP spindle	T-test	P-value	F2 test
DE_{all} (S.D.)	18.1(0.67)	17.09(0.38)	3.2119	0.0093	42.98
DE_{t3} (S.D.)	16.78(6.84)	12.75(2.25)	1.3709	0.2004	
DE_{t6} (S.D.)	78(1.68)	74.5(1.85)	3.4307	0.0064	
Product B_e					
DE_{all} (S.D.)	8.74(1.47)	8.58(0.45)	0.2549	0.8039	64.61
DE_{t3} (S.D.)	2.45(3.05)	3.09(1.0)	0.4884	0.6358	
DE_{t6} (S.D.)	48.95(2.44)	54.14(0.83)	4.9326	0.0006	
Product C_e					
DE_{all} (S.D.)	17.88(0.6)	14.46(0.68)	9.2376	0.0001	25.65
DE_{t3} (S.D.)	17.59(6.82)	3.58(0.68)	5.0070	0.0005	
DE_{t6} (S.D.)	76.13(2.28)	65.41(2.02)	8.6203	0.0001	

Table 4. Drug Release Profiles of Diltiazem (120mg) Extended Release Tablets (n=6) with the Crescent- Shaped Spindle at 25rpm and the USP Paddle Spindle at 100 rpm. DE: Dissolution Efficiency, t: Time in Hours

Product D_e	Crescent-shaped	USP spindle	T-test	P-value	F2 test
DE_{all} (S.D.)	10.68(0.96)	9.51(0.38)	2.7758	0.0196	57.73
DE_{t3} (S.D.)	3.58(0.68)	4.26(0.85)	1.5302	0.1570	
DE_{t6} (S.D.)	65.41(2.02)	53.85(0.79)	13.0550	0.0001	

Table 5. Drug Release Profiles of Diltiazem (120mg) Extended Release Capsules (n=6) with the Crescent- Shaped Spindle at 25rpm and the USP Paddle Spindle at 100 rpm. DE: Dissolution Efficiency, t: Time in Hours

Capsule	Crescent-shaped	USP spindle	T-test	P-value	F2 test
DE_{all} (S.D.)	4.14(0.65)	3.73(0.44)	1.2795	0.2296	45.48
DE_{t3} (S.D.)	2.47(7.95)	10.66(1.82)	2.4598	0.0337	
DE_{t6} (S.D.)	38.22(4.74)	35.43(3.82)	1.1226	0.2878	

profiles. The DE value at 3 hours indicated higher dissolution efficiency for official USP spindle compared to the crescent shaped spindle, however, 98% of diltiazem was released at 18 hours with the crescent shaped spindle compared to 93% at 21 hours in the USP spindle.

We found that dissolution profiles from the two spindles were sometimes similar at using the F_2 value but significantly different at certain time points using the DE values such as in the case of product A 120 mg tablets. The opposite may also occur in some cases, where the F_2 value indicated no similarity and the DE values showed no statistical significance like in the case of Product A 120 mg tablets.

It can be inferred that the F_2 value alone is not efficient to accurately describe and characterize the dissolution profiles of the products. This value reflects the percent dissolved of test and reference product but doesn't reflect the dispersion associated with each dissolution profile. For this reason we suggest to use the DE parameter instead of the F_2 value to describe the dissolution results.

The use of the crescent shape spindle demonstrated better product dissolution and better evaluation of the effect of formulation. The same product may behave differently and provide different dissolution profiles depending on the stirring mechanism and hydrodynamic environment within a dissolution vessel. Crescent-shaped spindle does not allow cone formation and assists in spreading the disintegrated materials. This results in increased surface area and thus better interaction of the solute with the medium providing higher dissolution rates as inferred from the DE_{all} value (complete dissolution time). It is important to note that, in current work, all DE_{all} values for the official USP spindle were equal or lower than the crescent shaped spindle which indicated less efficient product-medium interaction in the dissolution vessel.

Some concerns were expressed about the potential harsh effects of the crescent shaped spindle on the dissolution testing, describing these to be like the use of a Warring blender [19]. However, current work showed that the mechanical impact of the two spindles appeared to be similar. Because there was no instantaneous drug disintegration and release in any of the products, drug release appeared to be formulation/product dependent. Even for the IR tablet products, time for complete dissolution was three hours (as required in the USP monograph) [20]. In addition, ER products showed no evidence of crushing or harsh stirring. If there was any harsh condition in the dissolution apparatus, release time will be relatively faster and possibly abrupt rather than gradual. Contrary to that, our data indicated sustained release over 24 hours.

CONCLUSION

The comparison between the dissolution profiles of the same product using two spindles; the official USP spindle and the crescent shaped spindle showed that the release of the drug was different. Our studies also indicated that the crescent shape spindle may provide higher unit-to-unit variability than the USP Paddle spindle, thus better reflection of product characteristics and better unit-to-unit discrimination.

The similarity factor alone was not sufficient to describe the dissolution profiles or to discriminate between various ones. Calculations of dissolution efficiency at different time points helped of better understanding for the dissolution profiles and enabled comparison between them.

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