Research Article

Theme: Role of Dissolution in QbD and Drug Product Life Cycle

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Investigation of the Performance of the Disintegration Test for Dietary Supplements

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Abstract. The aim of this study was to investigate how beaker size, basket assembly, use of disk, and immersion medium impact the disintegration time of dietary supplements. The disintegration times were determined for five tablet and two capsule products. A two-station disintegration tester was used with Apparatus A or Apparatus B as described in the United States Pharmacopeia (USP) chapters, <701> and <2040>. Two beakers complying with the harmonized specifications were used, one with a volume of 1,000 mL and one with a 1,500-mL volume. The disintegration data were analyzed using ANOVA for the following factors: beaker size, equipment (App A and B) and condition (with/without disk). Two tablet products were not sensitive to any changes in the test conditions or equipment configurations. One product was only partially sensitive to the test conditions. The other products showed impact on the disintegration time for all test conditions. The results revealed that these tablet products might pass or fail current USP disintegration requirements depending on the equipment configuration. Similar results were obtained for the two investigated capsule formulations. One product might fail current USP disintegration requirements if the large beaker was used, but might pass the disintegration requirements when the small beaker was used. Hydroxy propyl methyl cellulose capsules were mostly influenced if sodium instead of a potassium buffer was used as the immersion medium. The results demonstrate that the current harmonized ICH specifications for the disintegration test are insufficient to make the disintegration test into reliable test for dietary supplements.

KEY WORDS: dietary supplements; disintegration; ICH; quality by design; USP.

INTRODUCTION

The disintegration test as a performance test for immediate release oral dosage forms is receiving more attention (1). This is due to dosage form specifications for which a dissolution test might not be the best fit, as shown by Han *et al.* for dosage forms like liquid-filled capsules (2) or fast-dissolving tablets (3,4).

Similarly, approaches like quality by design (QbD) might consider a disintegration test as the most appropriate performance test for fast dissolving biopharmaceutics classification system (BCS) class 1 drugs. In QbD, scientific approaches and appropriateness decide which compendial standard will be included into the overall quality and monitoring system of a product (1,5)

In QbD, a disintegration test might be justified to substitute a single-point dissolution test if the drug particle

size ensures a sufficient rate of dissolution and disintegration is the rate-limiting step for drug release (6). However, to be able to use the disintegration test as a performance test in QbD, its suitability as a performance test must be investigated. Today there is only very limited data available that describe the performance of the disintegration test.

USP (32) currently listed two chapters, which describe the disintegration test for dosage forms. Chapter <701> describes the general set-up with beaker specifications and basket assembly A (Apparatus A) (7). Chapter <2040> describes basket assembly B (Apparatus B) and test conditions and acceptance criteria for dietary supplements (8). Over the years the disintegration test specifications were changed. Donauer and Löbenberg reviewed these changes in detail (9). Both United States Pharmacopeia (USP) chapters list test conditions for different dosage forms, but there are some differences between the chapters. USP <701> uses water as the immersion medium for *hard gelatin capsules* while USP <2040> uses a pH 4.5-acetate buffer for *hard shell capsules*. The next difference between both chapters is that *soft gelatin capsules* are tested like uncoated tablets in USP <701> while <2040> uses a rupture test for *soft shell capsules*.

Non-gelatin shell capsules are gaining importance in the pharmaceutical and dietary supplement industry. Literature reports some evidence that non-gelatin capsules made out of

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hydroxy propyl methyl cellulose (HPMC) are sensitive to sodium and potassium ions used in dissolution media (9). However, no data exist in literature which describes the impact of such media on the disintegration test.

USP introduced a new test requirement: "At no time should the top of the basket-rack assembly become submerged" (7). This requirement makes the use of the wire cloth for capsules unnecessary. Since the basket assembly should not be submerged, it ensures that the dosage form will not float out the observation cylinder. The previous test condition only specified, "that at the highest point of the upward stroke the wire mesh remains at least 25 mm below the surface" (10). Schmid and Löbenberg investigated the impact of this change (11). The study concluded that the new test conditions impact the disintegration times and the fluid level requirements must be strictly followed to obtain reliable results.

