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RESEARCH ARTICLE

Influence of capsule shell composition on the performance indicators of hypromellose capsule in comparison to hard gelatin capsules

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Abstract

The purpose of this study was to assess the *in vitro* performances of "vegetable" capsules in comparison to hard gelatin capsules in terms of shell weight variation, reaction to different humidity conditions, resistance to stress in the absence of moisture, powder leakage, disintegration and dissolution. Two types of capsules made of HPMC produced with (Capsule 2) or without (Capsule 3) a gelling agent and hard gelatin capsules (Capsule 1) were assessed. Shell weight variability was relatively low for all tested capsules shells. Although Capsule 1 had the highest moisture content under different humidity conditions, all capsule types were unable to protect the encapsulated hygroscopic polyvinylpyrrolidone (PVP) powder from surrounding humidity. The initial disintegration for all Capsule 1 occurred within 3 min, but for other types of capsules within 6 min ($n = 18$). Dissolution of acetaminophen was better when the deionized water (DIW) temperature increased from 32 to 42 °C in case of Capsule 1, but the effect of temperature was not significant for the other types of capsules. Acetaminphen dissolution from Capsule 1 was the fastest (i.e. >90% in 10 min) and independent of the media pH or contents unlike Capsule 2 which was influenced by the pH and dissolution medium contents. It is feasible to use hypromellose capsules shells with or without gelling agent for new lines of pharmaceutical products, however, there is a window for capsule shells manufacturing companies to improve the dissolution of their hypromellose capsules to match the conventional gelatin capsule shells and eventually replace them.

Keywords

Dissolution, hard gelatin capsules, hygroscopicity, hypromellose capsules, initial disintegration time, powder leakage, resistance to stress, shell weight variation

History

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Introduction

HPMC-based capsule shells production market is expanding worldwide, but Qualicaps and Capsugel remain the main innovators and competitors in this market. The relatively recent introduction of these capsule shells in comparison to the commonly used hard gelatin capsules uses similar production equipment[1]. While pharmaceutical grade HPMC capsule shells have been used for pharmaceutical drug products only recently, some nutraceuticals encapsulated in HPMC capsules were available in the market for some time now. Qualicaps produces Quali-V® (Capsule 2), which consists of HPMC and carrageenan is used as a gelling agent. The small amounts of carrageenan work as a network former and include potassium chloride as a network promoter[2]. On the other hand, Capsugel produced two types of immediate release HPMC shells which are the Vcaps® consisting of HPMC and Gellan gum (gelling agent) and the more recently introduced Vcaps® Plus (Capsule 3) containing HPMC with no gelling agent. Studies indicated that the Vcaps® Plus capsule shells are superior to Vcaps®[3,4].

The gelling agents used in the HPMC capsule shells allow the manufacturing technique to mimic hard gelatin capsule shells, while the absence of the gelling agent will require the pins immersed in the dip pan during the shell production to be at higher temperature (i.e. 70 °C) in order for the film to be formed. This is because HPMC film is formed by the marked increase in the viscosity of the solution when the temperature is raised. There are indications that while the use of gelling agents facilitate the production of HPMC-based capsule, because it requires no modification to the standard equipments used in the production of hard gelatin capsules, they may actually decrease drug release from these shells when tested *in vitro*[4].

While hard gelatin capsules remain the classical encapsulating shells for most pharmaceutical products, some restrictions make the use of HPMC capsule shells an attractive alternative[4]. In addition to the classical use of hard capsules for oral administration, capsule made of HPMC has been suggested or

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recommended for encapsulating dry powders for inhalers using filled capsules[5–7]. On the other hand, the crosslinking of gelatin which hinders the release of some encapsulated drugs, the restriction for its use in capsules shells that it must be certified to be free of bovine spongiform encephalopathy (BSE), a transmissible spongiform encephalopathy (TSE) and the vulnerability of the shells to storage conditions are among factors encouraging the pharmaceutical industry to opt for HPMC ''vegetable'' capsules[4]. Additionally, not everybody can ingest gelatin-based capsules due to dietary restrictions or religious beliefs. Therefore companies producing HPMC capsules promote their shells as Kosher and Halal certified and are suitable for vegetarians and vegetarian minded users.

Although few researches have been published in this area qualifying the vegetable capsules as alternative to hard gelatin capsules, the results were conflicting in some cases reflecting the competitive pharmaceutical market, since most of the relatively small number published papers are originating from individuals affiliated to the shells manufacturing company[3,4,8–10]. Among those with conflicting or arguable results are related to capsule glossiness, powder leakage and gap between capsule's cap and body, fill weight variability and the resulting rejection rate from encapsulation, disintegration and dissolution results.

Therefore, the purpose of the current work was to independently investigate the potential for pharmaceutical industry to use HPMC capsules as alternative to hard gelatin capsules for their new pharmaceutical product lines by using different performance indicators and also to help determine the appropriate type of HPMC capsule shells whether containing a gelling agent or not.

Materials and methods

Materials

Acetaminophen (98%) was purchased from Sigma-Aldrich (St. Louis, MO). Polyvinylpyrrolidone (PVP) 40 000 (K30) was purchased from VWR International (Randor, PA). White opaque hard gelatin capsules (Capsule 1) and HPMC capsules containing carrageenan of sizes 0 and 2 (Capsule 2) samples were kindly supplied by Qualicaps Europe (Madrid, Spain), while the transparent capsules containing HPMC without a gelling agent (Capsule 3) sample was kindly provided by Capsugel (Bornem, Belgium). All other chemicals were of analytical grade and solutions and buffers were prepared in accordance to the USP37-NF32.

Methods

Filling of the hard capsule shells

The filling of the capsules was done manually while the weight was measured using sensitive digital balance (±0.1 mg) (AUX 220, Shimadzu, Kyoto, Japan). The weights used to fill the capsule were based on capsule capacity, the bulk density of the materials used and convenience. For acetaminophen containing capsules used as model drug, the fill weights were 250 and 125 mg for capsules sizes 0 and 2, respectively. For PVP which represents hygroscopic materials, 230–235 mg was filled inside size 0 capsules. No other additives were used in any of the filled capsules. The capsules were then stored initially at temperature 23 °C and 45% RH environment.

Capsule shells weight variation

Empty capsules of each type and size were weighed using sensitive balance (AUX 220, Shimadzu, Kyoto, Japan) and average weights and variability were determined for 10 randomly selected shells of each capsule type and size.

Hygroscopicity and stress testing

Samples of capsules were stored at 23 °C and at relative humidity of 15%, 45%, 70% and 90% for 4 days, when they reached the equilibrium moisture content, using constant climate chamber (Binder KMF 115, Tuttlingen, Germany). The samples consisted of 10 empty detached capsule bodies and caps, 10 empty closed capsules and 10 capsules filled with 230–235 mg PVP for size 0 of the three types of capsules. Samples of free PVP were also stored at the aforementioned conditions. PVP is well-known hygroscopic material and was used to challenge the different encapsulating shells for their ability to protect PVP from the effect of humidity. At high relative humidity (i.e. 70% and 90%), PVP absorbs moisture and the later becomes trapped within its converted gelatinous structure making it difficult to dry under the ordinary drying conditions used. Therefore, experiments where % loss on drying (LOD) was calculated for PVP or encapsulated PVP at 70% and 90% were based on calculation of the dry weight of the PVP and the capsules under the filling conditions, then weight gain during the 96 h was recorded. Percent loss on drying (%LOD) was calculated as the weight lost at 105 °C divided by the initial weight using Sartorius Moisture Analyzer (Model MA35, Goettingen, Germany). Empty closed and open capsule samples and free PVP powder were used as controls. Also completely dried closed capsules were used to assess, in the absence of water, their flexibility and ability to tolerate stress resulting from the free fall of 300 g weight over 30 cm height at the base of 250 mL plastic measuring cylinder. The completely dried closed capsules were obtained using the Sartorius Moisture Analyzer (Model MA35, Goettingen, Germany) and at the same conditions used to calculate the % LOD. Denting and/or capsule crack, shutter or breakage was assessed for each type of size 0 ($n = 10$ capsules).

