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Investigation of factors effected dissolution variations of hydroxypropyl methylcellulose capsule

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The objective of this study was to identify if the root cause of dissolution was from the HPMC shell differences and/or the insufficient robustness of dissolution method. Studying the dissolution behavior of 40 and 150 mg granules (with and without shells), followed by capsule dissolution with switched shells, the sink condition can be verified by the extent of granule dissolutions with switch shells. The effect of the apparatus, agitation speed and medium deaeration on dissolution variations was also studied. The surface dissolution behavior for shells with different moisture levels was probed in an aqueous medium utilizing an ActiPix SDI300 surface dissolution imaging system. The inter-vessel variability of 150 mg granules was low, while for 40 mg granules, the inter-vessel variability of the 40 mg granules was slightly higher. Basket method exhibited much slower dissolution and higher percent relative standard deviation (RSD) at early sampling-points when comparing the paddle apparatus. Degassed medium reduced the capsule-to-capsule variations at early sampling-points and improved the dissolution rate. The 40 mg granule with the 150 mg capsule shell had an average dissolution release of 88% at 20 min with 7.4% RSD for n = 6 samples. It was slower and more variable as compared to 96% release with 2.8% RSD from the original 40 mg capsules (40 mg granule in 40 mg capsule shell). Capsules with un-dried shells exhibited a slower and variable dissolution at early sampling-points, whereas a faster and consistent dissolution was obtained for capsules with dried shells. The root cause of the undesirable dissolution variations at early sampling-points and the intermittent failure for stage 1 specification was the higher moisture content in the HPMC shells of the high strength capsules. Insufficient hydrodynamics in dissolution vessels contributed to the intermittent low drug release, higher agitation speed and medium deaeration can improve dissolution rate and reduce dissolution variations for HPMC shells.

Key words: Hypromellose capsule, dissolution, hydrodynamics, medium deaeration.

INTRODUCTION

Hydroxypropyl methylcellulose (HPMC), now commonly known as hypromellose, is produced by synthetic modification of the naturally occurring polymer cellulose and is considered safe for normal consumption in humans. Due to its vegetable source, proof of cross-linking and inherent lower equilibrium moisture content as compared to the gelatin counterpart, the HPMC capsule shells are often used to improve drug product stability (for moisture moisture sensitive drug) and become the second only to gelatin capsules in terms of frequency of usage in pharmaceutical development.

However, the in vitro dissolution method development for HPMC capsules is of challenge as the dissolution performance of HPMC capsules varies from vendor to vendor and from process to process. For example, HPMC capsules made with gellan gum as a gelling aid or

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carrageenan as the gelling system have different dissolution rates in the physiological pH range of pH 1.2 to 6.8 (Moawia, 2010). Study has proved that the acid conditions and the presence of potassium cations hindered the opening of $HPMC_{gell}$ (Gellan gum as gelling aid) capsules due to the nature of the gel network that was formed in the presence of cations (Ewart et al., 2004). $HPMC_{carr}$ (carrageenan as gelling aid) solubility on the other hand was independent of pH (Robert et al., 2001). In pH 6.8 buffer, $HPMC_{carr}$ capsule showed significant difference in dissolution release when a potassium phosphate buffer was replaced by a sodium phosphate buffer; however, this effect was absent in the VCaps Plus® HPMC shells which did not use a gelling promoter (Sherry et al., 2010). The HPMC capsule dissolution was prolonged when stored under the high heat and high humidity (Irene et al., 2000). However, this observation was not confirmed in model drugs filled in Quali-V® HPMC capsules stored at 40°C/75% relative humidity for six month (Nagata, 2002).

The *in vitro-in vivo* correlation of HPMC capsule dissolution was also studied and reported in literatures. The HPMC shells made both with and without a gelling agent showed comparable *in vivo* performances in spite of the rupture time differences, demonstrating the rapid dissolution in animal and human pharmacokinetics studies (Sherry et al., 2010). The *in vivo* opening times for HPMC shells were longer than their gelatin counterparts but the differences in the regulatory important pharmacokinetics metrics of maximum observed concentration (Cmax) and area under the curve (AUC) were not significant for a Biopharmaceutical Classification System (BCS) class II compound (Irene et al., 2000). The composition of the dissolution media has been reported to influence the disintegration time of the HPMC capsules; however, the rate of disintegration may not correlate with the drug product *in vivo* bioavailability (Tuleu et al., 2007; El-Malah et al., 2007).

