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Comparison of the Rupture and Disintegration Tests for Soft-Shell Capsules

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ABSTRACT

The *USP* General Chapter <2040> Disintegration and Dissolution of Dietary Supplements introduced a rupture test as a performance test of soft-shell capsules. Traditionally, the disintegration test was used for determining the disintegration time of all solid oral dosage forms. The aim of this investigation was to investigate differences between the rupture test and the disintegration test using soft-shell capsules.

Five different soft-shell capsule products were chosen based on their filling contents and treated to simulate a production deficiency. The study design compared capsules as received with capsules that were treated by coating them with the liquid contents of another capsule. The capsules were incubated at room temperature and at 40 °C. The tests were repeated after two weeks, and at each time point, twelve capsules of each product were tested using the rupture and the disintegration tests. Six capsules were tested untreated, while the other six capsules were treated. Rupture and disintegration times were recorded as dependent variables in each experiment. The data were analyzed using ANOVA.

According to the *USP* definition for disintegration, the rupture of a soft-shell capsule can be seen as fulfilling the disintegration criterion if the capsule contents is a semisolid or liquid. Statistical analysis showed no advantage of the rupture test over the disintegration test. On a product-by-product basis, both tests were sensitive to certain investigated parameters. A noticeable difference between both tests was that in most cases, the rupture test reached the defined endpoint faster than the disintegration test.

Soft-shell capsules that are subject to a Quality by Design approach should be tested with both methods to determine which performance test is the most appropriate test for a specific product.

INTRODUCTION

Quality by Design (QbD) is a scientific approach that uses statistical methods for product design, quality testing (*1*), and predicting product performance from early product development to final product release (*2*). QbD is highly dependent on the appropriateness of test methods used and can only be successfully applied if a test is sensitive to the parameter that is tested.

The performance testing of soft-shell capsules is rather a challenge because the contents of soft-shell capsules can vary from solids to liquids (*3*). Dissolution methods used for solid oral dosage forms might not be appropriate for soft-shell capsules that have liquid or semisolid contents (*4*).

USP General Chapter <701> Disintegration describes the procedure to evaluate disintegration of oral dosage forms (*5*). The requirements of disintegration are met if all test units disintegrate or if not more than two units out of a total of 18 units fail to disintegrate within a predetermined time period.

USP General Chapter <2040> Disintegration and Dissolution of Dietary Supplements uses a rupture test as performance test of soft-shell capsules (*6*). In 2002 the rupture test was first published in *Pharmacopeial Previews* (*7*), then forwarded to USP's *In-Process Revision* (*8*), and in 2007 it was finally published in *USP 30–NF 25*. *USP 32* lists 14 monographs that use the rupture test performed in dissolution Apparatus 2 (paddle) operated at 50 rpm with 500 mL of water as the immersion medium. The test requirements are met if all capsules rupture within 15 min or if not more than 2 of the total of 18 capsules tested rupture in more than 15 but not more than 30 min. For any other oral dietary supplement dosage form, disintegration test Apparatus A or B is used if the monograph requires disintegration.

Another difference is that for hard-shell capsules, Chapter <2040> lists USP pH 4.5 buffer as the immersion medium while Chapter <701> lists water as the default medium if a monograph does not specify any other medium (Figure 1) (*9*). *USP* Chapter <2040> also lists Apparatus B, which is intended for dosage forms greater than 18 mm in diameter. Currently there are no scientific data available that compare the performance of the rupture test with that of the disintegration test. The aim of this study was to evaluate if there are advantages in using the rupture test over the disintegration test. A series of experiments was performed and statistical analysis was used to determine differences between the tests.

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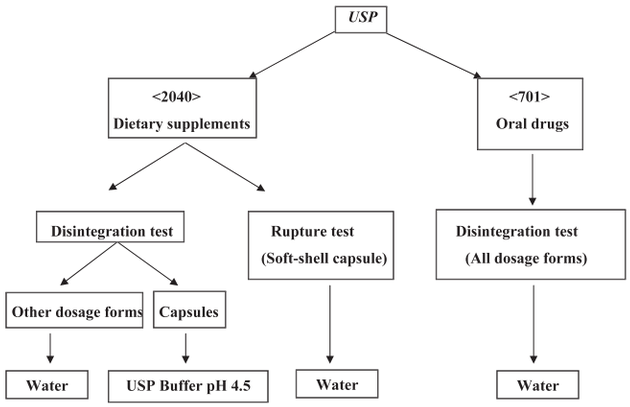

Figure 1. Schematic comparison of USP Chapters <2040> and <701>.