USP chapter <701> was recently harmonized under the International Conference of Harmonization (ICH) Q4B Annex 5 (12). The harmonized guide only applies to dosage forms under 18 mm. Since USP <701> did not specify any dosage form size limitations it can be assumed that any dosage form, which physically fit into the observation cylinder of 20.7 to 23 mm, was tested in Apparatus A before the guideline was published (12). In the future, dosage forms larger than 18 mm might be tested in Apparatus B as already required by USP <2040>; Size number 1 capsules are very commonly used. Their size is just above 18 mm and according to USP <2040> they have to be tested in App B. However, if their disintegration time was established in Apparatus A, it is not known if they pass the disintegration test in App B. No data exist which describes the impact of the basket assembly on the disintegration time of oral dosage forms.

As mentioned before, USP <2040> gives universal acceptance criteria for dosage forms like tablets and capsules *e.g.*, disintegration time less than 30 min. However, it is not known if the disintegration time will be similar if a different basket assembly is used.

In the past the USP beaker specifications were more stringent *e.g.*, USP 24, 103–108 mm (10). Now the harmonized monograph specifies the beaker size from 97 to 115 mm (3,12). No data exist which demonstrate that these changes do not affect the performance of the disintegration test.

The aim of this study was to systematically investigate how beaker sizes, basket assembly, use of disks and the nature of the immersion medium impact the disintegration of different commercially available dietary supplement products.

METHODS

The study investigated the influence of beaker size, apparatus, use of disks (when appropriate), and the nature of the immersion medium on the disintegration time of tablets and capsules. The disintegration times were determined for seven commercial tablets and capsule products. *Boswellia serrata* (The Vitamin Shoppe, Lot# 082658, exp 09/11), Cinnamon (The Vitamin Shoppe, Lot# 2036475, exp

08/12), Ester-C (American Health, Lot# 234536-07, exp 08/10), Oysterical (Puritan's Pride, Lot# 415720-10, exp 03/12) and glucosamine Move Free (Schiff, Lot# S2438D4, exp 08/10) were the tablet formulations and Chasteberry (Solaray, Lot# 93409850807, exp 10/11), and Zinc (The Vitamin Shoppe, Lot# 083332, exp 07/11) were capsules products, which were investigated.

A disintegration tester (model ED-2 L, Electrolab, Betatek Ontario) consisted of two stations; each was used with Apparatus A USP chapter <701> or Apparatus B as described in USP chapter <2040>. The small beaker (SB) had a nominal volume of 1,000 mL with an inside diameter of 101 ± 1 mm and the large beaker (LB) had a nominal volume of 1,500 mL and an inside diameter of 114 ± 1 mm.

Four different equipment configurations and two beaker sizes resulting in eight test conditions were investigated: An SB and USP Apparatus A (App A) with disk, SB App A without disk, SB USP Apparatus B (App B) with disk, SB beaker apparatus App B without disk, LB App A with disk, LB App A without disk, LB App B with disk and LB App B without disk. The tests were performed with 18 test units and the media employed for this study was water for all tests.

All the equipment and beaker sizes investigated for tablets were also applied to Chasteberry capsules. In addition, this study included the evaluation of three different media: water, USP buffer pH4.5, and USP simulated gastric fluid (SGF) ($n=18$).

The Zinc capsules did not disintegrate within 90 min. Therefore, no investigation was performed without disks for this product. The disintegration time determinations were performed using SB App A, SB App B, LB App A and LB App B, all with disk. Due to the cellulose nature (HPMC) of their hard shell body, five different media were tested in this study: water, USP buffer pH4.5, USP SGF, USP simulated intestinal fluid (SIF) a potassium-phosphate-based buffer and buffer pH 6.8 using sodium-phosphate ($n=18$).

