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Investigation of Dissolution Performance of Hard Gelatin Capsule Products Using Various Sinkers

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ABSTRACT

Dissolution testing is a commonly used tool for the quality control of various dosage forms. For this purpose, consistent test conditions are necessary to obtain reproducible test results. Typical issues that can affect the dissolution performance of tested capsule formulations are floating and coning. Recently, the International Conference on Harmonisation (ICH) guideline recommended the use of sinkers to prevent coning, although no accompanying data to support the recommendation has been published in the open literature to date. Therefore, we initiated studies designed to address the following key questions. A) Do all sinkers prevent flotation of the dosage form? B) Does using sinkers consistently increase the dissolution rate? C) Do sinkers consistently decrease coning? Three commercially available hard capsule drug products were studied: acetaminophen, fluconazole, and ketoprofen. Dissolution was performed without a sinker and with four commercially available sinkers (CLIPS, CAPLOTH, CAPWAST, and JP). Analysis of the results revealed that, although three of the four sinkers were able to adequately address flotation problems, in many cases their use led to artifactual increases or decreases in the dissolution of the capsules. Further, sinkers do not seem to be generally useful for addressing coning issues. Instead, an increase in the stirring speed or use of peak vessels should be considered.

KEYWORDS: Sinker, dissolution, hard capsules, coning, floating

INTRODUCTION

Dissolution testing is an important and commonly used tool for formulation optimization and quality control in pharmaceutical development and manufacturing, as it provides an indication of how well a dosage form will dissolve in the patient and thus be available for absorption in the small intestine (*1–3*). Dissolution can be affected in various ways. Changes in the formulation of the dosage form or process parameters during manufacturing can affect the dissolution performance as well as operational parameters like vibration, hydrodynamics, and position of the dosage form inside the vessel (*1–9*). In consideration of these effects, consistent test conditions are crucial to obtaining reproducible test results for the dissolution of the drug.

When United States Pharmacopoeia (USP) dissolution apparatus type 2 (paddle apparatus) is used for the testing of capsules, a problem that often occurs is floating of the dosage form. Floating leads to irregular and additional movement of the dosage form. The surface area exposed to the dissolution medium is decreased by floating as well. Further, the hydrodynamics of the dissolution medium around the dosage form depend on the position of the dosage form inside the vessel (*1, 5, 6, 8*). All these factors combine to produce different mass transfer rates, leading to variability in the dissolution data (*2, 8*). To overcome these issues, sinkers were introduced in the USP in 1978 together with the paddle apparatus and were harmonized with the Japanese and European Pharmacopoeias in 2013 (*9*). Over time, three different sinker types stood out: a) longitudinal sinkers that contact the capsule on the long axis; b) lateral, helical-shaped sinkers that entwine the capsule and come in contact with it at the top and the bottom, and c) screen enclosures, normally in the form of a wire cage that surrounds the whole capsule and corresponds to the description of sinkers in the *Japanese Pharmacopoeia* (*10*). Nowadays, all three types of sinkers are commercially available. Previous studies on sinkers have shown that the geometry of different sinker shapes can affect dissolution rates. Soltero et al. and Wu et al. showed that dissolution can be inhibited by the capsule content becoming trapped inside the loops or parallel spirals of the helical-shaped lateral sinkers due to collapsed parts of the softened gelatine capsule shell. Both groups concluded that lateral sinkers appeared to be the

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poorest choice, as they restricted the flow of dissolution media around the capsule, contributing to slower and more variable dissolution results (*11, 12*). By contrast, it was argued that longitudinal-shaped sinkers were the best choice, as they allowed faster, more complete, and less variable dissolution results than the lateral sinkers and caused less hindrance to the hydrodynamics than the lateral sinkers (*11, 12*). Wu et al. also pointed out that three-armed longitudinal sinkers typically do not have a high enough density to sink, especially for capsules with a low fill weight, and therefore overcome floating issues (*12*).

Recently, the International Conference on Harmonisation (ICH) M9 guideline recommended the use of sinkers to prevent coning, although no accompanying data to support the recommendation has been published to date in the open literature (*13*). Due to the paucity of data in the open literature on the ability of sinkers to overcome both coning and flotation problems, we initiated studies designed to address the following key questions:

A. *Do all sinkers prevent flotation of the dosage form?*

B. *Does using sinkers consistently increase the dissolution rate?*

C. *Do sinkers consistently decrease coning?*

For this purpose, three commercially available hard capsule drug products were studied, and dissolution was performed without sinker and with four commercially available sinkers of various types.

MATERIALS AND METHODS

Materials

Immediate release (IR) dosage forms of acetaminophen (Ben-u-ron 500 mg, 20 hard capsules, batches 705A181 and 702B171, bene Arzneimittel GmbH, München, Germany), fluconazole (Fluconazol 100 100 mg, 100 hard capsules batch HC8843, 1A Pharma GmbH, Oberhaching, Germany), and ketoprofen (Gabrilen N 50 mg, 100 hard capsules batch 180901, mibe GmbH Arzneimittel, Brehna, Germany) were used in the studies. The analytical standards of acetaminophen and fluconazole were purchased from Sigma Aldrich (Steinheim, Germany), and the ketoprofen standard was purchased from Alfa Aesar (Thermofischer GmbH, Kandel, Germany). Methanol, phosphoric acid (80%), and hydrochloric acid (HCl) (33%) were obtained commercially from VWR chemicals (Darmstadt, Germany). Disodium hydrogen phosphate and sodium dihydrogen phosphate were purchased from Merck KGaA (Darmstadt, Germany). The dosage forms are described in more detail in the Appendix (Supplemental Table 1).

Four different types of sinkers were purchased from Cole-Parmer-Kinesis (Cambridgeshire, UK) for the studies. Similar to the classification by Soltero et al., the sinkers were divided in four types (*11*).

1. A three-armed longitudinal sinker made from plastic (polypropylene, density: 0.92 g/mL) that contacts the capsule on the long axis (CAPLOTH-VK, "CLIPS").

