Performances of New Generation of Delayed Release Capsules

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ABSTRACT

Objective: The purpose of this study was to verify the claimed acid-resistant properties and other performance indicators for AR Caps (Capsule 5 from CapsCanada) and DRcaps (Capsule 6 from Capsugel) and compare them with the immediate release hydroxypropyl methylcellulose “HPMC” capsules (K-CAPS from CapsCanada).

Methods: Shell weight variability, reaction to different relative humidity conditions, empty shells response to stress under the absence of moisture, powder leaking, disintegration and dissolution properties were assessed.

Results: Shell weight variability was highest among Capsule 4. At 45% RH and 23°C different types of capsules had similar loss on drying (LOD range: 5.23% – 6.68%). In the absence of moisture and following the application of a stress, empty Capsule 4 shells performed the best with the highest percentage of intactness of capsules (80%) followed by Capsule 6 (50%) and then Capsule 5 (20%). Both disintegration and dissolution test results for Capsule 4 deemed satisfactory for conventional release purposes, but Capsule 5 and 6 do not comply with the USP requirement for delayed-release dosage form. None of the tested capsules have the ability to protect hygroscopic encapsulated material from humid conditions as generally claimed.

Conclusion: While HPMC capsule made for conventional release properties may be fit for that purpose, the new generation of capsules designed to protect the ingredient from the acid environment of stomach have not performed in such a manner as to comply with the USP requirements for disintegration and dissolution of delayed-release dosage form.

Key words: Acid-resistant capsules, AR Caps, DR Caps, K-CAPS, HPMC capsules.

INTRODUCTION

Enteric coated dosage forms are one kind of delayed release products that pass intact through the stomach and into the intestine before dissolving.¹ One justification for the use of enteric coating is to protect the stomach from an irritant drug as is the case with the non-steroidal anti-
inflammatory drugs “NSAIDs” diclofenac sodium and aspirin. Moreover, drugs that are degraded by the acidic pH of the stomach are protected by applying an enteric coat to the dosage form as with the proton pump inhibitor esomeprazole (e.g. Nexium®, AstraZeneca). Enteric coating has been applied to target the intestinal region to provide maximal drug concentration at local site as with the treatment of ulcerative colitis using mesalamine (e.g. Asacol®, Warner Chilcott: now taken over by Actavis). Dietary supplements such as probiotics have been prepared as enteric coated capsules with the aim of fortifying the intestinal tract with a high potency active *Lactobacillus* culture (e.g. Nature’s Way Primadophilus® Reuteri made with enteric-coated Vcaps). Some companies are now applying enteric coating to fish oil capsules (source for omega-3 fatty acids) in order to prevent “fish burps” if the capsule is digested in the stomach. One of such products is the Enteric Coated Omega-3 Fish Oils of Olympian Labs, USA.

To achieve enteric coating, various polymers have been used dissolving at media with pHs 5 to 7 and above while remaining intact at lower pHs. One of the leading brand of polymer coating materials is Eudragit® L and S (Evonik, Germany) which dissolve at the high pH values. Another enteric coating material is cellulose acetate phthalate with solubility above pH 6.2 (e.g. CAP enteric coating material by Eastman, USA and Aquacoat® CPD by FMC BioPolymer, USA). Another enteric coating material is hypromellose phthalate or hydroxypropyl methylcellulose phthalate (HPMCP). This polymer dissolves at pH 5.0 and above depending on the grade used. Capsules coated with HPMCP and filled with nanoparticles for oral delivery of insulin have provided protection to insulin from gastric pH while allowing their delivery in the duodenal region and thereby maintaining insulin bioavailability in diabetic rat model. Hypromellose acetate succinate (AQuAOT Shin-Etsu Chemical Co., Japan) and polyvinyl acetate phthalate (Opadry® Enteric 91 series, Coloron, USA) are designed to dissolve at pH 5.0 and above to produce enteric-release properties.