Powder leak test

The three types of capsules were assessed using the two sizes for possible powder leaking. Powder leaking may result from different stresses encountered by the capsule product during filling, carding, blistering, packaging and transportation. To simulate such stresses, 10 capsules containing acetaminophen from each capsule type and size were subjected to tumbling action using the equipment (TA 220, Erweka, Heusenstamm, Germany) designed to test tablets friability where the tablets fall from a distance of 15 cm on each drum rotation. The stress test involved 3000 drum rotations in two hours (25 rpm) and then checking any leaks visually and by weighing cleaned capsules. Because of the static charges evolving during drum rotation that may result in the sticking of the capsules to the rotating drum and therefore preventing free capsule tumbling, the drum was lightly coated with liquid paraffin before each run.

Disintegration testing of the filled capsules

The disintegration test was carried out in deionized water (DIW) and 0.1 M HCl at 37 °C (±2). The procedure was followed as in the USP37-NF32 regarding ''<701> Disintegration'' with the use of a removable wire cloth attached to the surface of the upper plate of the basket-rack assembly[11]. The state of disintegration for 18 filled capsules of size 0 for each type was observed at 1.5 min interval until all the capsules have undergone initial disintegration using the disintegration apparatus (PTZ-Auto 02, Pharma Test, Hainburg, Germany). The number of capsules showing disruption in their walls that would allow capsule content to be released (initial disintegration) was counted at each time interval and the rupture/dissolution patterns of the shells were observed.

Dissolution testing of the filled capsules

Dissolution testing was carried out for capsules filled with acetaminophen using dissolution apparatus 1 (DT 820, Erweka, Heusenstamm, Germany) at 100 rpm basket speed[12]. The use of the basket apparatus was to avoid any possibility for capsule floating that could lead to extra measures to be taken. All of the dissolution tests were carried out using media 900 mL and at 37 °C on all types of capsules. Exceptions were when the temperature was changed to 32 °C and 42 °C to see if this would influence drug dissolution from different types of capsule shells in DIW (pH 6.1). The pH values of the different media were measured using the FiveEasy FE 20, Mettler Toledo (Greifensee, Switzerland). Table 1 summarizes the dissolution testing carried out for all drug filled capsules types and the determined peak wavelengths (λ_{max}) at which the drug samples were analyzed by a spectrophotometer.

The samples withdrawn were filtered and immediately replaced by equivalent volume of the medium at the same temperature. The sampling times were at 2.5, 5, 7.5, 10, 15, 20, 25, 30, 40, 50 and 60. The samples were analyzed after proper dilution using a spectrophotometer (T70 UV/Vis spectrophotometer, PG Instruments, Lutterworth, UK).

Summarizing performance indicators

The performances of different capsule types were assigned an arbitrary score of minimum 1 (i.e. +) to maximum 3 (i.e. +++) for each single performed test. This will help interested pharmaceutical manufacturers to decide on which type of capsule to use for their new line of drug products. In the score system, if the best performing capsule type scores (+++), then the lesser preforming capsule is giving the score (++) provided that the difference between them is relatively small and has no major influence in practice. On the other hand, if performance test results were shown to be week for all capsules, then each type receives one point in the score system (i.e. +).

Statistical analysis

Descriptive and analytic statistics were performed using SPSS, version 21 (SPSS Inc, Chicago, IL). For inferential statistical analysis two-sided ANOVA and *t*-test analysis were used assuming $p < 0.05$. Graph figures were prepared using Microsoft Excel (Microsoft Office 2010, Redmond, WA).

Table 1. Dissolution test parameters used for testing the dissolutions from there types of capsules.

Dissolution medium and dissolution conditions	Determined λ_{max} (nm)
DIW at 37 °C, 900 mL, 100 rpm, capsule size 0 and 2	242
DIW at 32 °C, 900 mL, 100 rpm, capsule size 0 and 2	242
DIW at 42 °C, 900 mL, 100 rpm, capsule size 0 and 2	242
HCl buffer at 37 °C, 900 mL, 100 rpm, pH 1.2, capsule size 2	239
Acetate buffer at 37 °C, 900 mL, 100 rpm, pH 4.5, capsule size 2	242
Phosphate buffer at 37 °C, 900 mL, 100 rpm, pH 6.8, capsule size 2	240

Results

Shell weights variability

Although the weights of the empty shells of different types are close to each other, Capsule 2 of both sizes are lighter corresponding to Capsules 1 and 3 average weights ($p < 0.001$). The variability in shell weights was highest with Capsule 3. Table 2 summarizes the results of capsule shell weights of different types and sizes.

Loss on drying and response to applied stress

Through the use of appropriate controls, it was possible to look at the ability of the capsules to protect their contents once they are locked. At 70% RH, free PVP powder changed to hard gelatinous mass that was difficult to dry completely under the used drying condition (Figure 1a). On the other hand, free PVP powder was completely converted to liquid at 90% RH (Figure 1b) within 24 h and did not pick up any moisture thereafter. Similar conditions were observed for the encapsulated PVP indicating the inability of the different capsule shells to protect the encapsulated hygroscopic material (Figure 1c and d). This was further evident when empty closed and opened capsules had no tangible change in their moisture content at different relative humidity (Table 3). At low humidity (15% RH) Capsule 3 showed significant charges as evident while handling the shells. At 48 h and 96 h one and three of the Capsule 1 type, respectively, showed leaking of the liquefied PVP when stored at 90% RH (Figure 1e).

Stress on different types of empty closed capsules after they were dried and then challenged by the free drop of 300 g weight showed that Capsule 3 is more flexible than the other types of capsules (see Figure 2). While none of Capsule 3 showed any sign of cracks, Capsule 1 completely fragmented after the application of stress (Figure 3).

Leaking of powder

All types and sizes of capsules showed powder leakage of not more than 0.3% with Capsule 3 having the lowest leakage of $\leq$0.08%. Figure 4 shows the results of the leaking test.

In vitro disintegration testing

All of the capsules tested showed at least initial disintegration as previously defined within 6 min regardless of the capsule type or the medium used (Figure 5). Capsule 1 made of gelatin exhibited the fastest initial disintegration (1.5–3.0 min) compared to other capsules. There was slight delay in the initial disintegration of Capsule 3 where the first observation was at 4.5 min.

Table 2. Shell weights results from 10 empty capsules of different types and sizes.

	Capsule 1		Capsule 2		Capsule 3	
Size	0	2	0	2	0	2
Average (g)	0.09969	0.06247	0.09392	0.05735	0.09963	0.06138
Min. (g)	0.0986	0.0611	0.0909	0.0564	0.0939	0.0583
Max. (g)	0.1009	0.0642	0.0972	0.0583	0.1043	0.0638
% Range of average	98.91–101.21%	97.81–102.77%	96.78–103.49%	98.34–101.66%	94.25–104.69%	94.98–103.94%
RSD	0.71%	1.63%	2.26%	1.02%	3.15%	2.86%