METHOD

Five different soft-shell capsules were received from Banner Pharmacaps: amantadine HCl (lot No. 27060261XP), flaxseed oil (lot No. 203491-01), ginseng 100 mg (lot No.203491-01), pseudoephedrine HCl (lot No.XPP0410004B), and soybean oil (lot No. XPM0309004). These capsules were chosen based on their filling contents. Flaxseed oil, ginseng, and soybean oil are filled with an oil base, and pseudoephedrine capsules are filled with a water-miscible solution. Amantadine capsules contain a suspension.

The study design compared the products as received with capsules that were treated by coating them with the liquid contents of another capsule to simulate a production deficiency. This was done by pouring the liquid contents of one capsule over the remaining capsules in a 120-mL plastic bottle. The bottle was tumbled at 50 rpm for 30 min. Then the bottle was stored until the next experiment was performed according to the testing schedule.

The capsules were incubated at room temperature and 40 °C, and the tests were repeated after two weeks. At each time point, twelve capsules of each product were tested using the rupture and the disintegration tests. A disintegration tester (model ED-2L, Electrolab, Betatek Ontario) consisted of two stations; each was equipped with a basket assembly as described in *USP* Chapter <701>. The beaker had a nominal volume of 1,000 mLwith an inside diameter of 101 ± 1 mm (SOTAX) and was filled with about 750 mL of immersion medium to comply with the USP requirement not to submerge the basket assembly totally at any time point. All tests were performed without disks. The rupture test was performed in 500 mL of water at 37 °C and 50 rpm using USP dissolution Apparatus 2 Model 7020 (Varian, Inc.). Six capsules were tested untreated, while the other six capsules were from the treated batch. This was done to compare the sensitivity of the rupture and disintegration tests for detecting possible production errors during the manufacturing process. The uncoated capsules represent a correct batch, while the coated capsules represent a batch with a production deficiency. The rupture time for each unit was recorded when visible leakage of the contents was shown. The criterion of the disintegration test was that the contents must be released from the capsule shells, and then the disintegration time was recorded. In each experiment, the time was recorded as a dependent variable.

The analysis of variance (ANOVA) was performed to compare the rupture and disintegration mean times for each capsule and storage condition ($p = 0.05$) using Minitab® 15 software.

RESULTS

The mean and standard deviations from all conditions and capsules are shown in Table 1. The variability for the rupture and disintegration times for all capsules and test conditions are presented in Figure 2. The analysis of variance (ANOVA) was performed to compare the recorded mean times for the disintegration and rupture tests for all capsules and conditions. The *p*-values are indicated in Table 2.

Amantadine Soft-Shell Capsules

Amantadine capsules showed the highest variability among all capsule products for the rupture test (Figure 2a). For this product, the shortest recorded disintegration and rupture times were 9.3 ± 1.0 and 8.3 ± 0.9 min, respectively.

Differences between the uncoated and coated conditions ($p = 0.00$, $\alpha = 0.05$) were detected with the disintegration test (Table 2). However, the analysis of variance did not reveal any statistical differences in the mean times among the storage conditions using both tests (*p*-values of 0.57 and 0.89, $\alpha = 0.05$) (Table 2). Additionally, it was revealed that the rupture test was not faster than the disintegration test, but both test durations were similar (Table 1).

Flaxseed Oil Soft-Shell Capsules

Figure 2b reveals significant differences between the disintegration and the rupture test times for flaxseed oil capsules. The shortest test times were 7.7 ± 0.5 and 0.8 ± 0.4 min for the disintegration and the rupture tests, respectively (Table 1). The analysis of variance for the rupture test shows that the mean times for uncoated/coated and the storage conditions are statistically different ($p = 0.00$, $\alpha = 0.05$) (Table 2).