While all of the described coating polymers can be used in coating pharmaceutical preparations, limitations do exist when it comes to dietary supplements. Materials that can be used for coating has to be from the approved list of food additives in CFR - code of federal regulations title 21 or be generally regarded as safe (GRAS), otherwise pre-marketing review for approval is necessary. This narrows down the list of enteric coating polymers that can be applied to dietary supplements to materials such as shellac, a proprietary coating material from Coloron called Nutrateric® II. Originally organic solvents were used for dissolving the selected polymers, but there is a growing shift towards replacing them with water because of environmental and safety issues and the accompanied increased cost. Orange peel effect is another problem with use of organic solvents resulting from improper adhesion of the film coat onto the smooth surface of gelatin capsules. Replacing organic solvents with water is not devoid of problems; for hard gelatin capsules this means a lengthier and more sensitive process because of solubility of gelatin in water. Whether using organic solvents or aqueous vehicles a pre-coat may be necessary to reduce the subsequent problems.

Capsule shells made of HPMC have been available since three decades and they are gaining increasing popularity for encapsulating both nutraceutical and pharmaceutical formulations due to the cellulosic material being more acceptable than the conventional animal based gelatin. HPMC capsules with enteric coating are prepared in small scale using fluidized bed process and the coated capsule shells do not require sealing step after filling the capsules. There is a report on cross-linked dextran capsules, successfully produced in laboratory scale using conventional capsule production method, that are suitable for providing a colon-specific drug delivery.

A more recent innovation is the introduction of delayed release HPMC capsule shells by Capsugel with their product DRcaps capsules in 2011 and by CapsCanada with their acid resistant product AR Caps® capsules in 2013 (to be available in 2015). DRcaps capsules contain a gelling agent in addition to HPMC and have been advertised for nutraceuticals including probiotics enzymes and herbs. While Capsugel indicated that their capsule product is not meant to be enteric, they documented that it is a digestive resistant or delayed-release capsules as apparent from the capsules proprietary name. So, it is designed to slow down capsule opening after administration. On the other hand CapsCanada declared that their ready-to-use capsules are in fact acid-resistant with the materials being employed for this purpose contain HPMC to HPMCP in a ratio of 4:6 with HPMC. Their innovation lies in that HPMC and HPMCP are mixed together before the formation of the capsules resulting in the enteric-release capsule shells, offering many advantages over conventional enteric coated of the capsules. For the manufacturer of capsule filled formulation this means reduced capital investments, possible reduced manufacturing costs, reduced manufacturing steps, more flexible formulation and enhanced product appeal.

The objective of this study was to independently investigate
the in vitro performances of Capsule 5 and 6 as having delayed-release properties in comparison to the immediate-release Capsule 4 in terms of shell weight variability, hygroscopicity and ability to protect hygroscopic materials, tolerance to stress under the absence of moisture, powder leakage, disintegration and dissolution properties.

**MATERIALS AND METHODS**

**MATERIALS**

Acetaminophen (98%) was purchased from Aldrich, Germany. Transparent DRcaps capsules sample (Capsules 6) of size 0 (Lot No. 90208801) were obtained from Capsugel through CapsCanada. Transparent capsules: AR CAPS (Lot N. 107660-1; Capsules 5) and K-CAPS (Lot No. K1201000056; Capsules 4) of size 0 were generously supplied by CapsCanada. Other chemicals used were of analytical grade. Polyvinylpyrrolidone (PVP) 40,000 (K30) was bought from VWR, UK.

**METHODS**

Empty shells weight variation

100 empty capsules of each type were weighed individually using electronic digital balance (AUX 220, Shimadzu-Japan). The variability was assessed in terms of average and relative standard deviation and inferential analysis was carried out to compare between the capsules.

Hygroscopicity and Stress Testing

Capsules filled with 230-235 mg PVP for size 0 from the three types of capsules were stored at relative humidity of 15%, 45%, 70% and 90% for 4 days using constant climate chamber (Binder KMF 115, Germany) at a constant temperature of 23° C (n=10). PVP was used to assess the ability of the capsules to protect this hygroscopic material from surrounding humidity conditions. Similarly empty detached and locked capsules were stored at the same condition (n = 10) and were used as controls. Samples of free PVP were also stored at the aforementioned conditions. %LOD was used to assess hygroscopicity and was calculated as the weight lost at 105° C divided by the initial weight using Sartorius Moisture Analyzer (Model MA35, Germany). At high relative humidity (i.e. 70 % and 90%) PVP absorbs moisture and becomes gelatinous structure making it difficult to completely dry at the aforementioned drying conditions. The % LOD was calculated for PVP or encapsulated PVP at 70% and 90% based on the dry weight of the PVP and the capsules under the filling conditions, then following the weight gain during the 96 h of storage.