2. A helical sinker made from stainless steel (density: 8 g/mL) that entwines the capsule and comes in contact with it at the top and the bottom (CAPLOTH-2S, "CAPLOTH").

3. A longitudinal and helical sinker made from stainless steel (density: 8 g/mL) that wraps around and contacts the capsule along the long axis (CAPWAST-23, "CAPWAST").

4. A wire basket sinker made from stainless steel (density: 8 g/mL) that surrounds the whole capsule and corresponds to the description of sinkers in the general dissolution monograph of the Japanese Pharmacopoeia (*10*) (CUSBSK-JP, "JP"JP).

The four sinker types are illustrated in Fig. 1A-1D, respectively, and further described in the Appendix (Supplemental Table 2).

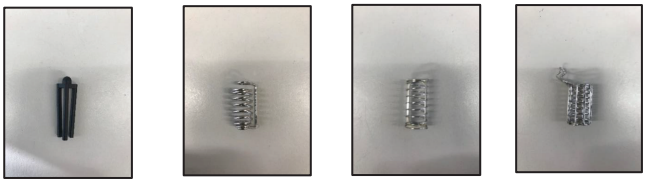

Fig.1. Photographs of the four sinkers studied, from left to right: CLIPS, CAPLOTH, CAPWAST, and JP. The CAPLOTH and CAPWAST sinkers correspond to the general description of a sinker according to the USP.

Dissolution Tests

The key dissolution and high-performance liquid chromatography (HPLC) parameters are shown in Table 1. For acetaminophen capsules, the conditions in the USP monograph were applied (*14*). The medium in this monograph is 900 mL deionized water, which was degassed and filtered immediately prior to running the dissolution test. The temperature of the medium was maintained at 37 ± 0.5 °C throughout the test. The dissolution tests were conducted in a calibrated USP

apparatus 2 (paddle) (DT 80, ERWEKA GmbH, Germany). Rotation speeds of 50, 75, and 100 rpm were applied. Samples were withdrawn at 5, 10, 15, 20, 30, and 45 min. The samples were filtered through a 0.45-µm polytetrafluoroethylene (PTFE) Filter (VWR, Leuven, Belgium), immediately diluted with mobile phase (1:10) and analyzed by HPLC. All studies were run with $n = 5$.

Table 1. Dissolution and Samples Analysis Parameters

	Acetaminophen	Fluconazole	Ketoprofen
Dissolution medium	Degassed, deionized water	0.1 N HCl degassed	Phosphate buffer pH 7.41 degassed
Volume	900 mL	900 mL	900 mL
Mobile phase and pH	MeOH:H2O 40:60 pH 3.35	MeOH:H2O 50:50 pH 3.03	ACN:H2O 50:50 pH 3.03
Flow rate	0.5 mL/min	0.5 mL/min	1.0 mL/min
Absorption	250 nm	261 nm	258 nm
Retention time	7.2 min	11.1 min	8.45 min
Correlation coefficient*	0.999	0.999	0.999
LOQ	1.6 µg/mL	5.8 µg/mL	2.2 µg/mL
Method Reference	Pappula and Chintala (*26*)	Corrêa et al (*17*)	Granero et al (*27*)

**The correlation coefficients were calculated for the calibration curves of the three high-performance liquid chromatography methods.*

For the fluconazole and ketoprofen capsules, the same operating parameters used for the acetaminophen capsules were applied, with the exception of the dissolution media. The dissolution medium for fluconazole was 0.1 N HCl. The USP method for fluconazole tablets calls for deionized water as the medium, but since fluconazole is only slightly soluble in water but has a higher solubility in acidic media, we opted for 0.1 N HCl as the medium (*15, 16*). This choice of medium was based on the studies by Corrêa et al., who observed that 0.1 N HCl has an advantage over water in terms of effecting complete dissolution and was confirmed by in-house pilot experiments (*17*). For the ketoprofen capsules, a medium consisting of 0.05 M phosphate buffer (pH 7.4) was applied, following the suggestion of the United States Food and Drug Administration (FDA) (*18*). For all three products, we applied a specification of Q = 75% dissolution in 45 minutes, which is the specification applied to acetaminophen capsules USP and fluconazole tablets USP and is a very common specification used in USP dissolution methods. This approach enabled us to compare the ability of the three products to meet a standard specification under different test conditions.

Due to the photoinstability of ketoprofen in aqueous solutions, the dissolution tests for ketoprofen capsules were performed under exclusion from light; the samples were transferred in brown-glass vials and analyzed after dilution with mobile phase (*19*).

Samples Analysis

Quantification of every sample was performed using an EliteChrom Hitachi HPLC system (VWR, Leuven, Belgium) equipped with a Lichrocart 250-4, 100 RP 18 5-µm, 250 x 4mm column (Merck KGaA Darmstadt, Germany). Further details of the HPLC methods and the drug product specific operation conditions can be found in Table 1.

Data Presentation and Statistics

Data are shown as the mean and standard deviation of $n = 5$ replications in all cases. The results of the dissolution measurements were compared using analysis of variance (ANOVA) and t-tests. For the calculation of the p-values with ANOVA and t-tests the individual dissolution values of the tested samples at the sampling time of 15 min were used. Dissolution profiles were also compared with the similarity factor (f_2) test and regarded as similar when values were 50 or higher. A value of 50 and higher represents an average difference of 10% for all compared sample times (*1, 4–7, 13, 20, 21, 22*). Although our studies were performed with $n = 5$ rather than 12 samples (which is recommended by FDA), this test is commonly applied in the pharmaceutical industry and can therefore serve as a practical benchmark for comparing dissolution performance.

RESULTS

Ketoprofen Capsules

Dissolution results for the ketoprofen capsules are shown in Table 2 and Figure 2.

Due to its properties as a weak acid, ketoprofen showed a high solubility at pH 7.4 (*23*), enabling 100% dissolution in all experiments, and all dissolution tests with ketoprofen capsules met the pharmacopeial specification (Q = 75% after 45 min). In the tests without a sinker, the capsules floated at the start of the test for a maximum of 30 seconds. Coning was not observed within the range of 50–100 rpm, irrespective of whether sinkers were used. As expected, increasing the rpm resulted in a faster dissolution rate (*24*). At 50 rpm, about 95% of the drug dissolved within 30 minutes, whereas the same amount of ketoprofen dissolved after 20 minutes at 75 rpm and in just 10 minutes at 100 rpm.