For the disintegration test, no statistical differences were observed for the uncoated/coated and the storage condition mean times (*p*-values of 0.86 and 0.27, respectively, $\alpha = 0.05$) (Table 2). For this product, the rupture test was able to differentiate the tested conditions, but no meaningful tendencies were observed between them. Furthermore, the rupture test was faster than the disintegration test.

Ginseng Soft-Shell Capsules

Figure 2c shows the mean and the standard deviation of ginseng capsules for the disintegration and the rupture tests. The shortest disintegration and rupture times were 8.2 ± 0.8 min (coated capsules after 2 weeks at room temperature) and 3.4 ± 1.8 min (uncoated capsules after 2 weeks at 40 °C), respectively (Table 1). For the rupture test, analysis of variance shows no statistically significant differences in the recorded mean times among the storage conditions ($p = 0.38$, $\alpha = 0.05$) or the coated and uncoated conditions ($p = 0.34$, $\alpha = 0.05$) (Table 2). However, the analysis reveals that the interaction between these factors (storage and uncoated/coated conditions mean times) was statistically significant ($p = 0.00$, $\alpha = 0.05$) (Table 2). For

Table 1. Disintegration and Rupture Times (min) for Amantadine, Flaxseed Oil, Ginseng, Pseudoephedrine, and Soybean Oil Capsules under Different Storage Conditions

			Storage Condition		
Capsule	**Test**	**Condition**	**RT**	**RT after 2 weeks**	**40 °C after 2 weeks**
Amantadine	Disintegration	coated	9.7 ± 0.3	10.0 ± 0.3	10.3 ± 0.15
		uncoated	9.3 ± 1.0	9.9 ± 0.3	9.4 ± 0.3
	Rupture	coated	9.5 ± 2.4	10.9 ± 0.4	8.9 ± 1.9
		uncoated	9.7 ± 1.3	8.3 ± 0.9	9.8 ± 1.8
Flaxseed Oil	Disintegration	coated	8.2 ± 0.7	7.7 ± 0.5	8.3 ± 0.2
		uncoated	8.3 ± 0.9	8.1 ± 0.3	7.9 ± 0.5
	Rupture	coated	2.2 ± 0.2	0.8 ± 0.4	3.1 ± 0.3
		uncoated	2.5 ± 0.4	2.9 ± 0.4	1.9 ± 0.4
Ginseng	Disintegration	coated	12.1 ± 0.5	8.2 ± 0.8	13.5 ± 1.3
		uncoated	11.0 ± 0.6	8.9 ± 0.7	10.9 ± 2.9
	Rupture	coated	4.7 ± 1.5	3.9 ± 1.2	5.8 ± 1.3
		uncoated	3.8 ± 0.6	5.9 ± 1.1	3.4 ± 1.8
Pseudoephedrine	Disintegration	coated	6.9 ± 1.1	7.2 ± 0.7	6.8 ± 0.6
		uncoated	6.1 ± 0.3	7.0 ± 0.7	5.9 ± 0.6
	Rupture	coated	5.6 ± 0.7	3.4 ± 0.6	2.6 ± 0.3
		uncoated	4.1 ± 0.7	3.5 ± 0.8	1.9 ± 0.5
Soybean Oil	Disintegration	coated	13.0 ± 0.7	9.0 ± 0.7	9.2 ± 0.8
		uncoated	8.8 ± 1.4	8.6 ± 0.3	7.6 ± 0.6
	Rupture	coated	1.5 ± 1.1	3.5 ± 1.9	3.1 ± 1.6
		uncoated	0.9 ± 0.2	1.6 ± 0.9	1.9 ± 0.9

RT: room temperature.

the disintegration test, the storage and the uncoated/coated conditions presented significant differences ($p = 0.00$, $\alpha = 0.05$). Despite its higher mean times, the disintegration test seems to have better discriminating properties.

Pseudoephedrine HCl Soft-Shell Capsules

Figure 2d shows the mean and standard deviations for pseudoephedrine capsules. The shortest disintegration and rupture times were 5.9 ± 0.6 and 1.9 ± 0.5 min, respectively, both for capsules stored at 40 °C for two weeks (Table 1). The rupture and the disintegration tests showed no significant statistical differences for the uncoated/coated mean time conditions (p-values of 0.89 and 0.36 for the rupture and disintegration tests, respectively, $\alpha = 0.05$). However, both tests presented significant differences for the storage conditions ($p = 0.00$, $\alpha = 0.05$) (Table 2). From the statistical analysis, the disintegration and the rupture tests seem to have similar discriminating properties. However, the rupture test was faster (Table 1).