To assess the flexibility and ability of the capsules to tolerate stress in the absence of water, completely dried and locked capsules were subjected to the free fall of 300 g weight over 30 cm height at the base of 250 mL plastic measuring cylinder. Denting and/or capsule crack, shutter or breakage was assessed for each type of size 0 (n = 10 capsules).

Leaking test

10 completely filled capsule bodies of each type with potassium permanganate were subjected to a provoked stress utilizing tablet friabilator equipment. The completely filled capsules were subjected to a total of 1000 rotation at the speed of 25 rpm. The capsules were completely filled with the powder in order to make the fall at each rotation harder and therefore to increase the challenge and also to prevent the sticking of the capsule to the drum’s wall. To prevent the later effect, the inner side of the friabilator drum was lightly coated with mineral oil.

Disintegration

The disintegration protocol followed using the USP general chapter on disintegration <701> for delayed-release (enteric-coated) tablets\(^1\) using the disintegration apparatus PTZ-Auto 02, Pharma Test, Germany. For acidic medium, simulated gastric fluid TS without pepsin enzyme (SGF) of the pH 1.2 was used and disintegration were observed for one h as stipulated in the pharmacopeia. The tested capsules were then transferred to a medium of simulated intestinal fluid TS without pancreatin enzyme (SIF) for one h. The capsules used in the disintegration test were filled with 100 mg potassium permanganate as a model drug since it is readily soluble in water and can be easily detected visually by the formation of pink or purple solutions as it dissolves. This allows the determination of initial leaking/disintegration time more precisely.

Dissolution

Method B of the USP general chapter on dissolution <711> for delayed-release dosage forms was used in conjunction with the apparatus 1 (basket apparatus, DT 820, Erweka, Germany).\(^2\) In acidic medium, 1000 mL of 0.1 N HCl was used for each vessel and the basket rotation was set to 100 rpm. Acetaminophen 250 mg was manually filled in each capsule as a model drug and one filled capsule was placed in each basket for the dissolution test. Once the capsules completed acidic medium testing stage for 2 h, they were immediately shifted to phosphate buffer stage (pH 6.8) for additional 45 min. During the acidic stage 10 mL samples were withdrawn at 5, 10, 15, 20, 30, 45, 60, 75, 90, 105 and 120 min and replaced with a blank medium at the same temperature. During the phosphate buffer stage samples were similarly withdrawn and substituted at 5, 10, 15, 20,
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Statistical analysis
All statistical analysis were carried out using IBM® SPSS® Statistics version 21, a trademark of International Business Machines Corp. For inferential statistical analysis two-sided ANOVA and t-test analysis were used assuming $p < 0.05$. Graph were plotted using Microsoft Excel (Microsoft Office 2010).

RESULTS

Weight Variation of Empty Shells
The averages weights for all capsule types differ significantly from each other ($p < 0.001$). Capsule 4 type had the highest relative standard deviation of 4.21% while Capsule type 5 and 6 had small relative deviations (Table 1). The Capsule 6 type had the lowest weight variation.

Hygroscopicity and Stress Testing
No major differences between empty detached and locked capsules were found (Table 2). Also, apparently none of the capsule shells had the ability to protect the hygroscopic material PVP from surrounding humidity. At ideal storage condition of 23°C and 45% RH empty locked Capsule 4, 5 and 6 had % LODs of 5.52, 6.31 and 6.12 which are close to each other. On the other hand, when the RH was 90% empty Capsule 5 absorbed more moisture (LOD =31.68% for the locked capsules) than the corresponding Capsule 4 (LOD =22.87% for the locked capsules) and 6 (LOD =23.20% for the locked capsules).