In all cases the disintegration time was recorded as an independent variable. Next, statistical analysis was performed using two different statistics programs: Minitab 15 (MINI-TAB Inc.) and SPSS 17 (Statistics Grad Pack). The mean and standard deviation was calculated for all tablets and capsules. The data were analyzed using the two-way ANOVA for the following factors: beaker size (small and big) and equipment (App A with disk, App A without disk, App B with disk, App B without disk). Any value exceeding the critical value of 0.05 indicates no statistical significance. For both tablets and capsules, the ANOVA analysis was repeated using only two factors (beaker size and apparatus). The aim was to investigate the impact of the apparatus and beaker size on the performance of the disintegration test. For capsules, a further ANOVA was performed for each equipment configuration using immersion media as a factor. For Zinc capsules, the impact of the beaker size and apparatus on the performance of the disintegration test was investigated using disks only because the capsules did not disintegrate without disks. Tukey's test was then applied to specify which media exactly caused a statistical impact. To be able to apply ANOVA the test data must meet certain assumptions: The sample populations must be normally or approximately normally

Table I. Disintegration Times (Means and Standard Deviations) for *Boswellia serrata*, Cinnamon, Ester-C, Oystercal and Glucosamine Tablets using SB and LB, App A and B and without Disk (1) and with Disk (2)

Tablet	Beaker	Apparatus	Condition	Mean±sd
Ester-C	SB	A	1	34.5±1.2
			2	24.6±0.5
		B	1	31.7±1.5
			2	19.6±1.1
	LB	A	1	36.0±5.4
			2	25.6±0.9
		B	1	37.6±1.0
			2	22.7±0.8
Oystercal	SB	A	1	6.6±0.7
			2	5.1±0.8
		B	1	5.9±0.8
			2	6.0±0.7
	LB	A	1	6.6±0.5
			2	5.0±0.9
		B	1	6.7±1.0
			2	6.1±0.5
Cinnamon extract	SB	A	1	50.1±2.0
			2	33.4±1.4
		B	1	51.6±2.6
			2	25.1±1.5
	LB	A	1	58.7±2.8
			2	36.0±1.3
		B	1	63.2±5.2
			2	31.6±2.0
<i>Boswellia serrata</i>	SB	A	1	7.5±3.4
			2	7.4±1.2
		B	1	8.3±2.7
			2	7.9±2.4
	LB	A	1	7.2±1.5
			2	7.4±1.0
		B	1	7.5±2.1
			2	7.5±1.3
Glucosamine	SB	A	1	25.8±1.6
			2	22.7±0.8
		B	1	24.1±1.0
			2	17.4±0.8
	LB	A	1	27.6±1.4
			2	24.4±0.9
		B	1	28.0±1.3
			2	20.2±2.6

distributed. Also, the samples must be independent. Moreover, the variances of the population must be equal; this criterion was checked using Leven's (any continuous distribution) and Bartlett test (normal distribution).

RESULTS

Tablets

Five tablet formulations were investigated: *Boswellia serrata*, Cinnamon, Ester-C, Oystercal, and glucosamine. Table I summarizes the mean disintegration times of all tablet products tested. The influence of the equipment configuration on the disintegration times was investigated using analysis of variance (ANOVA) and is summarized in Table II.

Boswellia serrata tablets showed that neither beaker size (LB or SB) nor the test conditions (with or without disk) were significant with regard to the disintegration times. Only the apparatus presented statistical significance ($p=0.030$, Table II). App A produced lower disintegration time means compared to App B (Table I). Similarly, the interactions among these factors were not significant too. The mean disintegration times for the eight different test conditions varied from 7.2 $\pm$ 1.5 to 8.3 $\pm$ 2.7 min (Table I). The test for equal variance (Levene's test, for any continuous distribution) showed no significant difference among the variances for the eight conditions studied ($p=0.170$, data not shown). Although the difference may not be considered significant using Levene's test, SB App B, with and without disks, had the highest standard deviations, 2.4 and 2.7 min, respectively (Table I).