At 50 rpm, the fastest dissolution rate was observed without a sinker due to the free movement of the capsule in the vessel and its dispersion in the dissolution medium.

Table 2. Dissolution from Ketoprofen Capsules at 50, 75, and 100 rpm

Time (min)	Without Sinker		JP Sinker		CLIPS Sinker		CAPLOTH Sinker		CAPWAST Sinker	
	Release (%)	SD	Release (%)	SD	Release (%)	SD	Release (%)	SD	Release (%)	SD
Dissolution from Ketoprofen Capsules at 50 rpm										
5	33.28	13.97	39.01	13.78	28.18	10.90	38.59	11.67	32.65	4.75
10	79.10	10.81	67.86	16.11	69.95	17.23	67.17	12.64	70.05	8.55
15	88.85	6.37	78.33	13.17	87.40	14.06	79.06	10.90	81.22	4.87
20	95.72	5.62	85.27	10.15	92.33	12.08	85.24	9.97	91.39	2.87
30	101.48	2.36	92.81	6.30	97.49	7.91	91.79	7.19	96.02	2.23
45	103.86	0.65	96.54	2.69	98.88	4.35	94.69	4.02	96.63	1.87
Dissolution from Ketoprofen Capsules at 75 rpm										
5	42.11	20.98	44.68	10.16	46.39	13.46	68.10	29.73	44.12	26.76
10	83.33	10.81	82.57	10.45	99.37	1.81	83.51	27.00	76.63	17.85
15	90.30	5.32	95.39	4.12	103.13	1.86	88.45	19.61	89.40	10.76
20	95.68	3.96	97.69	2.52	103.36	1.58	89.48	15.04	94.93	8.44
30	98.08	2.13	98.42	0.78	102.59	2.20	93.28	9.37	99.83	4.94
45	98.83	1.16	98.60	1.06	102.62	1.77	95.34	4.69	101.29	1.52
Dissolution from Ketoprofen Capsules at 100 rpm										
5	43.04	11.97	42.99	27.11	31.84	11.98	79.69	14.85	64.51	14.61
10	93.98	3.11	86.67	11.13	93.08	11.18	98.97	2.11	97.50	3.55
15	98.38	2.56	96.10	3.29	100.99	1.25	99.93	1.57	99.70	2.86
20	99.40	1.39	97.77	2.36	101.50	1.15	98.99	1.97	100.22	2.72
30	99.45	1.50	98.89	2.33	101.43	1.13	99.01	1.67	99.01	2.67
45	99.66	1.93	98.81	3.11	100.76	1.20	99.26	1.97	98.68	2.77

Drug release data are presented as mean values (n = 5).

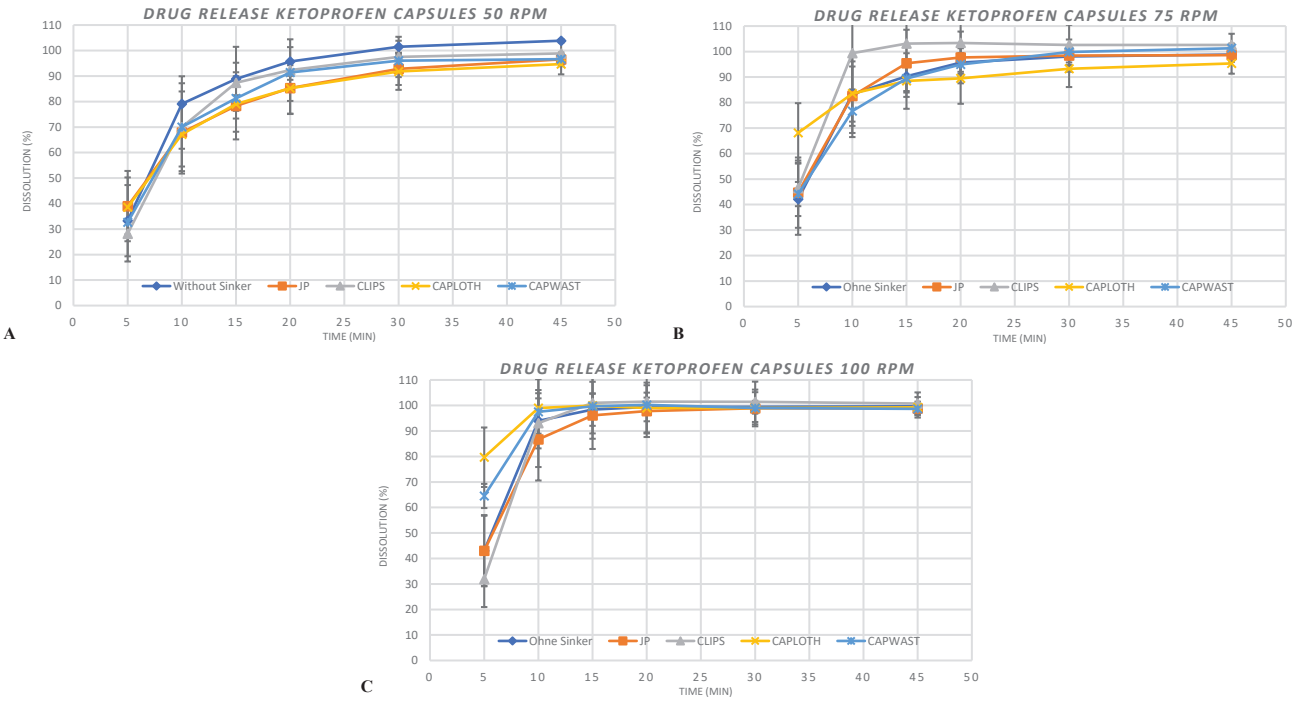

*Figure.2. Dissolution profiles from ketoprofen capsules at 50 (**A**), 75 (**B**) and 100 rpm (**C**). Data are presented as mean values (n = 5).*

The unhindered movement of the capsule in the vessel effectively reduces the thickness of the diffusion layer around the capsule shell, as well as around each drug particle, resulting in faster dissolution of both the capsule shell and contents. The second highest dissolution rate was observed in tests using the CLIPS sinker. Because of its low density, the sinker rotated together with the capsule contents in the dissolution medium, encouraging dispersion throughout the medium and resulting in a higher dissolution rate.