To date, the inconsistent dissolution performance of the HPMC capsules and a lack of understanding of the correlation between the shell properties and shell disintegration/dissolution remain challenges for dissolution scientists. It is advantageous to develop a systematic approach in solving dissolution variations for formulations with HPMC shells and share the knowledge among formulators and dissolution scientists. A highly variable dissolution may cause product to fail quality control (QC) specification and requires stage 2 or 3 test which may not be operational effective. It is desirable that a dissolution method is discriminating yet sufficiently rugged and reproducible for the day-to-day operation (Michael, 2011).

EXPERIMENTAL

Reagents and materials

The low density lipoprotein (LDL) and high density lipoprotein (HDL) capsules under the investigation were made internally by Hekelishi the chemical limited company (Luzhou City, Sichuan province). Drug substance reference standard was qualified and provided by the reference standard material group in Hekelishi the chemical limited company. A concentrated hydrochloride acid was purchased from Urumqi chemical reagent factory (China). Ultra-pure water (Urumqi chemical reagent factory, China) was used for the dissolution medium throughout the analysis. The HPMC capsule shells (Size 1, Lot E0905048N) used in the capsule formulations were purchased from Qualicap®, Inc. 0.01 N HCl was prepared by dissolving 0.85 ml of concentrated hydrochloride acid into each liter of the Mili-Q purified deionized water. Degassed 0.01 N HCl media was prepared by purging the medium with helium.

Equipment

A Leap UV-Fiber Optical OPT-DISS™ Dissolution testing system with a Distek Evolution 6100 dissolution bath was used throughout the study. The dissolution samples were analyzed by using UV detection at 258 nm with a background subtraction wavelength of 300 nm. Six 1-mm and six 10-mm arch™ probes were used aimed at achieving the optimal UV response for *in-situ* dissolution measurement for the HDL and LDL capsules, respectively.

Dissolution testing

The validated dissolution method employed the USP apparatus 2 (paddle) at 75 rpm and1000-ml of 0.01 N HCl as the dissolution medium operated at 37 ± 0.5°C. The *in-situ* dissolution measurement was performed in six vessels simultaneously in 1 min interval by UV-fiber optical probes.

Moisture content determination

A Mettler-Toledo Halogen Moisture Analyzer HR83 was used to determine the moisture content in capsule shells via thermogravimetric measurement. The emptied shells were weighed and heated at 120°C with an infrared radiator (halogen lamp). The moisture content was automatically calculated based on the difference in weight. Eight empty shells were used for each measurement and duplicate measurements were made for each type of the shells.

Surface dissolution characterization

An ActiPix SDI 300 UV area imaging system was used to enable the quantitative imaging of surface erosion and dissolution of HPMC capsule shell in dissolution media. Samples were prepared by pressing a parafilm into a sample cup to form a surface on which the sample can be pressed, followed by cutting a 2.0-mm diameter disc from a shell and pressed onto the parafilm surface in the sample press using 50 cNm torque. After establishing background absorbance at all pixels in the imaged area using appropriate dissolution medium in the flow cell, the sample was inserted into the flow cell and the cell was refilled with the dissolution medium. The flow rate was then increased in steps from 0.3 ml/min for 15 min, stopped for 5 min and followed by 2.0 ml/min for 2 min. A sequence of images was taken during this time using a 254 nm wavelength filter.

RESULTS AND DISCUSSION

Typical dissolution variation of the highly variable batch is

presented in Table 1, 2 and Figure 1. About 10% of the stability samples from this high strength batch encountered the stage 1 dissolution failures in six month test period which either required stage 2 or 3 testing or demanded significant investigation effort. Considering the rapid and consistent dissolution for the low strength batch, formulation variables and dissolution method variables that could contribute to the differences in rate and inter-vessel variability were examined.

A possible variable that could contribute to the slower and variable dissolution of the high strength batch was the lower microcrystalline cellulose (MCC)/drug ratio due to the 75% drug loading in this formulation. On the other hand, the low strength batch has a higher MCC/drug ratio due the 25% drug loading. MCC was used as a filler and also it acted as a disintegrant. The lower MCC/drug ratio would provide less disintegration capacity when inadequate dissolution surface area was presented due to a slow erosion of the capsule shells. The first in human (FIH) batch that exhibited this behavior was a 150 mg capsules formulated with a BCS class III compound as shown in Table 3. It has a 75% drug loading (HDL), contains MCC, silicon dioxide and magnesium stearate as the excipients, and uses Quali-V® HPMC capsule shells. The Quali-V® HPMC capsule shells were selected based on available supply and the consideration of low equilibrium moisture content in capsule shells (4 to 6% as per manufacturer specification) that could prevent the undesirable drug degradation. The other FIH batch (40 mg capsules) that was manufactured at the same time has a 25% drug loading (LDL), and contains the same type of excipients and uses the same lot of the HPMC shells. The HPMC shells used for the 40 mg capsule manufacturing were stored in a package that was previously opened, whereas the shells for the 150 mg capsule batch were acquired from an un-opened package