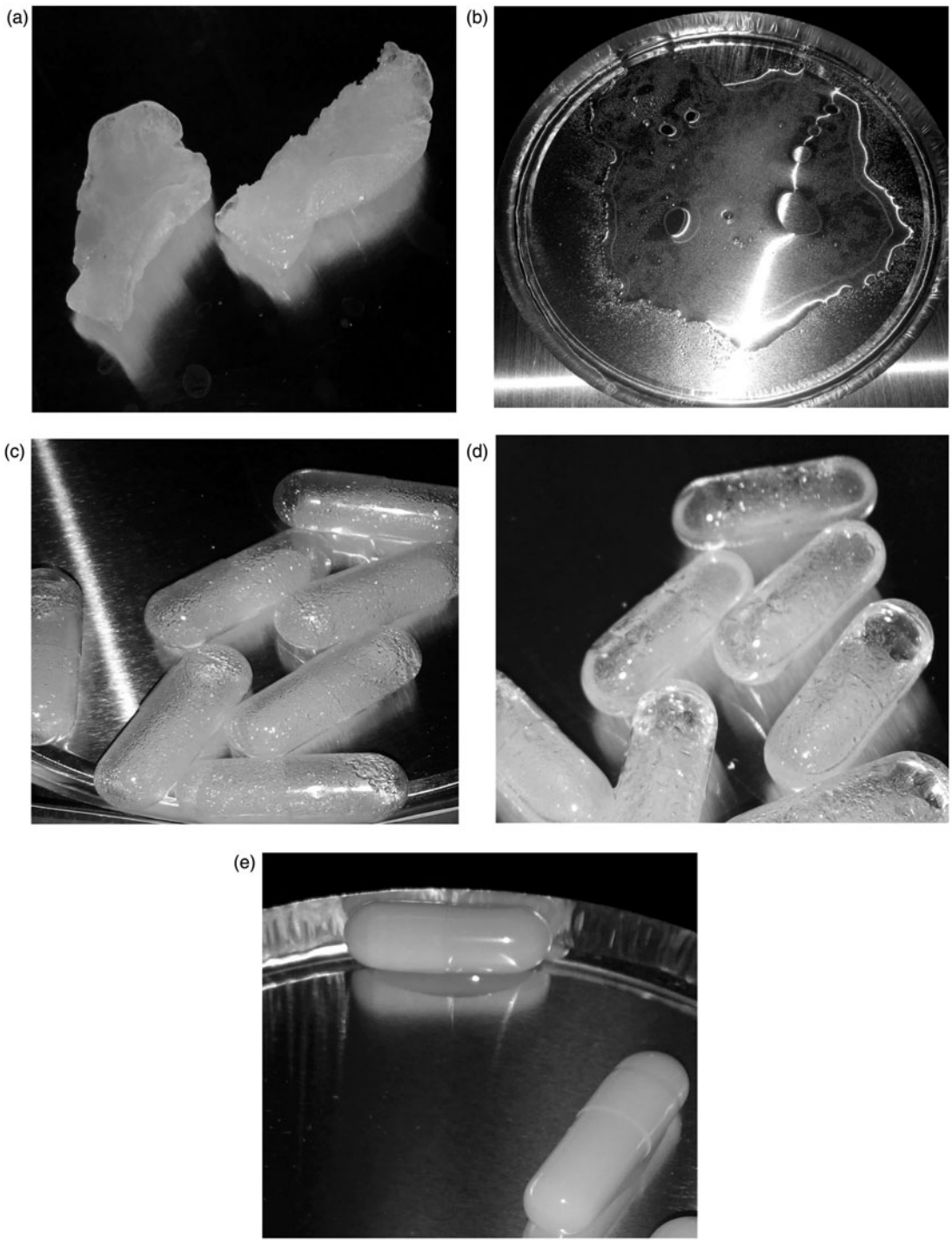

Figure 1. (a) PVP following 96 h storage at 23 °C and 70% RH. (b) PVP following 24 h storage at 23 °C and 90% RH. (c) Encapsulated PVP using Capsule 3 following 96 h storage at 23 °C and 70% RH. (d) Encapsulated PVP using Capsule 3 following 24 h storage at 23 °C and 90% RH. (e) Liquefied PVP Leaking from one capsule of Capsule 1 type encapsulating PVP following 48 h storage at 23 °C and 90% RH.

In vitro dissolution testing

Acetaminophen release in DIW at different temperatures

The effect of the DIW temperature on the dissolution of acetaminophen was assessed at 32, 37 and 42 °C. Figures 6–8 show the dissolution profiles of acetaminophen in DIW from different capsule types of different sizes. The critical period that differentiates drug release among the different types and sizes of capsules is the first 30 min and especially in the first 10 min in all of the dissolution studies.

Acetaminophen releases in the first 30 min for all capsule types and sizes were significantly different at 32 °C (see Tables 4 and 5). Capsule 1 of different sizes achieved the fastest release initially, while this was not the case at 60 min when almost 100% of acetaminophen release was achieved in all tested capsules. Likewise was the release of acetaminophen from different capsules of different sizes at 37 °C in DIW. Similar inferential statistical results were also obtained for acetaminophen release at 42 °C.

The effect of temperature on the release of acetaminophen was evident for Capsule 1. The release was improved from Capsule 1 of sizes 0 and 2 as the temperature increased in the first 5 and 10 min, respectively. The effect of temperature on the dissolution of acetaminophen from Capsules 2 and 3 was not as evident as

compared to Capsule 1 (Table 6). When comparing Capsule 2 and Capsule 3 of size 2 at different temperature, there appears to be significantly better acetaminophen release from Capsule 2 at temperatures 37 and 42 °C at the first 10 min and the first 5 min, respectively (Table 7).

The effect of capsule size on the acetaminophen from each capsule type at each temperature was not clearly demonstrated at 5, 10, 30 and 60 min.

Acetaminophen release in buffers of different pH values

The release profiles of acetaminophen in buffer media of pH values, namely 1.2, 4.5 and 6.8, are provided in Figures 9–11 consecutively. The release profiles demonstrate the superiority of Capsule 1 to release acetaminophen in different buffer media during the first half-an hour of the test and especially the first 10 min (see Tables 8 and 9 for statistical analysis). The majority (>90%) of Capsule 1 content dissolved in the first 10 min. The slow release of Capsule 2 was evident during the first 10 min in HCl buffer of pH 1.2 and phosphate buffer of pH 6.8 (see Table 10). Capsule 3 release of acetaminophen was independent of the media pHs or contents but was generally slower than Capsule 1.

Table 3. Loss on drying (% LOD) for PVP powder, empty detached and locked capsules and PVP filled capsules of different types of size 0 capsules.

Material	15% RH	45% RH	70% RH	90% RH
% LOD (Free PVP)	7.17	14.49	24.42*	40.56*
% LOD (Open Capsule 1)	9.97	13.89	15.36	27.61
% LOD (Closed Capsule 1)	10.25	13.63	15.56	26.39
% LOD of encapsulated PVP, Capsule 1	7.34	14.37	21.88*	37.89*
% LOD (Open Capsule 2)	2.84	5.87	9.96	23.89
% LOD (Closed Capsule 2)	2.70	5.32	9.78	23.07
% LOD of encapsulated PVP, Capsule 2	5.37	11.30	20.24*	36.07*
% LOD (Open Capsule 3)	3.45	6.16	9.82	23.00
% LOD (Closed Capsule 3)	2.91	5.99	9.15	22.51
% LOD of encapsulated PVP, Capsule 3	5.16	10.80	19.57*	35.47*

*Calculated based on the initial dry weight and the weight gain in the constant climate chamber (Binder KMF 115, Germany) following 96 h of storage at the relevant temperature and humidity.

Summary of the results

The performance indicators of shell weight variation, hygroscopicity, resistance of the shells to stress under 0% moisture, powder leaking, initial disintegration and dissolution are tabulated in a score system (Table 11).

As such the highest score was for Capsule 3 as it scored 25 out of 30 in the performed tests, followed by Capsule 1 with the lowest score achieved by Capsule 2.

Discussion

Shell weight variability may affect the capsule rejection rates from some encapsulating machines[3]. While the variability in the

Figure 3. Fragments of dried Capsule 1 following the free fall of 300 g weight over 30 cm height.

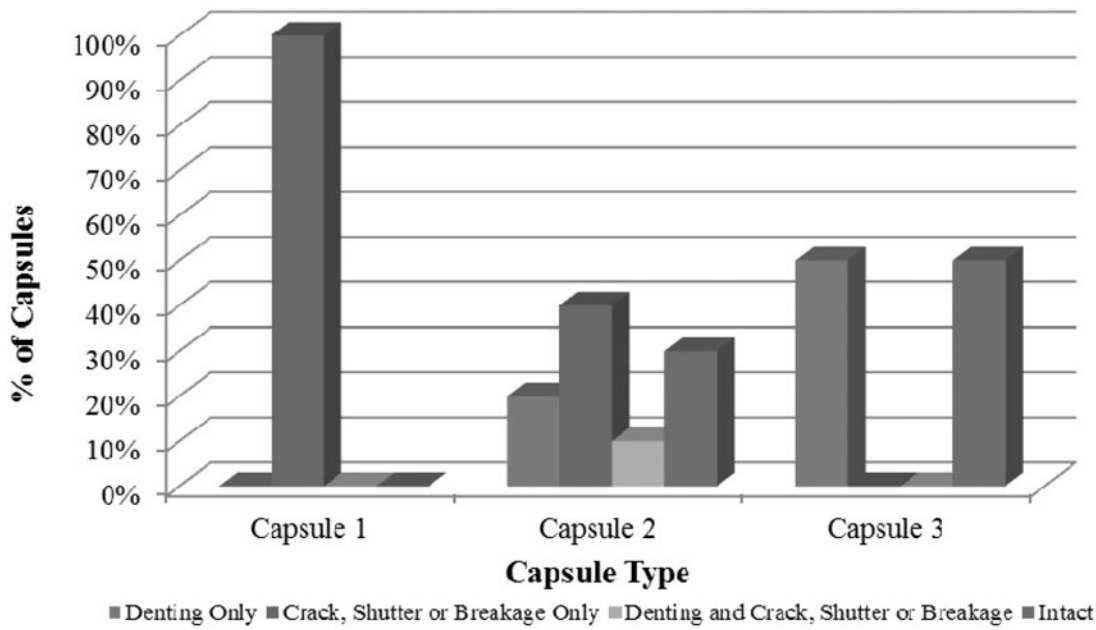

Figure 2. Dented, cracked and/or intact capsules following the free fall of 300 g from a height of 30 cm over the three types of size 0 dried capsules ($n = 10$).