Interestingly, at 75 rpm the dissolution in the presence of the CLIPS sinker was faster than without a sinker, with almost 100% ketoprofen dissolution within 10 min with the CLIPS sinker, but only around 83% dissolution in the same time span in tests without a sinker ($p = 0.004$). At this stirring speed each of the other three sinkers produced similar results for percent of drug dissolved at 15 minutes to those without a sinker (CAPLOTH: $p = 0.84$; CAPWAST: $p = 0.78$; JP: $p = 0.12$). The dissolution performances of the capsules in the tests with the JP, CAPLOTH, and CAPWAST sinkers were also similar at 50 rpm and 75 rpm.

At 100 rpm, there was practically no difference in the dissolution performance with and without sinker or among sinkers, as more than 95% of ketoprofen was released within 15 minutes irrespective of sinker use or type.

Fluconazole Capsules

Dissolution results for the fluconazole capsules are shown in Table 3 and Figure 3.

In the tests with fluconazole capsules, increasing the rpm not only resulted in a faster dissolution rate but also in more extensive dissolution. At 50 rpm, only around 56%–60% of fluconazole dissolved within 45 min compared to around 73%–85% at 75 rpm and 73%–90% at 100 rpm. In contrast to ketoprofen, none of the tests met the specification for fluconazole of Q = 75% in 45 minutes at 50 rpm, whereas at 75 rpm the tests without sinker and with the CAPLOTH and the CLIPS sinkers met the specification. An f_2 test (albeit with $n = 5$) revealed a value of 39 between dissolution of fluconazole at 50 and 75 rpm without a sinker. At 100 rpm, all tests passed, with the exception of the JP sinker.

During the tests with fluconazole, three observations were made. First, the capsules floated for around 5 min when no sinker was used but also when the tests were run with the CLIPS sinker. As the capsules were filled compactly, it appears that even a small amount of air in the capsule shell can lead to floating. Second, all capsules at all rotation speeds showed some plug formation, albeit to different degrees, which negatively affected the dissolution performance. Third, during some tests, the dissolution of the capsule shell was impeded by the sinker. Instead of dissolving, the capsule shell partially collapsed ("melted") and entrapped parts of the capsule content, which encouraged plug formation and slowed dissolution.

The fastest dissolution rates were observed in tests with the CAPLOTH sinker, and the slowest rates were with the JP sinker. Due to the small openings in the wire mesh, the flow of dissolution media around the capsule inside the JP sinker is restricted, encouraging the capsule shell to melt or collapse on the contents instead of dissolving. Furthermore, the collapsed capsule shell clogged some openings in the wire mesh, preventing the circulation of dissolution media. These observations explain the slower dissolution when capsules are encased in the JP sinker. In contrast to the other sinkers, the dissolution of fluconazole was not decreased by the CAPLOTH sinker. The capsules had enough space inside the CAPLOTH sinker to dissolve unimpeded. The higher and faster dissolution rate was in accord with the formation of a smaller plug of the capsule content. During the tests without a sinker, some of the capsules stuck to either the vessel wall or to the paddle shaft, restricting the area available for dissolution. This effect was reduced at higher stirring speeds, as in this case the capsule was freed from the wall/shaft by the increased hydrodynamics. The slow dissolution rate with the CLIPS sinker was unexpected, as this type of longitudinal sinker has been reported to cause less hindrance to the hydrodynamics than the helical sinkers (*11, 12*). However, since the sinker contacts the capsule along three longitudinal axes and at the top of the capsule, the capsule shell collapses on the contents at these points instead of dissolving. For the dissolution performance with the CAPWAST sinker, two observations made during the test are important. On the one hand the capsules were "sliced" by the thin helical part of the sinker, which tends to improve the dissolution rate. On the other hand, the sinker comes in contact with the capsule along the long axis, causing the capsule shell to collapse on the contents, which has a negative effect on the dissolution performance.

Acetaminophen Capsules

Dissolution results for the acetaminophen capsules are shown in Table 4 and Figure 4.

Without a sinker, the acetaminophen capsules floated for around 10 min at all three stirring rates at the beginning

Table 3: Dissolution from Fluconazole Capsules at 50, 75, and 100 rpm

Time (min)	Without sinker		JP Sinker		CLIPS Sinker		CAPLOTH Sinker		CAPWAST Sinker	
	Release (%)	SD	Release (%)	SD	Release (%)	SD	Release (%)	SD	Release (%)	SD
Dissolution from Fluconazole Capsules at 50 rpm										
5	6.75	1.73	8.46	3.51	5.70	5.20	11.25	4.66	8.51	4.87
10	17.91	2.50	18.12	4.66	14.03	9.35	23.27	3.75	17.23	6.66
15	27.16	2.58	25.34	5.53	22.17	11.33	33.76	2.90	26.21	8.46
20	32.96	3.46	32.63	6.04	30.69	11.87	42.41	2.72	31.33	9.44
30	45.84	5.69	45.44	7.10	41.62	11.48	53.98	3.66	46.34	10.13
45	58.11	5.82	56.87	6.05	56.25	9.98	65.96	4.56	60.03	10.92
Dissolution from Fluconazole Capsules at 75 rpm										
5	13.95	8.60	17.03	6.86	15.37	4.80	29.27	11.08	21.18	8.25
10	30.68	11.64	28.79	9.38	30.03	6.11	45.79	14.31	36.69	10.48
15	42.76	13.23	38.93	10.20	42.31	5.85	57.64	15.61	46.73	10.84
20	49.74	14.41	47.23	10.23	53.66	4.97	61.32	15.22	56.36	11.11
30	66.38	15.36	59.77	10.65	68.12	5.83	75.53	13.19	64.32	11.08
45	79.75	10.81	73.01	9.28	81.07	5.39	84.33	9.71	73.08	9.90
Dissolution from Fluconazole Capsules at 75 rpm										
5	24.96	16.20	15.50	4.93	14.84	6.53	38.09	16.88	24.38	10.71
10	43.93	16.51	28.68	6.06	28.47	6.25	48.04	16.69	39.50	10.54
15	56.25	14.28	39.15	6.79	42.62	6.59	58.17	13.58	47.13	11.75
20	65.58	11.05	49.16	6.72	51.14	7.83	66.38	12.04	58.65	11.41
30	78.06	8.13	60.60	6.34	71.23	7.51	74.02	7.95	65.94	9.90
45	90.99	2.05	73.69	3.96	82.73	4.42	83.88	2.62	76.93	8.44