Effect of the sink condition on the rate and extent of the drug release

The capsule formulations under the investigation contained a BCS class III compound (high solubility and low permeability) with an aqueous solubility of approximately 0.6 g/ml across physiological pH range of 1.2 to 6.8. The validated dissolution method employed a dissolution medium (0.01 N HCl) based on the consideration of the physiological relevance of the medium, the solubility of the active pharmaceutical ingredients (API) as well as the Quali-V® HPMC shell and the stability of the API. Dissolution sink factor for a 150 mg strength in1000 ml of 0.01 N HCl can be obtained by using Equation 1:

$$\text{Sink factor} = V \times C_S / \text{Maximum dissolvable dose}$$

where V is the dissolution medium volume, C_S is the saturated solubility of the compound, maximum dissolved dose is the capsule strength (Cynthia et al., 2004).

The dissolution sink condition is dictated by the solubility of the API and the dissolution volume. For a 150 mg dose, the sink is calculated as 4000, which is significantly higher than the recommended 3 to 10×, which is the volume required to completely solubilize the dose. For the 40 mg strength, the sink factor is 15000, which is approximately four times of that of the 150 mg dose. The effect of the sink on the dissolution rate and extent was accessed by performing dissolution using only stock granulations. Samples from both stock granulations were made by opening and transferring entire content of one capsule into a vessel that contains 1000 ml of 0.01 N HCl. Dissolutions were performed on n = 3 LDL and HDL granulations as per method and the results are plotted in Figure 2. The dissolution release for both granulations was rapid with approximately 95% released in 2 min. The inter-vessel variability of 150 mg granules was low, with a relative standard deviation (RSD) of approximately 1% across all sampling-points. For 40 mg granules, the RSD is approximately 4%. The slightly higher inter-vessel variability of the 40 mg granules was due to a low percent drug release in a 40 mg vessel caused by incomplete emptying of the capsule or lose of the capsule content during sample transferring. When adequate API solubility (sink factor) and the dissolution surface area (without shell) were presented, both granulations exhibited rapid and complete release. On the basis of these results, we concluded that the drug release rate and extent for both granulations are the same. The slower and variable dissolution of the 150 mg capsules was not due to the granules.

Effect of USP apparatus, agitation speed and medium deaeration to dissolution rate and dissolution variations

Factors controlling the dissolution rate can be described by Equation 2 based on Noyes-Whitney equation:

$$dm/dt = D/V \times S/h\ (Cs-Ct)$$

where dm/dt is the dissolution rate; D is the diffusion coefficient; S is the surface area; h is the thickness of the diffusion film adjacent to the dissolving surface; Cs is the saturation solubility of the drug molecule; Ct is the concentration of the dissolved solute; and V is the volume of the dissolution medium (Aristides and Panos, 2006).

From Equation 2, one can conclude that increasing the diffusion coefficient or increasing the surface area or decreasing the diffusion layer would enhance the dissolution rate and reduce the variations. The diffusion coefficient is affected by the solvent viscosity and the molecular size of the solute which in our case is considered the same for the low strength and high strength

Table 1. Example of the dissolution profile of a highly variable batch (HDL) that failed internal specification.

Sampling point	1	2	3	4	5	6	Mean	% RSD
10	55	45	28	6	17	55	35	62.9
20	94	98	70	64	45	86	78	25.1
30	97	99	90	86	72	94	93	11.9
45	97	98	96	99	93	100	99	3.8
60	97	97	97	99	95	98	97	1.6

Figure in red represent result which failed the proposed specification of 75%(Q)+5% at stage I (1000 ml of 0.01 N HCl and USP apparatus II (Paddle) at an agitation speed of 75 rpm).

Table 2. Dissolution profile of a low strength batch (LDL) (n = 6).