After drying each type of capsules at 105° C to a constant weight, empty locked capsules were challenged by the free drop of 300 g weight along 30 cm height. Capsule 4 showed the highest proportion of intactness capsules (80%) followed by Capsule 6 (50%) and finally Capsule 5 (20%), while none of the capsules showed any denting following the test (Figure 1).

Leaking test
The three types of capsules showed no sign of leaking after the 1000 rotations at the speed of 25 rpm. This was found whether by observing for any trace for potassium permanganate outside the capsule and in the drum or by measuring the weight difference of the filled capsules before and after the test.

Disintegration
For Capsule 4 in SGF, the change in the medium color and the rupturing of two of the capsules were evident at 3 and 4 min respectively. At 20 min all of the capsules disintegrated. On the other hand, all capsules disintegrated at about 14 min in SIF (Figure 2).

Capsule 5 type failed the disintegration test for delayed-release product. At about 4 min, the capsules started to show sign of leaking/rupturing as evident from the change in SGF colour. At 15 min one of the capsule showed evidence of rupturing (Figure 3). The number of visibly ruptured capsules and the size of rupture increased with time and by the end of the 1 h test all capsules showed rupturing.

Because all Capsule 5 ruptured by the end of 1 h in SGF, fresh 6 capsules were freshly filled with potassium permanganate for testing in the SIF. At about 2 min it was evident that all capsules started to rupture and this rupture increased quickly with time. At about 7 min the capsules disappeared completely from each of the basket tubes (Figure 4).

With Capsule 6 leaking/rupturing was evident from the first 4 min by the change in the medium color. At the end of the 1 h test, all capsules showed clear rupturing even though not all parts of the capsules passed through the wired mesh (Figure 6).

Dissolution
There was a retarded release of acetaminophen in the first 5 min (Figure 7). The mean dissolution of acetaminophen from Capsule 4 at 45 min was 68.6% (95 CI 57.9% - 79.3%). Capsule 5 released 15.7% (95% CI 13.6% – 17.8%) of acetaminophen in the acid stage. The high variability of the Capsule 5 release of acetaminophen in the buffer stage (Figure 8) is noticeable. Capsules observed after the end of the buffer stage indicated the failure of some capsules to release all of its contents (Figure 9a and b). It seems that in some cases the capsule shells collapse on the encapsulated powder forming resistive barrier around it.

30 and 45 min. Quantitative analysis of acetaminophen was carried out spectrophotometrically at 240 nm.

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Table 1: Shell weights results from 10 empty capsules of different types and sizes.

<table>
<thead>
<tr>
<th>Capsule</th>
<th>Average (g)</th>
<th>Minim. (g)</th>
<th>Max. (g)</th>
<th>% Range of Average</th>
<th>RSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsule 4</td>
<td>0.105273</td>
<td>0.09663</td>
<td>0.11874</td>
<td>91.79-112.79</td>
<td>4.21%</td>
</tr>
<tr>
<td>Capsule 5</td>
<td>0.113608</td>
<td>0.10857</td>
<td>0.12348</td>
<td>95.57-108.69</td>
<td>2.63%</td>
</tr>
<tr>
<td>Capsule 6</td>
<td>0.094907</td>
<td>0.09038</td>
<td>0.10194</td>
<td>95.23-107.41</td>
<td>2.60%</td>
</tr>
</tbody>
</table>

Table 2: Loss on drying (% LOD) for PVP powder, empty detached and locked capsules and PVP filled capsules of different types of size 0 capsules.