The results for Ester-C tablets were quite different from those observed for *Boswellia serrata* tablets. The ANOVA for the Ester-C tablets showed significant differences among the conditions used. The factors (beaker size, apparatus, and disk) as well as their interaction significantly influenced the disintegration times ($p<0.01$) (Table II). The shortest disintegration time was obtained using the SB App B with disk, 19.6 $\pm$ 1.1 min (Table I). The remaining studies with disk showed disintegration times equal to 25.6, 22.7, and 24.5 min for LB App and B and SB App B, respectively. All studies performed without disk (SB or LB, App A and B) showed disintegration times above 31 min. The test for equal variance ($p=0.161$, Levene's test) revealed no significant difference among the variances although the test performed without disk using LB App A had the highest standard deviation,

Table II. *P* values Result from ANOVA for Disintegration Time under the Following Conditions: SB App A with and without Disk; SB App B with and without Disk; LB App A with and without Disk; LB App B with and without Disk for *Boswellia Serrata*, Ester-C, Oystercal, and Glucosamine

Source	<i>Boswellia serrata</i>	Ester-C	Oystercal	Glucosamine
Beaker	0.534	<0.001	0.241	<0.001
Beaker/disk	0.974	<0.001	0.167	0.185
Beaker/apparatus	0.180	<0.001	0.066	0.001
Disk	0.726	<0.001	<0.001	<0.001
Disk/apparatus	0.266	<0.001	<0.001	<0.001
Apparatus	0.030	<0.001	0.002	<0.001
Beaker/desk/apparatus	0.471	0.001	0.258	0.231

Table III. Disintegration Times (Means and Standard Deviations) for Zinc and Chasteberry Capsules using SB and LB, Apparatus A and B in Different Media

Capsule	Beaker	Apparatus	Medium	Mean±sd
Zinc capsules	SB	A	1	9.8±2.9
			2	8.3±5.0
			3	11.6±3.0
			4	17.5±6.0
			5	9.9±2.7
		B	1	3.6±0.8
			2	4.0±1.0
			3	4.5±1.3
			4	3.8±1.3
			5	4.4±1.0
	LB	A	1	10.0±2.9
			2	11.5±8.0
			3	14.0±4.9
			4	20.0±6.2
			5	13.3±4.5
		B	1	5.2±1.3
			2	6.2±2.3
			3	5.0±1.3
			4	7.6±2.3
			5	6.3±1.7
Chasteberry extract-vegicaps	SB	A	1	32.5±5.9
			2	23.6±6.0
			5	28.8±4.6
		A ¹	1	17.1±3.4
			2	14.7±1.6
			5	28.8±4.6
		B	1	29.9±5.3
			2	25.8±1.6
			5	37.6±8.7
		B ¹	1	5.8±1.0
			2	6.7±0.7
			5	6.5±1.0
	LB	A	1	40.2±7.3
			2	28.2±1.9
			5	36±4.6
		A ¹	1	19.1±3.3
			2	16.3±1.7
			5	20.5±4.7
		B	1	36.1±5.3
			2	33.2±3.7
			5	42.1±5.9
		B ¹	1	9.2±3.2
			2	9.4±1.0
			5	9.9±1.9

A Apparatus A without disks, B Apparatus B without disks, A¹ Apparatus A with disks, B¹ Apparatus B with disks, 1 water, 2 buffer pH 4.5; 3 USP simulated intestinal fluid pH 6.8 (potassium buffer); 4 pH 6.8 Buffer (Na-phosphate), 5 pH 1.2 (USP SGF); sd standard deviation

5.4 min (Table I). The means of the tests using disks varied from 19.6±1.1 to 25.6±0.9 min and without disks varied from 31.7±1.5 to 37.6±1.0 min clearly indicated that the use of disks decreased the disintegration times. The data showed that all selected conditions without disk would statistically result in disintegration times of more than 30 min and the product fails compendial acceptance criteria independent of which set-up might be used.