Soybean Oil Soft-Shell Capsules

Figure 2e shows that the disintegration and rupture times (mean and standard deviation) for soybean oil capsules were clearly different. The shortest disintegration and rupture times were 7.6 ± 0.6 and 0.9 ± 0.2 min, respectively (Table 1). However, both tests presented statistically significant differences for the uncoated/coated mean time conditions ($p = 0.00$, $\alpha = 0.05$). The disintegration test was also able to differentiate the storage conditions ($p = 0.00$) (Table 2). Thus, for this product, the rupture test had the shortest test duration, but the disintegration test was able to reveal the differences among the storage and the uncoated/coated conditions.

DISCUSSION

The introduction of the rupture test in the *USP* as a performance test for dietary supplement soft-shell capsules triggers the question of what are the advantages of this test over the disintegration test. In the future, can the rupture test, if advantageous, also replace the disintegration test for pharmaceuticals?

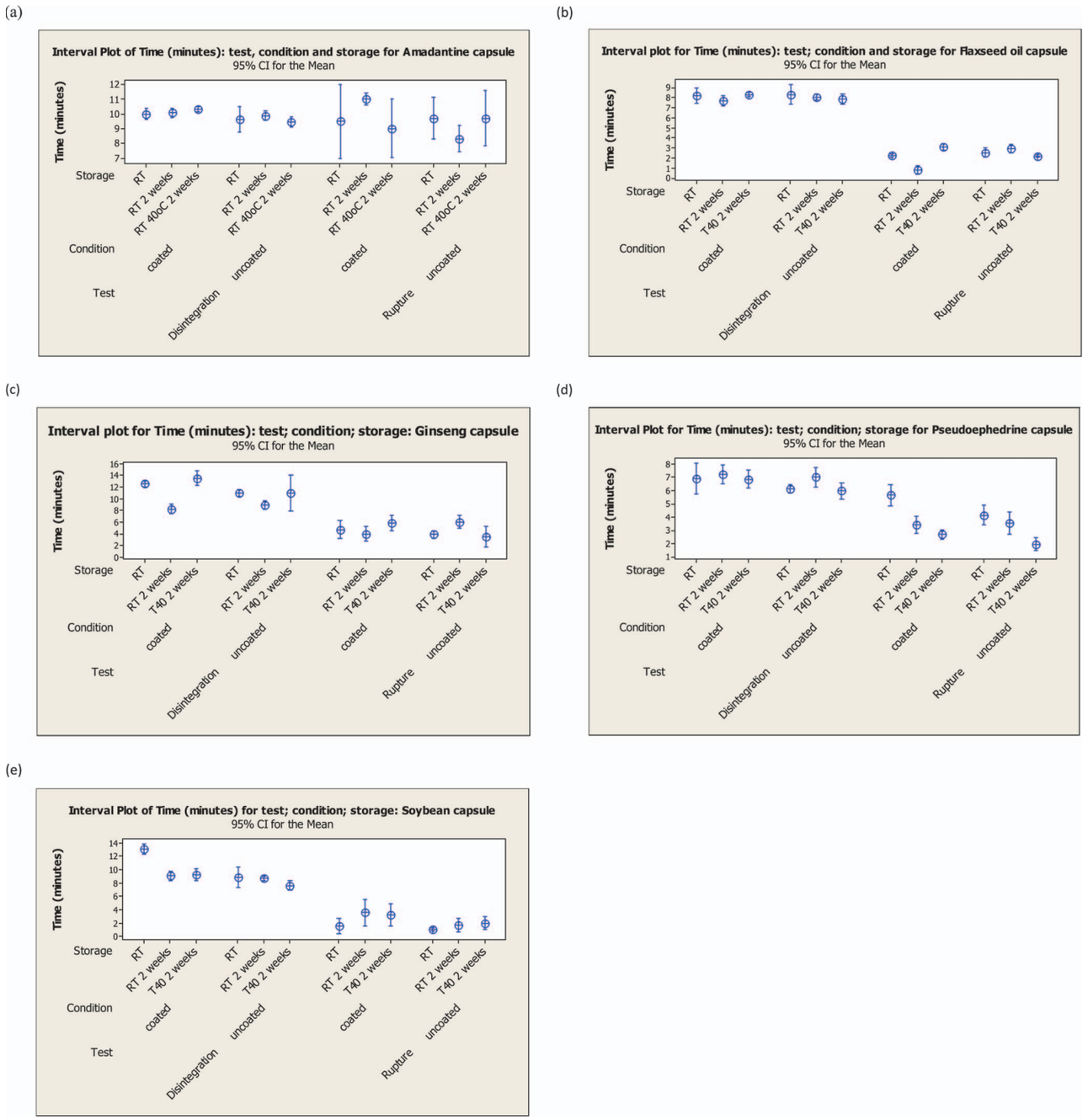

Figure 2. Interval plot of the disintegration and the rupture times (min) for coated and uncoated capsules of (a) amantadine, (b) flaxseed oil, (c) ginseng, (d) pseudoephedrine, and (e) and soybean oil under different storage conditions: RT (room temperature), RT after 2 weeks, and 40 °C after 2 weeks.

The present work is the first study to address this question scientifically. Disintegration is defined by *USP* as "that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus or adhering to the lower surface of the disk, if used, is a soft mass having no palpably firm core" (*5*). According to this definition, the rupture of a soft-shell capsule fulfills the endpoint criterion of the disintegration test if the capsule contents are semi-solid or liquid. For these products, the endpoint is the same for the rupture test and the disintegration test (*5*, *6*). However, in practice we observed that it was much easier to detect capsule rupture in a dissolution apparatus than capsule disintegration in the disintegration tester because of the basket assembly and its constant up and down movements. Therefore, this study defined the disintegration endpoint as the time needed to release the entire capsule contents from the shells. This endpoint could be visually determined by observing the empty shells on the

Table 2. P-values from Analysis of Variance for All Products Versus the Storage (RT, RT after 2 Weeks, 40 °C after 2 Weeks) and the Uncoated/Coated Conditions