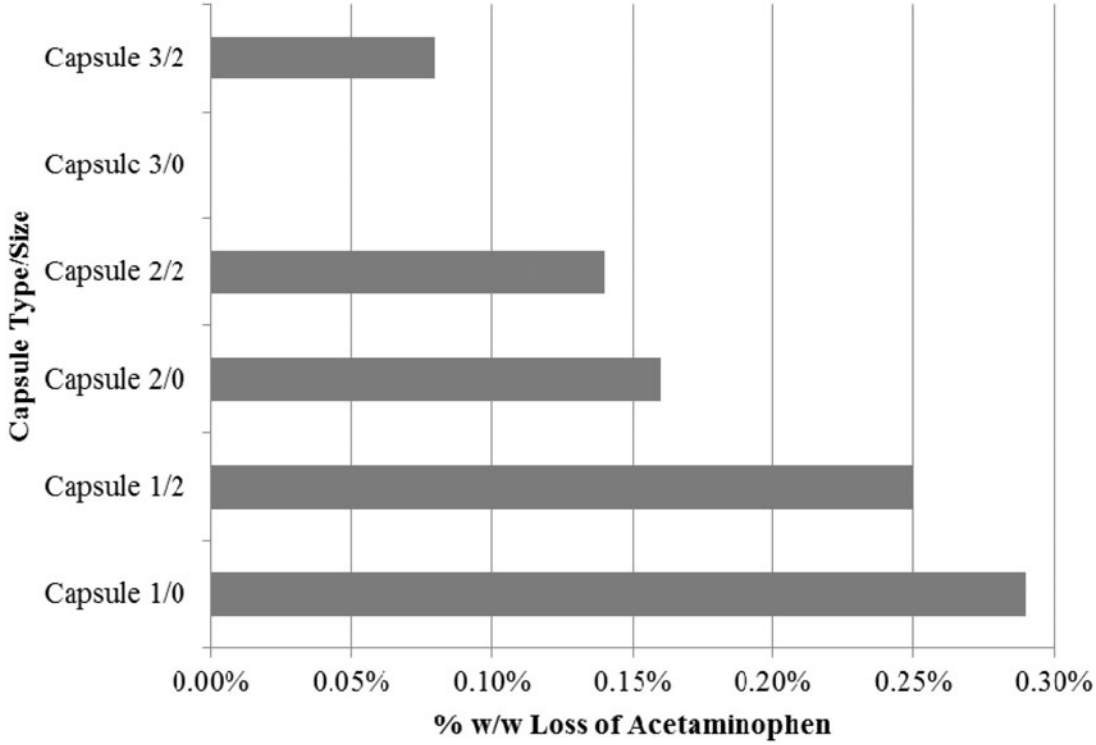

Figure 4. Leaking results from 10 filled capsules shells of different types and sizes after subjecting them to 3000 rpm in a friabilator.

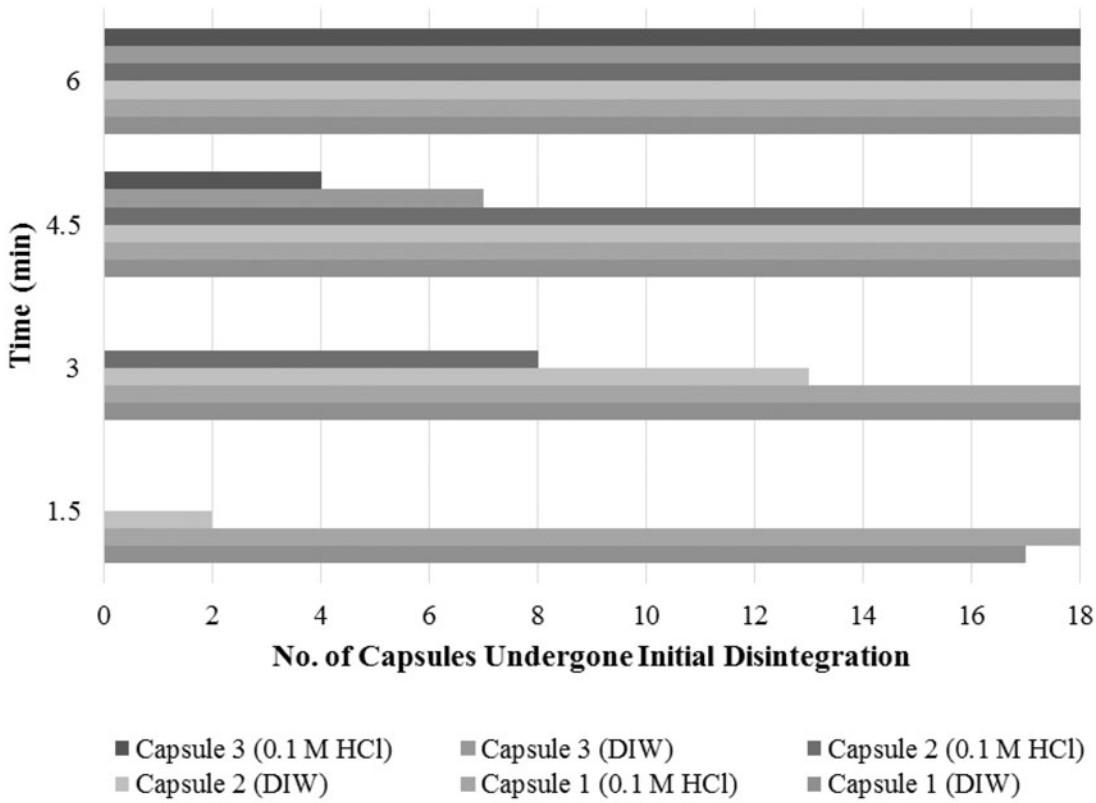

Figure 5. The effect of capsule composition on the number of capsules that have undergone initial disintegration in DIW or 0.1 M HCl at 1.5, 3.0, 4.5 and 6.0 min.

capsule shells weight was highest with Capsule 3, all capsules types and sizes showed RSD of less than 3.5%. USP requirement for the uniformity of dosage units is RSD of 10 individual capsule contents do not exceed 6%. Considering the weights of the empty shells vary from approximately 60 to 100 mg for sizes 2 and 0 capsules, respectively and can accommodate (with manual filling) an amount of 125 and 250 mg of acetaminophen, respectively, the amount of filled drug makes more than two-third of the total filled