Sampling point	1	2	3	4	5	6	Mean	% RSD
10	27	56	94	98	92	47	68	42.0
20	96	100	96	98	101	95	99	3.8
30	97	101	96	96	102	96	99	3.9
45	96	102	97	95	101	98	99	3.9
60	97	101	96	96	104	95	98	4.0

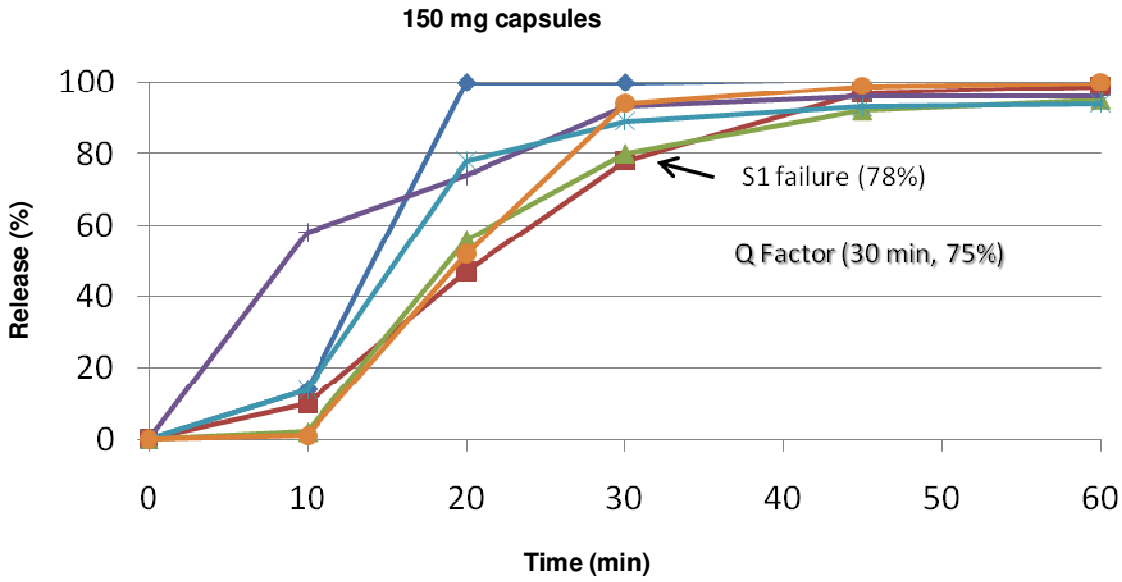

Figure 1. Dissolution profile of a highly variable batch (HDL) that failed internal specification (n = 6).

Table 3. Formulation composition.

40 mg capsules	150 mg capsules
25% drug loading	75% drug loading
MCC	MCC
Silicon dioxide	Silicon dioxide
Magnesium stearate	Magnesium stearate
Quali-V® HPMC capsule shells	Quali-V® HPMC capsule shells

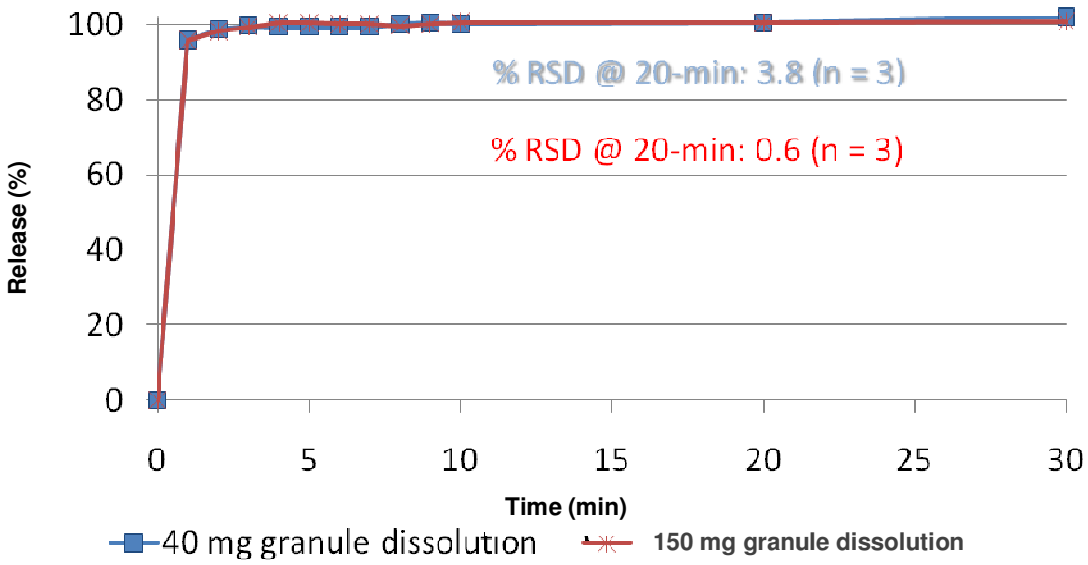

Figure 2. Granule dissolution 40 mg and 150 mg stock granulations. 40 mg granule dissolution: % RSD at 20min: 3.8 (n = 3); 150 mg granule dissolution: % RSD at 20 min: 0.6 (n = 3).