	Disintegration			Rupture		
	Storage	**Uncoated/Coated**	**Interaction**	**Storage**	**Uncoated/Coated**	**Interaction**
Soybean Oil	0.00	0.00	0.00	0.86	0.00	0.45
Ginseng	0.00	0.02	0.02	0.38	0.34	0.00
Amantadine	0.57	0.00	0.15	0.89	0.27	0.03
Flaxseed Oil	0.27	0.86	0.20	0.00	0.00	0.00
Pseudoephedrine	0.00	0.36	0.04	0.00	0.87	0.04

RT: room temperature; $p < 0.05$ (significant, $\alpha = 0.05$).

screen, whereas the moment of the shell opening was not easily observed. Therefore, the rupture test was faster than the disintegration test, except for amantadine capsules.

As shown, the standard deviations of the rupture test were sometimes higher than the standard deviations of the disintegration test and vice versa. Moreover, although we hypothesized that the rupture test may show better performance as a quality control tool for soft-shell capsules as compared with the disintegration test, from a broad statistical perspective, none of the tests showed an advantage over the others. The rupture and disintegration apparatus were only sensitive to some test conditions depending on the individual product. The disintegration or rupture of a soft-shell capsule is controlled by its shell (*3*). Therefore, product-specific factors such as shell composition, gelatin age, and fill contents will impact the performance of a soft-shell capsule. The study shows that both tests were suitable as universal performance tests for soft-shell capsules (*10*). However, the ability of both performance tests to detect differences was product-specific.

CONCLUSIONS

Statistical analysis comparing the rupture and the disintegration tests proved that both tests are comparable and equally sensitive in detecting simulated production deficiencies or storage conditions of soft-shell capsules. The only statistically significant difference between the rupture and disintegration tests was the time needed to reach the defined endpoint. The rupture test needed less time than the disintegration test. However, because its endpoint determination depends on an observation, it might not be easily automated. The study showed the case-by-case sensitivity of both performance tests for discriminating between test conditions. Products that are developed in a Quality by Design approach should be investigated by both test methods to determine which performance test is more sensitive to the specific product characteristics.

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