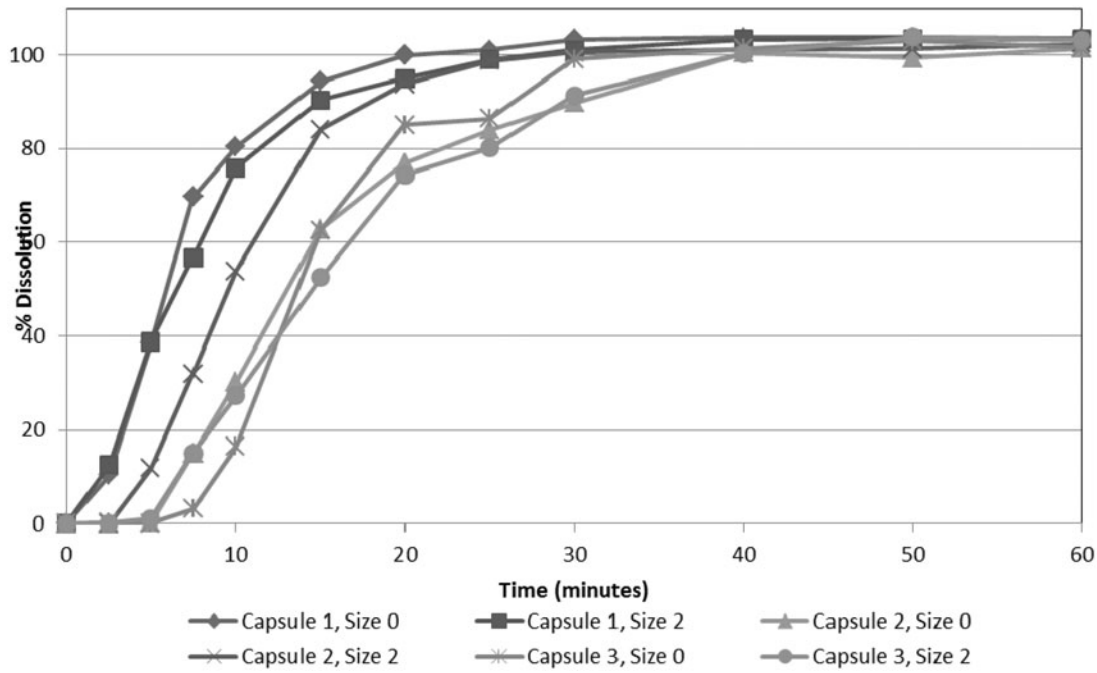

Figure 6. Dissolution profile of acetaminophen from the different types and sizes of capsules in DIW at 32 °C (pH 6.1, $n = 6$).

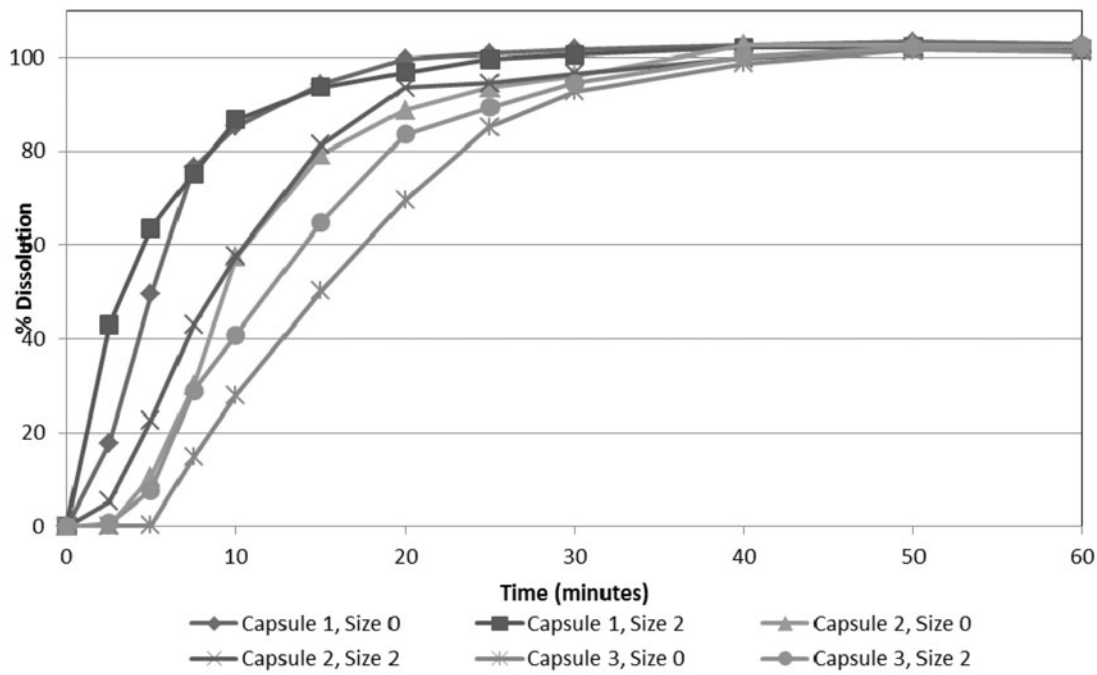

Figure 7. Dissolution profile of acetaminophen from the different types and sizes of capsules in DIW at 37 °C (pH 6.1, $n = 6$).

capsule weight and therefore contributes to a larger extent to the final variability of the filled capsule weights.

The results from varying humidity indicate that take up and the loss of moisture is affecting all types of capsules with relatively lower moisture content of Capsules 2 and 3 compared to Capsule 1. While different capsules may slow down the absorption of moisture by lowering permeation to water vapor, they all failed to protect the encapsulated hygroscopic material under high relative humidity and therefore contradicts the suggestion that capsule made from HPMC are ideally suited for water unstable formulations[2].

Under low moisture content Capsule 1 behaved badly under the applied stress. The entire capsules used in the test fragmented. It is well documented that hard gelatin capsule normally contains approximately 13–16% at relative humidity of about 40–60%. The water content of the capsule is essential for the capsule flexibility. Therefore, if the moisture content of gelatin capsule drops below certain level, problems are expected during filling and handling of the capsules. On the other hand, capsules made solely of HPMC showed the greatest flexibility, where none of the capsule showed any crack following the application of stress, while the presence of the gelling gent carrageenan seems to reduce such flexibility.

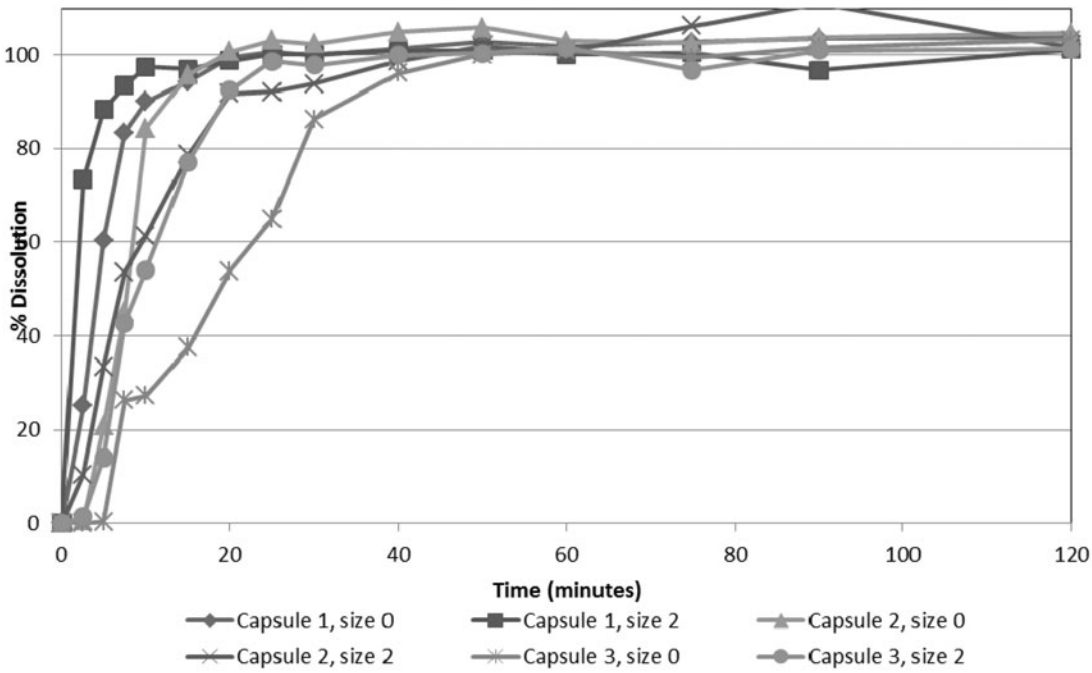

Figure 8. Dissolution profile of acetaminophen from the different types and sizes of capsules in DIW at 42 °C (pH 6.1, $n = 6$).