Drug release data are presented as mean values (n = 5).

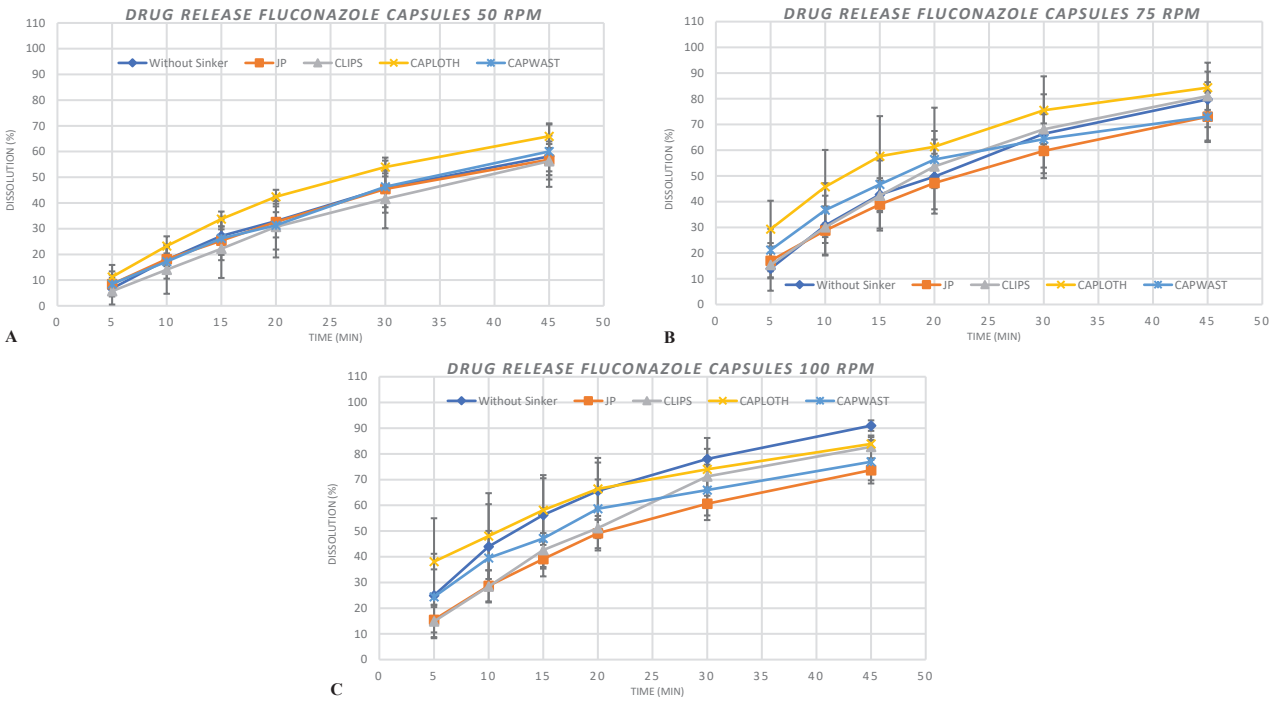

*Figure 3. Dissolution profiles from fluconazole capsules at 50 (**A**), 75 (**B**) and 100 rpm (**C**). Data are presented as mean values (n = 5).*

Table 4. Dissolution from Acetaminophen Capsules at 50, 75, and 100 rpm

Time (min)	Without sinker		JP Sinker		CLIPS Sinker		CAPLOTH Sinker		CAPWAST Sinker	
	Release (%)	SD	Release (%)	SD	Release (%)	SD	Release (%)	SD	Release (%)	SD
Dissolution from Acetaminophen Capsules at 50 rpm										
5	32.26	2.57	25.79	4.70	20.58	2.66	23.67	7.19	18.12	2.25
10	52.62	2.36	39.67	2.43	50.75	2.00	39.31	7.53	29.21	3.19
15	57.96	1.80	46.61	2.94	63.31	2.84	45.13	5.88	34.65	3.18
20	60.56	2.23	51.81	4.22	68.25	2.94	50.97	5.50	39.52	3.11
30	69.90	3.06	60.20	4.56	75.69	4.57	56.28	7.00	45.44	2.88
45	79.02	5.73	69.87	5.12	83.74	3.52	65.41	5.62	55.09	3.23
Dissolution from Acetaminophen Capsules at 75 rpm										
5	43.05	5.76	38.42	3.89	47.28	5.60	41.97	9.13	32.59	3.95
10	75.03	6.34	56.91	5.59	88.96	3.84	65.48	3.59	49.84	4.67
15	81.41	4.68	64.53	4.78	94.54	3.09	71.45	4.53	57.91	5.33
20	83.42	3.19	70.02	4.91	97.71	2.56	75.68	3.21	63.62	4.60
30	88.76	5.08	76.63	4.87	97.28	2.38	82.14	2.52	69.48	3.66
45	91.69	3.25	81.48	3.04	98.09	1.56	87.17	3.53	76.67	4.03
Dissolution from Acetaminophen Capsules at 75 rpm										
5	54.70	5.53	64.81	8.42	59.29	7.83	64.37	5.47	55.71	2.29
10	83.47	12.11	87.81	9.24	97.50	2.20	88.34	4.44	74.66	3.19
15	89.93	7.11	91.52	8.21	98.69	1.18	92.96	3.60	80.11	5.30
20	92.73	5.52	95.56	5.92	99.48	1.52	95.23	2.91	84.24	4.65
30	97.24	3.13	96.70	5.24	100.75	1.07	95.90	3.11	89.72	3.96
45	98.38	1.27	97.59	2.63	100.84	0.55	96.93	1.43	94.84	1.90

Drug release data are presented as mean values (n = 5).