Similarly to the *Boswellia serrata* tablets, the ANOVA for Oysterical tablets indicated that the interaction between the disk, apparatus, and beaker were not statistically significant for the disintegration times (Table II). Neither were the influences of beaker, beaker–disk interactions nor beaker–apparatus interactions. The results clearly indicated that the conditions performed with App A and with disk presented the shortest disintegration times, 5.0±0.9 and 5.1±0.8 min for LB App A with disk and SB App A with disk, respectively. A second group showed the following intermediate disintegration times; 5.9±0.8, 6.0±0.7, 6.1±0.5 min for SB App B without disk, SB App B with disk, and LB App B with disk, respectively; and a third group that presented the highest disintegration times; 6.6±0.7, 6.6±0.5, and 6.7±1.0 min for SB App A without disk, LB App A without disk and LB App B without disk, respectively (Table I). The test for equal variances showed no significant differences among the conditions (Levene and Bartlett tests, data not shown).

The glucosamine tablets followed the same pattern as observed for the Ester-C tablets. The ANOVA showed that the disintegration times were significantly influenced by all conditions (with disk or without disk), the beaker size, by the apparatus and their interactions, except for the beaker and disk interaction as well as the beaker, disk and apparatus interaction showing $p=0.185$ and 0.231 , respectively (Table II). The disintegration times were highly influenced by the disk using the SB App B or LB App B. In these conditions the difference between the disintegration times reached approximately 7.0 min (17.4±0.8 and 24.1±1.0 for SB App B with and without disk, respectively) (Table I). The shortest disintegration time was 17.4±0.8 min observed for the SB App B with disk. Although the test for equal variance showed no significant differences among the standard deviations (Levene test), the highest standard deviation was observed for LB App B with disk (2.6 min).

For the Cinnamon tablets, the test for equal variances for the disintegration times in the different conditions revealed a significant difference for both tests employed: Levene (any continuous distribution) and Bartlett (normal distribution). Thus, there was a significant difference among the variances observed for all the tests. It was observed in three distinct groups of standard deviation for the tests. The first one, 1.4, 1.5 and 1.3 min for SB App A with disk, SB App B with disk and LB App A with disk, respectively; the second group, 2.0, 2.6, 2.8 and 2.0 min for SB App A without disk, SB App B without disk, LB App A without disk and LB App B with disk, respectively; and the highest mean and standard deviation observed was 63.2±5.2 min for LB App B without disk (Table I). Only one condition met the compendial requirement (below 30 min), SB App B with disk (25.1±1.5 min). This clearly showed that the current USP beaker specifications might cause a fail or pass of a batch due to the beaker used, but not necessarily due to a batch failure. As observed for Ester-C tablets, the tests performed with disk showed lower disintegration times compared to the tests without disk. Among the conditions with disk, the test for equal variance (data not shown) revealed no statistical difference for the standard deviations ($p=0.372$ and 0.320 for Levene and

Table IV. *P* Values of ANOVA for Disintegration Time under the Following Conditions: SB App A with and without Disk; SB App B with and without Disk; LB App A with and without Disk; LB App B with and without disk and Different Media (Water, USP Simulated Intestinal Fluid (Potassium Based): SIF, SIF-NaP=Sodium Based Buffer pH 6.8, Buffer pH=4.5 and SGF) for Chasteberry Capsules

Source	Chasteberry capsules
Apparatus	<0.001
Apparatus/beaker	0.376
Apparatus/disk	<0.001
Apparatus/medium	0.217
Beaker	<0.001
Beaker/disk	<0.001
Beaker/medium	<0.001
Disk	<0.001
Disk/medium	0.014
Medium	<0.001
Apparatus/beaker/disk	0.336
Beaker/disk/medium	<0.001
Apparatus/beaker/medium	0.001
Apparatus/beaker/disk/medium	0.006

Bartlett tests, respectively). The two-way ANOVA for these conditions (with disk) revealed that the disintegration time means that for SB App A, SB App B, LB App A and LB App B were statistically different, highly influenced by the beaker size (SB or LB) and the type of apparatus (A or B) ($p < 0.001$ for the factors and their interaction).