Table 4. Average % release of acetaminophen from different types and sizes of capsules in DIW kept at 32, 37 and 42 °C.

Temperature	Time (min)	Capsule 1, Size 0	Capsule 1, Size 2	Capsule 2, Size 0	Capsule 2, Size 2	Capsule 3, Size 0	Capsule 3, Size 2
32 °C	5	38.4	38.8	0.2	11.8	0.1	1.1
	10	80.3	75.9	30.3	53.8	16.5	27.4
	30	103.3	101.0	89.7	100.5	99.1	91.3
	60	103.5	103.3	101.4	102.4	101.5	103.1
37 °C	5	49.4	63.5	10.5	22.7	0.2	7.6
	10	85.2	86.6	57.3	57.6	28	40.7
	30	101.6	100.5	96.0	96.5	92.7	94.5
	60	102.7	101.7	102.2	101.5	101.2	102.3
42 °C	5	60.6	88.3	20.8	33.5	0.4	14.2
	10	90.0	97.3	84.4	61.4	27.3	54.1
	30	99.8	100.0	102.3	93.8	86.2	97.8
	60	101.8	100.1	102.9	100.6	100.9	101.4

Table 5. Statistical comparison of acetaminophen release (%) from different types and sizes of capsules in DIW kept at 32, 37 and 42 °C.

Time (min)	p Value (32 °C)	p Value (37 °C)	p Value (42 °C)
5	<0.001	<0.001	<0.001
10	<0.001	<0.001	<0.001
30	<0.001	0.0013	<0.001
60	0.162	0.112	0.058

Because gelatin and HPMC are quite different with respect to their chemical and physical properties and because water acts as a plasticizer for gelatin, such anti-stress response was expected. In a similar study conducted by using Capsugel tube, consisting of 100 g load dropping from a height of 8 cm on 50 closed capsules, it was found that at lower humidity gelatin capsules were brittle in comparison to the more flexible capsule shells made of HPMC material without a gelling gent[3].

Capsules are expected to undergo some kind of stress during coating, blister packaging, transport or during patient handling. There was no visible powder leaking in the friabilator drum or on the surfaces of capsule shells following their tumble in a rotating drum. Weight difference on the other hand before and after the test was small (i.e. <0.3% w/w), but highest for Capsule 1. In a trial of blistering and carding evaluation of HPMC capsules (Vcaps® Plus), all carded blisters showed no powder leakage[3]. In the same study, an experiment mimicking transportation showed Quali-V® capsule to leak at a rate of 6% around the joint of capsule body and cap, a result that was not supported by our study.

The disintegration results show that although the capsules made of gelatin have the fastest initial disintegration time compared to other tested capsule types, the difference is not expected to have significant effect on the bioavailability of encapsulated drug. Studies comparing gelatin capsules to HPMC capsule containing carrageenan as gelling agent did not find any significant difference in the mean disintegration time whether in fasted or fed subjects[13,14]. Also, in a study of different shell materials for their *in vitro* dissolution while applying stress simulating gastric motility, it was found that drug release from HPMC capsules was very well comparable to HGC[15].

DIW was used as the dissolution medium in order to study the drug release without the presence of salts since their concentration and type have been implicated in retarding drug dissolution from

Table 6. Statistical comparison of the effect of temperature (32, 37 and 42 °C) on the % release of acetaminophen from different capsule shells.

Time (min)	*p* Value (Capsule 1, size 0)	*p* Value (Capsule 1, size 2)	*p* Value (Capsule 2, size 0)	*p* Value (Capsule 2, size 2)	*p* Value (Capsule 3, size 0)	*p* Value (Capsule 3, size 2)
5	<0.001	<0.001	0.243	0.080	0.298	<0.001
10	0.103	<0.001	<0.001	0.837	0.0657	0.046
30	0.254	0.925	0.003	0.025	0.0871	0.153
60	0.359	0.132	0.264	0.590	0.786	0.479

Table 7. Statistical comparison between Capsule 2 and Capsule 3 of size 2 for the release of acetaminophen at different temperature (32, 37 and 42 °C).

Time (min)	*p* Value (32 °C)	*p* Value (37 °C)	*p* Value (42 °C)
5	0.192	0.033	0.029
10	0.078	0.042	0.571
30	0.09	0.326	0.121
60	0.13	0.452	0.550

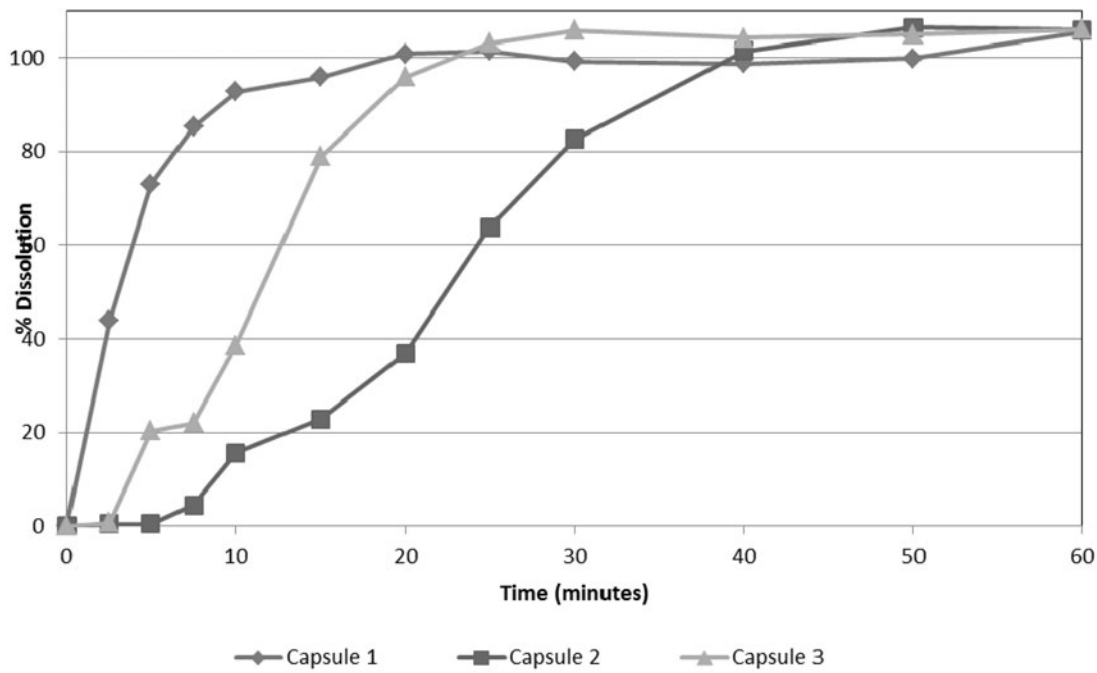

Figure 9. Dissolution profiles of acetaminophen from the different types of size 2 capsules in HCl buffer medium (pH 1.2, $n = 6$) at 37 °C.

certain types of capsules. Moreover, since gelatin as a material dissolves faster at increasing temperature while the opposite is true for HPMC because the later dissolution is exothermic, it was of interest to study the effect of temperature on acetaminophen release from the studied capsules at different temperatures. According to the obtained results, acetaminophen dissolution improved from Capsule 1 as temperature increased from 32 to 42 °C through 37 °C, but that was not the case with Capsules 2 and 3. This agrees with a study recommending that gelatin capsules are better administered with a warm drink whereas HPMC capsules could be given with cold or warm drinks[16]. When comparing Capsules 2 and 3 of size 2 at different temperature points, there is evidence showing that with Capsule 3 a lag time exists before a burst of dissolved acetaminophen is detected which may be attributed to the hydration time for HPMC. On the other hand, it seems that in the presence of carrageenan and the absence of potassium ions in the solution, the wetting of HPMC in Capsule 2 is improved. The effect of capsule size on acetaminophen was not noticeable and this agrees with a study finding that rupture time of hypromellose capsules was dependent on both the medium and the grade of the capsule, and was independent of capsule size[17].