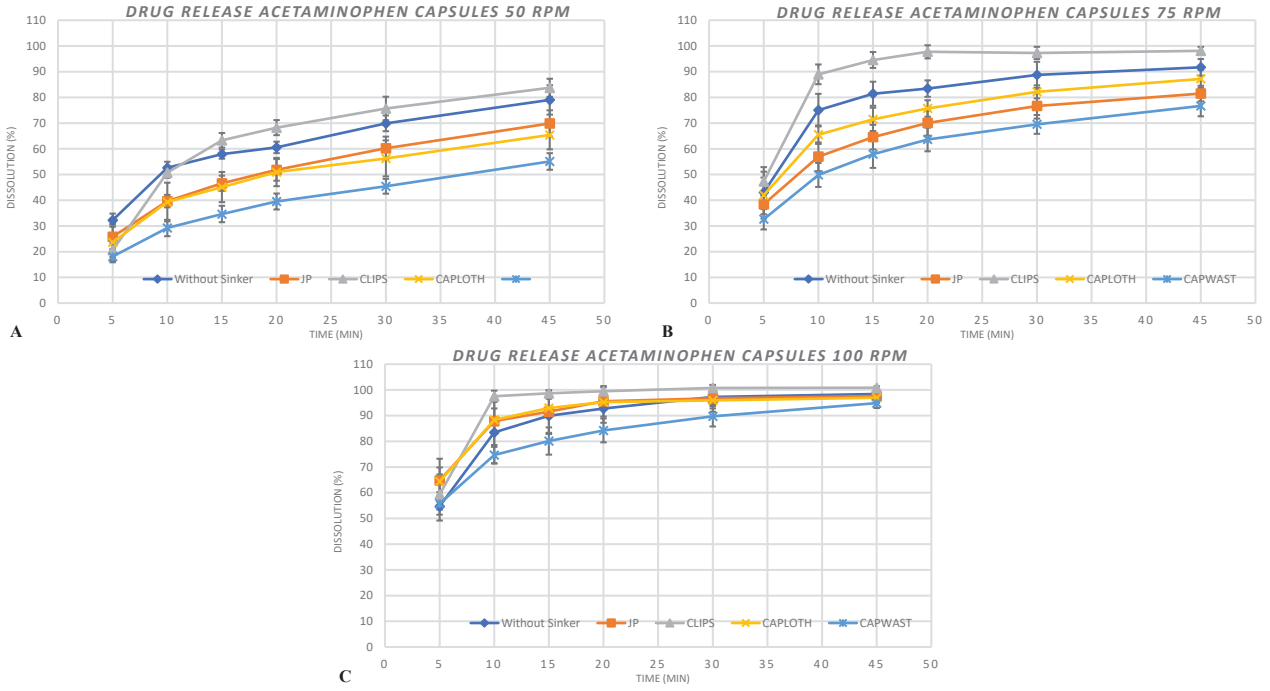

Figure 4. Dissolution profiles from acetaminophen capsules at 50 (A), 75 (B) and 100 rpm (C). Data are presented as mean values (n = 5).

of the test. The flotation time was long because the capsules were not filled compactly, and a substantial amount of air was trapped inside the capsules. In tests with acetaminophen capsules, faster and more extensive dissolution occurred when the rpm was increased, consistent with results for fluconazole and ketoprofen. A slight coning was observed in all tests.

At 50 rpm, only the test with the CLIPS sinker met the specification of 75% release in 45 minutes, whereas all tests passed at 75 rpm and 100 rpm. An f_2 test (albeit with n = 5) revealed a value 34 between dissolution of acetaminophen at 50 and 75 rpm without a sinker. The incomplete release at 50 rpm is attributed to coning (see arrow in Fig. 5). At 50 rpm, the drug release of acetaminophen without a sinker was almost 10%–30% higher than with three of the four sinkers tested. In tests with the CLIPS sinker, a higher drug release was observed because the sinker rotated together with the capsule contents, which helped to disperse both the slight coning mound and the already dispersed fraction of the capsule contents.

Figure 5. Observed coning (arrow) during the dissolution tests of Acetaminophen at 50 rpm.

The largest differences in the extent of drug release between testing with and without sinkers were observed at 50 rpm, less at 75 rpm, and no difference was observed at 100 rpm. This was partly because coning was reduced by increasing the stirring speed (*25*).

Although acetaminophen is highly water-soluble, at 50 rpm only the capsules we tested without sinkers or with the CLIPS sinker met the specifications (*26*). In spite of the good solubility of the API, it appears that some sinkers affected the drug release negatively (JP, CAPLOTH, CAPWAST) and others improved the drug release via affecting the hydrodynamics (CLIPS) compared to the testing without a sinker.

The slowest dissolution rate was observed with the CAPWAST sinker at all rotation speeds. In addition to the effects of the CAPWAST sinker discussed above for fluconazole, the release of acetaminophen was also restricted by the tight fit of the capsules in the sinker, resulting in a higher tendency of the capsule shell to collapse onto the contents. The dissolution performance with the JP and CAPLOTH sinkers were quite similar, although similar observations to those mentioned for fluconazole with regard to the sinker causing the capsule shell to collapse onto the contents were made. It appears that these two sinkers affect the drug release in a similar way and that these effects can be reduced in both cases by increasing the stirring speed.

DISCUSSION

In most of our tests, the standard deviation in the data stayed about the same or increased when a sinker was used. In consideration of this, five key issues can be addressed from the results of our investigations.