<table>
<thead>
<tr>
<th>Material</th>
<th>15% RH</th>
<th>45% RH</th>
<th>70% RH</th>
<th>90% RH</th>
</tr>
</thead>
<tbody>
<tr>
<td>% LOD (Free PVP)</td>
<td>7.17</td>
<td>14.49</td>
<td>24.42*</td>
<td>40.56*</td>
</tr>
<tr>
<td>% LOD (Open Capsule 4)</td>
<td>3.15</td>
<td>5.23</td>
<td>10.23</td>
<td>24.21</td>
</tr>
<tr>
<td>% LOD (Closed Capsule 4)</td>
<td>2.79</td>
<td>5.52</td>
<td>9.68</td>
<td>22.87</td>
</tr>
<tr>
<td>% LOD of Encapsulated PVP, Capsule 4</td>
<td>6.09</td>
<td>10.95</td>
<td>18.53*</td>
<td>34.53*</td>
</tr>
<tr>
<td>% LOD (Open Capsule 5)</td>
<td>4.14</td>
<td>6.68</td>
<td>12.55</td>
<td>32.04</td>
</tr>
<tr>
<td>% LOD (Closed Capsule 5)</td>
<td>3.56</td>
<td>6.31</td>
<td>12.16</td>
<td>31.68</td>
</tr>
<tr>
<td>% LOD of Encapsulated PVP, Capsule 5</td>
<td>6.39</td>
<td>11.46</td>
<td>19.83*</td>
<td>36.40*</td>
</tr>
<tr>
<td>% LOD (Open Capsule 6)</td>
<td>3.93</td>
<td>6.31</td>
<td>10.98</td>
<td>23.59</td>
</tr>
<tr>
<td>% LOD (Closed Capsule 6)</td>
<td>3.22</td>
<td>6.12</td>
<td>10.44</td>
<td>23.20</td>
</tr>
<tr>
<td>% LOD of Encapsulated PVP, Capsule 6</td>
<td>5.20</td>
<td>11.58</td>
<td>20.12*</td>
<td>35.36*</td>
</tr>
</tbody>
</table>

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.

Figure 1: Dented, cracked and/or intact capsules following the free fall of 300 g from a height of 30 cm over the dried three types of size 0 dried capsules (n=10).

Figure 2: The state of disintegration basket at 14 min when Capsule 4 type was tested for disintegration in SIF.

Figure 3: One of the Capsule type 5 started to show clear rupture at 15 min in SGF.
Figure 4: The disintegration apparatus basket at 7 min showing the absence of any of the Capsule.

Figure 5: The disintegration apparatus basket at 60 min showing the remains of Capsule 6 type on the mesh when tested in SGF.

Figure 6: The disintegration apparatus basket at 60 min showing the remains of Capsule 6 type on the mesh when tested in SIF.

Figure 7: Dissolution of acetaminophen from Capsule 4 in acid stage over time as mean percent ± standard deviation.

Figure 8: Dissolution of acetaminophen from Capsule 5 in the acid and then buffer stage over time as mean percent ± standard deviation.
and preventing the free dissolution of acetaminophen. At 45 min a mean of 46.8% of acetaminophen was released in the SIF (95% CI 31.2% - 62.4%). By the end of the acid stage Capsule 6 released 19.6% of acetaminophen (95% CI 12.9% - 26.3%). As with Capsule 5, Capsule 6 showed (Figure 10) high variability in the buffer stage and at 45 min a mean of 34.2% of acetaminophen was released (95% CI 13.7% - 54.7%).

DISCUSSION

The lower the variability of the capsule shells weights the lower the expected rejection rate from encapsulating machines. In a similar way, the more lightweight the capsule shells, the less is their expected contribution to the rejection rate. In capsule filling machines, typically plugs are formed from the formulation before filling into capsule bodies. These filled and locked capsules are then automatically sorted, so that over or under weight capsules are rejected. Therefore the shell weight variability does influence the rejection rate. Many factors affect shell weight variability for the capsules of the same size and these includes shell composition, shell thickness and other production process variability. The high variability of Capsule 4 could contribute to a higher rejection rate when filled with formulations of low weights.

One of the advantages a capsule may have is its ability to protect its content from surrounding atmosphere, particularly in relation to humidity when a hygroscopic material is encapsulated. None of the tested capsules had the ability to protect encapsulated PVP powder from absorbing or losing moisture when stored at different relative humidity conditions. The initially low moisture content of the tested capsules in comparison to well-known high moisture content of gelatin capsules, does not warrant their use for encapsulating hygroscopic
While the normal presence of moisture is important for shell functionality and flexibility, it is not the only determinant factor. Other shell composition plays a role in this regard. Ku et al. found that capsules made of HPMC are less affected by the low level of moisture and that they maintain their elasticity and resist breakage unlike capsules made of gelatin. The complete absence of moisture in Capsule made of HPMC only resulted in only 20% of the shell being cracked. On the other hand capsule made of HPMC together with HPMCP 80% of cracked capsules.