In HCl buffer of pH 1.2 and phosphate buffer of pH 6.8, the results of dissolution agree with the finding of a study conducted by Sherry Ku et al., comparing carrageenan containing HMPC to HPMC capsules with no gelling agent[8]. The potassium containing buffer solution (phosphate buffer) and the acidic buffer medium of pH 1.2 appeared to give Capsule 3 certain advantages over Capsule 2 in the first 10–30 min, while in acetate buffer the advantage is lost to Capsule 2 at 5 min. The later result can be attributed to the absence of potassium cations in the acetate buffer, while we propose that carrageenan in such case aids the hydration of Capsule 2 even though the mean difference is small (2.5%). HPMC of different grades have been used as gelling agents to modify the release of the from certain dosage forms[18–21]. The hydration of Capsule 3 may be improved by the

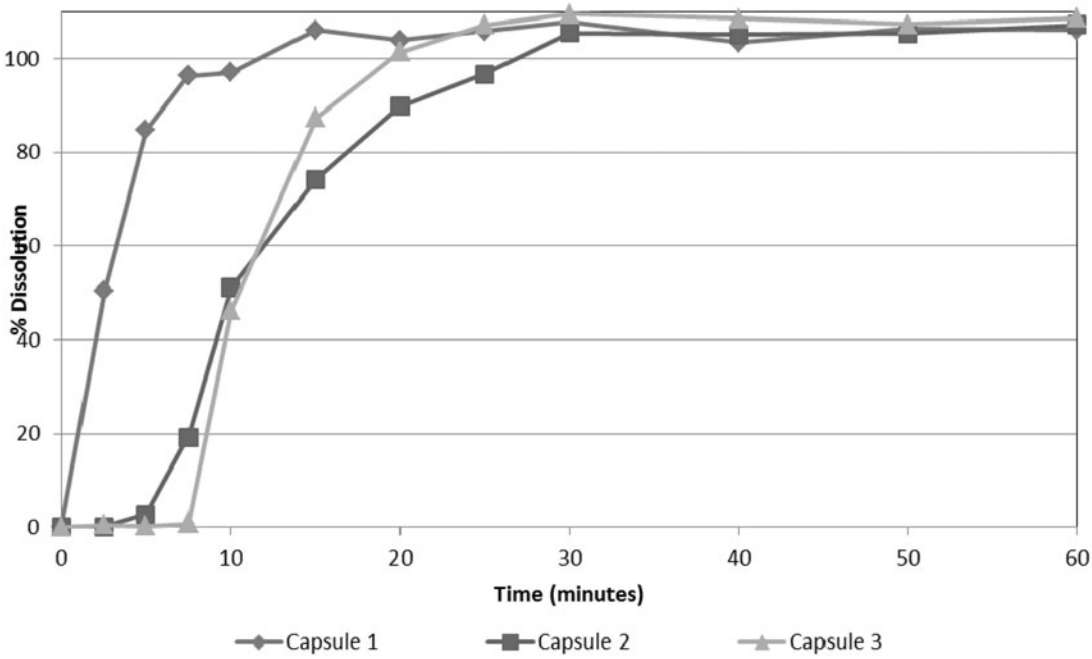

Figure 10. Dissolution profiles of acetaminophen from the different types and sizes of capsules in acetate buffer (pH 4.5, $n = 6$) at 37 °C.

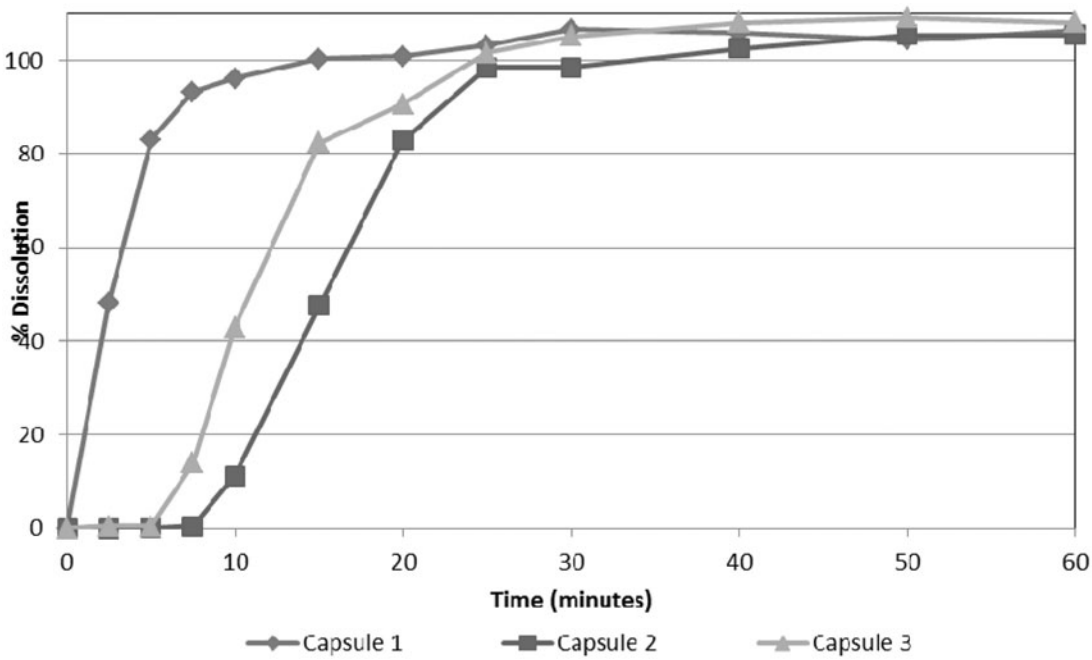

Figure 11. Dissolution profiles of acetaminophen from the different types and sizes of capsules in phosphate buffer (pH 6.8, $n = 6$) at 37 °C.

incorporation of hydroxypropyl starch with HPMC in the casting of hard shells which improves the shell-wetting property[22].

The effect of pH on acetaminophen release from Capsule 2 is evident at 5 min ($p = 0.00749$) and 10 min ($p < 0.001$). Potassium ions have been implicated previously in retarding the dissolution of drugs from HPMC capsule containing carrageenan, because potassium is effective in inducing gelation and enhancing gel strength of carrageenan (Kappa type). Therefore, a suggestion was put forward to have the type of dissolution/disintegration medium used for in *in vitro* testing be capsule type dependent[23]. In acidic pH of 1.2 hydrolysis of carrageenan polymer occurs, resulting in loss of viscosity and gelling capability which does not explain why the dissolution of acetaminophen is rather retarded. Release of acetaminophen from Capsule 1 was superior to Capsules 2 and 3 in the first 10 min which corresponds well to its *in vitro* disintegration supremacy. Studies however have shown that such differences do not result in major differences in real practice[13,14,24].

Although Capsule 3 had the highest overall score in the performance indicators tested, this does not take into account the impact of each test in real practice since the top score for any single performance test is equal (i.e. three points). Also, not all types of tests were carried out. For example, Capsule 3 showed some trouble being handled when in dry conditions indicating the presence of surface charges, but such performance was not evaluated because no clear measures were available to the authors

Table 8. Average % release of acetaminophen from different types of capsules of size 2 in different buffer media of pH values of 1.2, 4.5 and 6.8.

pH	Time (min)	Capsule 1, size 2	Capsule 2, size 2	Capsule 3, size 2
1.2	5	73.0	0.5	20.3
	10	92.6	15.6	38.6
	30	99.2	82.5	105.7
	60	105.3	105.9	105.9
4.5	5	84.7	2.8	0.3
	10	99.6	51.0	46.2
	30	107.8	105.5	109.5
	60	106.1	107.1	108.6
6.8	5	83.0	0.1	0.6
	10	96.2	11.3	43.0
	30	106.6	98.6	105.2
	60	106.5	105.5	108.1

Table 9. Statistical comparison of acetaminophen release from different types of size 2 capsules in different buffer media at 37 °C.

Time (min)	*p* Value (HCl buffer, pH 1.2)	*p* Value (acetate buffer, pH 4.5)	*p* Value (phosphate buffer, pH 6.8)
5	<0.001**	<0.001**,++	<0.001**,*+
10	<0.001**,*+	<0.001**	<0.001**,*+
30	0.109	0.119	0.006*,*+
60	0.893	0.456	0.496

*Acetaminphen release from Capsule 1 is significantly faster than from Capsule 2.
**Acetaminphen release from Capsule 1 is significantly faster than from Capsules 2 and 3.
++Acetaminphen release from Capsule 2 is significantly faster than from Capsule 3.
*+Acetaminphen release from Capsule 3 is significantly faster than from Capsule 2.