1. Do All Sinkers Prevent Flotation of the Dosage Form?

Both the pharmacopeia and the ICH M9 guideline recommend the use of sinkers during dissolution testing via paddle apparatus to ensure consistent test conditions in cases where floating or coning of the capsules occurs (*13, 22*). With regard to dosage forms that float, it makes little sense to use a sinker if it is not able to ensure that the dosage form sinks into the dissolution medium, unless there is some other benefit. Of the four sinkers tested, the CLIPS sinker was the only one that did not correct the flotation issue. Instead, the CLIPS sinker floated together with the capsule at the beginning of the test. This is not surprising, as it is constructed from plastic rather than a denser (i.e., metal) material. The floating behavior leads to two opposing effects on dissolution. On one hand, the dissolution of the capsule shell can be accelerated due to the increased movement of the capsule on the surface of the dissolution media. On the other hand, dissolution can be impeded by the restricted contact of the capsule with the dissolution media. As observed in our experiments and by others, the first effect was more pronounced at 75 and 100 rpm, as the relative movement of the sinker/capsule increases with increased rotation speed and therefore in a faster dissolution rate (*5, 21*). On the other hand, this positive effect can be counteracted by

the contact of the sinker on the longitudinal axes of the capsule, impeding dissolution, as observed at 50 rpm for all three drugs, with the effect more pronounced for fluconazole and acetaminophen.

2. Does Using Sinkers Consistently Increase the Dissolution Rate?

Using a sinker can have a positive or a negative influence on the dissolution performance. In our tests, the CLIPS sinker was able to increase the dissolution rate by encouraging dispersion throughout the dissolution medium, either by helping disperse a slight coning mound or maintaining good dispersion of the capsule contents. This also applies to the dosage forms that floated. Depending on the design of the sinker, the dissolution rate can also be improved through speeding up the dissolution of the capsule shell by slicing, as in the case of the CAPWAST sinker.

On the other hand, the sinker can restrict the flow of the dissolution media around the dosage form (JP sinker), resulting in slower dissolution of the capsule shell and capsule content. Contact of the sinker with the capsule along longitudinal axes (CAPWAST, CAPLOTH, and CLIPS) can also impede the dissolution rate, as this may cause the capsule shell to collapse onto the capsule contents instead of dissolving (*11, 12*). Entrapped by the collapsed capsule shell, the capsule contents can form a plug, which in turn slows down the dissolution and may even prevent complete dissolution of the drug. The extent of this effect on the dissolution performance appears to depend on the solubility of the API and the rotation speed used in the dissolution test. If the API is not very soluble, then the dissolution can be additionally impeded by the effects we mentioned before (restriction of the flow of dissolution media around the dosage form, encouraging the capsule shell to collapse onto the capsule contents instead of dissolving), and the dissolution falls out of specification. If the API is generally highly soluble, then other factors can affect the dissolution both positively (via the sinker's ability to move with the capsule in it) or negatively (due to a tight fit of the capsule in the sinker). As will be discussed in section 5, any adverse effects of the sinkers can be counteracted by increasing the rotation speed.

3. Do Sinkers Consistently Decrease Coning?

The ICH M9 Guidance suggests the use of a sinker during dissolution testing with the USP apparatus 2 as a potential solution to coning issues (*13*). Our investigations of the acetaminophen capsules showed that, depending on which type of sinker is used, coning can be decreased (CLIPS sinker) or increased (CAPWAST, CAPLOTH, JP sinker), resulting in significant differences in the dissolution performance. Due to its low weight, the CLIPS sinker rotated together with the capsules. This movement of the sinker enabled already dispersed fractions of the capsule contents as well as the coning mound, which was observed for the acetaminophen capsules, to be better dispersed. The net result was that the dissolution rate of acetaminophen at 50 rpm was similar with the CLIPS sinker to the dissolution rate observed in tests without a sinker at 50 rpm (f_2 = 57). As the movement of the sinker increased with the rotation speed, the dissolution rate with the CLIPS sinker at 75 rpm and 100 rpm was significantly higher than without a sinker at the same rpm after 15 min (75 rpm: p = 0.0007; 100 rpm: p = 0.02).

In contrast to this beneficial effect, coning can actually be increased by the use of a sinker if the sinker restricts the flow of dissolution media around the dosage form (JP sinker) or inhibits dissolution of the capsule shell because of the large contact surface between sinker and dosage form (CAPWAST, CAPLOTH, JP sinker), leading to a lower contact area between the capsule and the dissolution medium. These negative impacts on the dissolution performance led to increased coning and slowed down the dissolution rate compared to the tests without a sinker at the same rpm. Thus, it seems that, at least for acetaminophen capsules, sinkers cannot be relied upon across the board to prevent coning.

Since these three key issues indicated that sinkers do not always have the desired effects on dissolution, alternative approaches need to be considered. As an often-recommended remedy to coning is to adjust the rotation speed, we also analyzed our data to determine whether an increase in rotation speed is helpful.

4. Does Increasing the Rotation Speed Consistently Decrease Coning?

As expected, the coning observed in tests with the acetaminophen capsules was decreased when the rotation speed was increased from 50 rpm to 75 rpm or 100 rpm. Through this simple approach, the dissolution went from being too slow to meeting the specification easily. Coning distorts the dissolution results and is an artifact caused by the hydrodynamic pattern in the Type 1 and 2 apparatus (*1, 4, 5*). By reducing the coning, the dissolution performance will depend largely on the physico-chemical properties of the API and the excipients, improving the relevance of the dissolution results.

5. Does Increasing the Rotation Speed Consistently Increase the Dissolution Rate?

The dissolution rate in all tests performed with the ketoprofen or acetaminophen capsules was increased

significantly by increasing the rotation speed, irrespective of whether a sinker was used or not. For fluconazole, increasing the rpm substantially increased the dissolution rate when no sinker was used, while for tests with a sinker, there was a considerable improvement of the dissolution rate between 50 and 75 rpm but only a slight increase between 75 and 100 rpm. When the sinkers were implemented, the increase in dissolution with rpm appeared to be offset by the strong propensity to plug formation.

Notably, increasing the stirring speed brought the dissolution at all tests with all products within specification, except for fluconazole with the JP sinker, which was unable to meet specification at any rpm due to severe plug formation.