Capsules leaking can result in companies abandoning the use of certain types of capsules. In the three tested capsule types none showed any sign of leakage of the filled powder. Making the test more challenging by increasing the number of rotation to 3000 rounds rather than 1000 may differentiate between the different capsules for future experiments.

According to the USP test for disintegration of delayed-release (enteric coated) tablets, none of the units show any sign of disintegration, cracking or softening after one hour of testing in SGF. For immediate release capsules this is usually between 15 to 30 min. While the claimed immediate release capsules (Capsule 4) completely disintegrated in an acceptable time, neither Capsule 5 nor Capsule 6 demonstrated the capability of protecting the encapsulated drug from the gastric acidic environment. The fact that SGF color changed just few min from the start of disintegration test without noticeable capsule rupture also indicates the need for enteric band around the edge of the caps sealing them to capsule bodies, therefore adding complexity to that capsule filling process.

The monograph for the dissolution of acetaminophen from capsules specify Q as not less than 75% of the labeled amount dissolves in 45 min. It could be argued that whether the encapsulated acetaminophen passes the USP dissolution test when filled in Capsule 4 because of different specified medium, basket rotation speed and/ or formulation used since the manufacturing company claims that their K-caps is USP/EP dissolution compliant. The first 5 min of acetaminophen release from Capsule 4 was slow and this can be attributed to the time required for the hydration of HPMC shells and the ingress of medium through the shell. Capsule 5 and 6 showed signs of leaking but without any noticeable rupture initially which may indicate the need for an enteric band to seal the cap onto the body of the capsules if these capsules are to function properly. These capsules clearly demonstrated the dissolution of more than 10% acetaminophen after two h in acid stage. A study by Garbacz et al. indicated that a release of 8.6% of caffeine from DR Caps in HCl medium at 40 min but no data were given beyond that time to assess the functionality of Capsule 6. The level A in the USP for the dissolution of the drug in the acidic stage stipulate that no individual unit should have dissolved drug exceeding 10%, while in our test all units exceeded that standard value. This is giving evidence of the failure of the capsules to protect the drug in the acidic stage. In the buffer stage USP stipulate for level B, that from each unit Q + 5% of the drug should have dissolved. This means that at least 80% of the drug should have dissolved at 45 min in the buffer stage. None of the individual units for Capsule 5 or Capsule 6 reached such value. Therefore, the capsules behaved more like extended-release rather than delayed-release even with the improved dissolution in the buffer stage. The high variability of drug release in the buffer stage for capsule 5 and 6 is attributed to the failure of some capsules to release the acetaminophen content. The shells appear to soften and collapse over the powder creating a viscous barrier for the diffusion of acetaminophen. (Figures 8-10)

The variability in the drug release in the buffer stage from Capsule 5 and Capsule 6 may prevent their use even for extended-release purposes. However, the correlation between these obtained results and in vivo experiments are yet to be established independently. In an article published at their website, Capsugel used in vivo scintigraphic study to document that their DR Caps began release in a mean time of 52 min after ingestion, that is when leaving the stomach and completely released the ingredients in a mean time of 72 min after ingestion. Capsugel advertise their capsule shells (Capsule 6) for dietary supplement ingredients protection from acidic environment. This reduces the burden on the manufacturer to conduct extensive bioavailability studies. On the other hand, Capsule 5 manufacturing company claims that their empty capsules are suitable for enteric release and ideal for a wide range of pharmaceutical applications. Using these capsules (whether Capsule 5 or 6) for PAIs warrants mandatory bioavailability studies.

CONCLUSION

Shell weight variability may affect filled capsules rejection rate and has to be taken into account when choosing a particular brand of capsules. Unlike the marketing claim,
none of the tested capsules are able to protect hygroscopic and moisture sensitive materials from surrounding humidity. While capsules made of HPMC and designed for conventional drug release may perform accordingly, the other designed enteric or acid-resistant capsules are yet to prove their fit for the purpose.

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CONFLICT OF INTEREST

The authors report no declarations of interest.

REFERENCES