Capsules

For capsules, the disintegration times were determined for two products: Chasteberry and Zinc capsules. The mean data are summarized in Table III.

For the Chasteberry capsules, the disintegration times were evaluated using the same eight conditions as for the tablets. In addition, the impact of the different media was evaluated. The Zinc capsules had a hard shell made from HPMC and therefore, the impact of sodium buffers in comparison to potassium buffers was evaluated.

The disintegration time for the Chasteberry capsules was highly influenced by the type of apparatus, the beaker size, the type of the medium, the use of a disk (with or without) and by the interaction of all these factors, except for the apparatus–beaker, apparatus–medium and the apparatus–beaker–disk interactions with $p = 0.376$, 0.217 and 0.336 , respectively (Table IV). The shortest disintegration times were observed for SB App B with disk, 5.8 ± 1.0 , 6.7 ± 0.7 , and 6.5 ± 1.0 min for water, pH=4.5 and SGF, respectively. For the tests using LB App B with disk, the disintegration times were 9.2 ± 3.2 , 9.4 ± 1.0 and 9.9 ± 1.9 , for water, pH=4.5 and SGF, respectively (Table III). Clearly, the tests performed using disks showed the lowest disintegration times. Among the conditions with a disk, the test for equal variance showed no statistical difference for the standard deviations ($p = 0.058$ for Levene tests), the lowest standard deviations were for those tests performed using disks.

The Zinc capsules behaved differently compared to the Chasteberry capsules. This product disintegrated under any chosen condition under 30 min. The shortest disintegration

time was observed for SB App B (4.0 ± 1.0 min) (Table III). This apparatus also produced very similar results for all media tested, 4.0 ± 1.0 , 4.5 ± 1.3 , 4.4 ± 1.0 , 3.8 ± 1.3 , 3.6 ± 0.8 min for buffer pH 4.5, SIF, SGF, pH 6.8 Na-phosphate buffer and water, respectively. The test for equal variance showed no statistical difference for the standard deviations ($p = 0.387$ and 0.305 for Bartlett and Levene tests, respectively) among the tests performed with the media for SB App B. The One-way ANOVA showed that the media was not significant for the disintegration times obtained ($p = 0.053$). Tukey's comparison (individual confidence level=99.34%, data not shown) revealed that the disintegration times for all media are not statistically different when the condition SB App B was used.

CONCLUSION

The study showed that some tablet products were sensitive to the chosen test conditions and other tablets (*Boswellia serrata* and Oystercal) were not. This is somewhat surprising since Kamba *et al.* showed that the use of disks adds destructive forces to the disintegration test (13). A third product (glucosamine tablets) only showed a partial impact of the beaker size and the equipment used on the disintegration time when no disks were used. The other tablets (Cinnamon and Ester-C) showed a clear impact on the disintegration time when disks were used. The results showed that these tablet products might pass or fail current USP disintegration requirements depending on which equipment configuration was chosen.

Similar results were obtained for the two capsule formulations investigated. The results showed that the equipment configuration and immersion medium used could have a significant impact on the disintegration times of these products. Chasteberry capsules failed to pass current USP disintegration requirements if the LB was used, but passed the disintegration requirements when the SB was used. The Zinc capsules, which had a cellulose-based shell, were mostly influenced in their disintegration times if sodium instead of a potassium buffer was used as the immersion medium. A similar observation was reported for the dissolution behavior of capsule products with HPMC (9).

The study clearly shows that the current beaker specifications are insufficient for the disintegration test of dietary supplements. The USP expert committee for performance testing of dietary supplements has used the findings of this study to change the beaker specification in USP chapter <2040>. The changes were published in (7) PF 35(2) (July–Aug 2009) and will become official in USP 33 2S. Furthermore, the results demonstrate that the current harmonized ICH specifications for the disintegration test are insufficient to make the disintegration test into a reliable performance test for dietary supplements. The impact of the current specifications on drug products needs to be investigated especially if the disintegration test is intended as a performance test in a QbD approach for pharmaceutical dosage forms.

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