Besides increasing the stirring rate, another approach that is widely used in the pharmaceutical industry is to use peak vessels, rather than round-bottom dissolution vessels (*4–7*). Through the indentation at the bottom of the peak vessel, the undispersed mound (cone) of capsule content is forced into a region with more hydrodynamic activity, such that the whole surface of the dosage form is constantly and uniformly exposed to the dissolution medium (*7*). Additionally, the influence of external factors (for example vibration) and internal factors (for example air bubbles in the dissolution medium, vibration, stirring speed) is lower compared to conventional round-bottom vessels (*7*). Therefore, not only is the dissolution rate increased when peak vessels are used, it will also be more complete (*6, 7, 20*). As this simple modification reduces several artifactual effects commonly encountered in dissolution, peak vessels have often been recommended as a good alternative to increasing the rotation speed. Oddly, these recommendations have not been adopted by the pharmacopeia or in regulatory documents such as the recent ICH M9 guidance on biowaivers (*13*).

Some Tips for the Use of Sinkers

In consideration of the key issues mentioned above, what should an analyst watch for when deciding *a) whether to use a sinker* and *b) which one to use* if using a sinker is warranted?

When should a sinker be used?

As discussed in section 1, the ICH M9 guideline and pharmacopeia recommend the use of sinkers to overcome floating and coning, if these are affecting the dissolution performance (*13, 22*). Generally, if USP apparatus 2 is used for dissolution testing of capsules, especially hard capsules, a sinker should be used to prevent the dosage form from floating (*11*). However, the disadvantages of using a sinker for the dissolution test (as discussed in sections 2 and 3 above) should be considered, and a sinker should be identified that does not artifactually change the dissolution in other ways. With respect to coning, the use of a sinker should be discouraged because there are more efficient ways to counteract this problem such as increasing the rotation speed or using peak vessels (*6, 7, 20*).

Which Sinker?

As their name suggests, the sinkers should sink. If the capsule has a small size and a low fill weight such that air is trapped within it, floating is possible when using the CLIPS sinker (due to its low density relative to other sinker types). Soltero et al. recommend this type of sinker for dissolution testing, as it was best able to meet their criteria for a good sinker shape (*11*). However, as discussed in section 2, this type of sinker does not overcome floating issues and can even have a negative impact on dissolution. As floating of the sinker leads to less consistent dissolution conditions, another sinker type (made from stainless steel for example) should be used for dosage forms that float in an effort to achieve good reproducibility of results.

Next, the sinker should be the right size for the capsule, as a too-tight fit of the capsule in the sinker can impede the dissolution of the capsule shell and therefore the dissolution performance of the capsule contents. The effect of the geometric shape of the sinker on the dissolution performance was also investigated by Soltero et al. and could be confirmed in our investigations (*11*). In the experiments by Soltero et al., release rates were inhibited when the formulation became trapped inside the loops or between the parallel coils of lateral, helix-shaped sinkers (*11*). The helix-shaped sinkers they used are similar to the CAPWAST and CAPLOTH sinker used in our studies. By contrast, in the case of a too-loose fit, it is possible for the capsule to fall out of the sinker (for example with the CAPLOTH sinker), making the use of the sinker pointless.

Third, if the capsule to be tested shows other phenomena that affect the dissolution performance, like plug formation or coning, the impact of the sinker type on these effects should be investigated. As discussed in section 3, coning can be encouraged through the use of a sinker, despite the ICH guideline recommendation (*13*). On the other hand, also discussed in section 3, coning can be decreased in certain cases. But, as this beneficial effect on the coning was only observed for one sinker type (CLIPS sinker, acetaminophen capsules, 75 and

100 rpm), the negative effects appear to outweigh any positive effect for most of the sinker types. Thus, we cannot recommend using a sinker to overcome coning; increasing the rotation speed or peak vessels should be considered instead (*6, 7, 20*).

CONCLUSIONS

The effects of four types of sinkers on dissolution of three different drugs (acetaminophen, fluconazole, and ketoprofen) from commercially available hard capsule products were studied. Analysis of the results revealed that although three of the four sinkers were able to adequately address flotation problems, in many cases the use of sinkers led to adverse effects on the dissolution properties of the capsules. It also appears that sinkers may not be consistently useful for addressing coning issues and instead an increase in the stirring speed or use of peak vessels should be considered. Generally speaking, different sinker designs produce different effects on the dissolution process. Given that other factors such as the physicochemical and mechanical properties of the products also affect the dissolution performance, it seems unrealistic to expect a consistent impact of sinkers across products.

CONFLICT OF INTEREST

The authors disclosed no conflicts of interest related to this article.

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APPENDIX

Supplementary Table S1. Mass, Capsule Size, Relative Density, and Qualitative Composition of the Tested Products

Capsules	Mass, mean (mg)	Size	Relative Density (g/mL)	Qualitative Composition
Acetaminophen	654 mg	00E	0.549	Acetaminophen; talcum; gelatin; titan dioxide; indigo carmine
Fluconazole	299 mg	2	0.661	Fluconazole; lactose; lactose-monohydrate; mg-stearate; cornstarch; Na-dodecylsulfate; siliciumdioxide; gelatin; titan dioxide; indigo carmine
Ketoprofen	201 mg	3	0.566	Ketoprofen; lactose-monohydrate; Mg-stearate; siliciumdioxide; gelatin; titan dioxide; iron oxide; erythrosin; indigo carmine

Supplementary Table S2. Mass, Sinker Size, Density, and Material of the Sinkers

Sinker	Mass (mg)	Size	Density (g/mL)	Material
CLIPS	0.90 g	Length: 32.9 mm Width: 9.9 mm	0.92	Polypropylene
JP	4.57 g	Length: 26.5 mm Width: 14.9 mm	~8	Stainless Steel
CAPLOTH	2.72 g	Length: 26.8 mm Width: 13.7 mm	~8	Stainless Steel
CAPWAST	0.94 g	Length: 24.8 mm Width: 10.6 mm	~8	Stainless Steel