Table 10. Statistical comparison of media pHs on the release of acetaminophen release from each type of capsules of 2 at 37 °C.

Time (min)	*p* Value (5 min)	*p* Value (10 min)	*p* Value (30 min)	*p* Value (60 min)
Capsule 1	0.227	0.390	0.411	0.840
Capsule 2	0.007*,+,*+	<0.001*,+,*+	0.123	0.523
Capsule 3	0.105	0.585	0.499	0.566

*Acetaminphen release from Capsule 2 at pH 4.5 is faster than from pH 1.2.
*+Acetaminphen release from Capsule 2 at pH 4.5 is faster than from pH 6.8.
+Acetaminphen release from Capsule 2 at pH 1.2 is faster than from pH 6.8.

at the time. The presence of charges on the capsule shells could in fact have an impact on their rectification and filling operations.

Conclusion

Unlike a previous study implicating Capsule 2 in powder leakage, no clear evidence was found in our study. When investigating the impact of water on capsule flexibility, it was found that gelatin shell flexibility is highly dependent on their moisture content unlike capsules made of HPMC only. The pH and the dissolution medium constituents appear to have significant effect on the dissolution from capsules made of HPMC with carrageenan and

Table 11. Summary of the performance indicator for different types of capsules using a score system.

Performance indicator	Capsule 1	Capsule 2	Capsule 3
Shell weight variation	+++	+++	++
Effect of humidity on the shells (% LOD)	+	++	++
Protection of hygroscopic encapsulated material under high relative humidity	+	++	++
Resistance to stress under 0% moisture	+	++	+++
Powder leaking	++	++	+++
Initial disintegration time	+++	++	++
Sensitivity to dissolution medium temperature (32–42 °C)	++	+++	+++
Sensitivity to dissolution medium pH	+++	+	+++
Sensitivity to dissolution medium contents	+++	+	+++
General speed of dissolution	+++	++	++
Total points	22	20	25

therefore implicating the gelling agent used despite its presence in small proportion. The *in vitro* dissolution of acetaminophen and the initial disintegration of hard capsules indicate the superiority of classical gelatin capsules type. The main disadvantage of capsules made of HPMC with the gelling agent carrageenan over gelatin capsules is the retardation of drug release with potassium ions in the dissolving medium while those made of HPMC lack behind in the speed of the shell hydration, which may provide a window for improvement if a wetting material such as hydroxypropyl starch is used along with HPMC. The differences that were observed in the dissolution of acetaminophen from all types of capsules are mainly in the first 10–30 min and disappear by one hour which altogether unlikely to have significant effect in real practice. HPMC pharmaceutical-based capsule shells may therefore offer attractive alternative to the classical gelatin capsules for new lines of pharmaceutical drug products.

Declaration of interest

The authors report no conflicts of interest.

References

1. Jones BE. Manufacture and properties of two-piece hard capsules. In: Podczeck F, Jones BE, eds. Pharmaceutical capsules. 2nd ed. London: Pharmaceutical Press; 2004:79–88.
2. Ogura T, Furuya Y, Matsuura S. HPMC capsules: an alternative to gelatin. Pharm Tech Eur 1998; Publication No. 0310.
3. Ku MS, Li W, Dulin W, et al. Performance qualification of a new hypromellose capsule: part I. Comparative evaluation of physical, mechanical and processability quality attributes of Vcaps Plus, Quali-V and gelatin capsules. Int J Pharm 2010;386:30–41.
4. Al-Tabakha MM. HPMC capsules: current status and future prospects. J Pharm Pharmaceut Sci 2010;13:428–42.
5. Torrisi BM, Birchall JC, Jones BE, et al. The development of a sensitive methodology to characterise hardshell capsule puncture by dry powder inhaler pins. Int J Pharm 2013;456:545–52.
6. Al-Tabakha MM, Arida AI. A study of the effect of jet milling process with or without pre-treatment on aerosolisation characteristics of FITC-dextran particles. J Med J 2006;40:250–61.
7. Nakate T, Yoshida H, Ohike A, et al. Formulation development of inhalation powders for FK888 using the E-haler to improve the inhalation performance at a high dose, and its absorption in healthy volunteers. Eur J Pharm Biopharm 2005;59:25–33.
8. Ku MS, Lu Q, Li W, Chen Y. Performance qualification of a new hypromellose capsule: part II. Disintegration and dissolution comparison between two types of hypromellose capsules. Int J Pharm 2011;416:16–24.

9. Jones BE, Podczeck F. Letter to the Editor: on the performance qualification of hypromellose capsules. Int J Pharm 2012;434: 503–6.
10. Jones BE, Podczeck F. ''Performance qualification of a new hypromellose capsule. Part I. Comparative evaluation of physical, mechanical and processability quality attributes of Vcaps Plus, Quali-V and gelatincapsules and Part II. Disintegration and dissolution comparison between two types of hypromellosecapsules'' by M. Sherry Ku et al. Int J Pharm 2012;423:589–92.
11. Hard gelatin capsules, USP General Test Chapters on DISINTEGRATION <701>, USP 37-NF 32, The United States Pharmacopeial Convention, Rockville, MD.
12. Immediate Release Dosage forms, Apparatus 1 (Basket Method), USP General Test Chapters on DISSOLUTION <711>, USP 37-NF 32, The United States Pharmacopeial Convention, Rockville, MD.
13. Jones BE, Basit AW, Tuleu C. The disintegration behaviour of capsules in fed subjects: a comparison of hypromellose (carrageenan) capsules and standard gelatin capsules. Int J Pharm 2012; 424:40–3.
14. Tuleu C, Khela MK, Evans DF, et al. A scintigraphic investigation of the disintegration behaviour of capsules in fasting subjects: a comparison of hypromellose capsules containing carrageenan as a gelling agent and standard gelatin capsules. Int J Pharm 2012;423: 589–92.
15. Garbacz G, Cadé D, Benameur H, Weitschies W. Bio-relevant dissolution testing of hard capsules prepared from different shell materials using the dynamic open flow through test apparatus. Eur J Pharm Sci 2014;57:264–72.
16. Chiwele I, Jones BE, Podczeck F. The shell dissolution of various empty hard capsules. Chem Pharm Bull 2000;48:951–6.
17. El-Malah Y, Nazzal S, Bottom CB. Hard gelatin and hypromellose (HPMC) capsules: estimation of rupture time by real-time dissolution spectroscopy. Drug Dev Ind Pharm 2007;33:27–34.
18. Cao QR, Choi JS, Liu Y, et al. A formulation approach for development of HPMC-based sustained release tablets for tolterodine tartrate with a low release variation. Drug Dev Ind Pharm 2013;39:1720–30.
19. Rogers TL, Wallick D. Reviewing the use of ethylcellulose, methylcellulose and hypromellose in microencapsulation. Part 3: applications for microcapsules. Drug Dev Ind Pharm 2012;38: 521–39.
20. Rogers TL, Wallick D. Reviewing the use of ethylcellulose, methylcellulose and hypromellose in microencapsulation. Part 1: materials used to formulate microcapsules. Drug Dev Ind Pharm 2012;38:129–57.
21. Rogers TL, Wallick D. Reviewing the use of ethylcellulose, methylcellulose and hypromellose in microencapsulation. Part 2: techniques used to make microcapsules. Drug Dev Ind Pharm 2011; 37:1259–71.
22. Zhang L, Wang Y, Liu H, et al. Developing hydroxypropyl methylcellulose/hydroxypropyl starch blends for use as capsule materials. Carbohydr Polym 2013;98:73–9.
23. Donauer N, Löbenberg R. Historical perspective: a mini review of scientific and pharmacopeial requirements for the disintegration test. Int J Pharm 2007;345:2–8.
24. Ouellet D, Grossmann KF, Limentani G, et al. Effects of particle size, food, and capsule shell composition on the oral bioavailability of dabrafenib, a BRAF inhibitor, in patients with BRAF mutation-positive tumors. J Pharm Sci 2013;102: 3100–9.