Table 4. Effect of apparatus I and II on dissolution.

Sampling point (min)	Mean % release		% RSD	
	Basket at 100 rpm	Paddle at 75 rpm	Basket at 100 rpm	Paddle at 75 rpm
10	2	45	45.5	42
20	24	80	75.5	10.8
30	69	95	10.5	7.7
45	95	97	2.9	4.4
60	97	97	2.1	3.3

formulations. The dissolution surface area and the diffusion layer are dictated by the disintegration rate of the capsule shells and the dissolution apparatus and agitation speed. The API dissolution surface area in a HPMC capsule formulation is affected by the rate of the disintegration of capsule shells and API particle size. The disintegration of the HPMC shells is affected by the water penetration through the shell walls and the hydrodynamics in dissolution vessels. Increasing the agitation speed could reduce the diffusion layer, help disintegration process, thereby increasing the surface area, exposing more drugs to the dissolution medium and improving the rate.

During our initial dissolution method development for the drug product, USP apparatus II (paddle) with 50 rpm was evaluated and partially intact capsule was observed at the end of the 60 min. The disintegration of HPMC shell was slow and inadequate; therefore, 75 rpm was justified with supporting data that was generated at the time. However, as formulation and product knowledge continued to evolve, failure in dissolution specification occurred, further investigation on dissolution parameters became necessary. As part of the investigation, an alternative apparatus of basket (40-mesh) with 100 rpm was evaluated using the intermittent inconsistent batch with the aim to identify if the basket apparatus would provide a more robust dissolution. Table 4 shows the two sets of data demonstrating that basket method exhibited much slower dissolution and higher percent RSD at early sampling-points when compared with the paddle apparatus. This is likely due to the thicker diffusion layer generated by the basket apparatus. The basket dissolution however did catch up at 45 min sampling-point and thereafter, but it would have failed the stage 1 dissolution specification of non-torque loading (NTL) 80% at 30 min. Media deaeration is another important factor that could affect drug dissolution surface area as air bubbles could partially cover the surface of the drug particles, and that portion of the surface will not be exposed to the dissolution medium and this leads to a decrease in the dissolution rate (Sherry et al, 2010). Air bubbles can act as a barrier to dissolution if present on the dosage unit or cause particles to cling to the apparatus and vessel walls and thus introduce dissolution variations. To evaluate if

Table 5. Effect of medium deaeration on dissolution (n = 6).

Sampling point (min)	Mean % release		% RSD	
	With degas	Without degas	With degas	Without degas
10	45	24	41.9	75.3
20	80	80	11.0	19.4
30	95	89	7.8	11.2
45	95	98	4.5	2.7
60	98	97	3.3	1.9

Table 6. Summary of capsule shell investigation 40 mg granulation in 40 and 150 mg shells (n = 6).

Sampling point (min)	Mean % release		% RSD	
	40 mg Shell	150 mg Shell	40 mg Shell	150 mg Shell
10	77	60	19.1	43.6
20	95	89	2.8	7.4
30	97	92	2.4	2.9
45	98	94	2.3	3.1
60	99	94	2.4	3.5

Table 7. Summary of capsule shell investigation 150 mg granulation in 150 and 40 mg Shells (n = 6).

Sampling point (min)	Mean % release		% RSD	
	40 mg Shell	150 mg Shell	40 mg Shell	150 mg Shell
10	35	26	24.0	75.4
20	83	80	14.9	19.4
30	89	91	9.7	11.2
45	94	98	4.3	2.5
60	98	99	2.5	1.9

medium deaeration has an effect on dissolution performance of the HPMC formulations, both degassed and non-degassed media were used in the dissolution testing of the intermittent inconsistent batch. Results demonstrated that degassed medium reduced the capsule-to-capsule variations at early sampling-points and improved the dissolution rate which warranted the inclusion of the medium deaeration in the method revision Table 5. Based on the data, it is concluded that higher agitation speed and medium deaeration can improve dissolution rate and reduce dissolution variations.

HPMC shell investigation

Disintegration of capsule shell was not only affected by the hydrodynamics in dissolution vessels, but was also affected by the rate of medium penetration through the shells. Switching shells between the two formulations would indicate if the problem follows the shells, because dissolution variations were only seen in the high strength batch. Our experimental design involved redistributing the contents from the batch of capsules (40 mg) which exhibited consistent dissolution with the batch of capsules (150 mg) which provided intermittent, inconsistent results. Dissolutions of each of the original and filled capsules (n = 6) were performed as per method, and the summaries of the results are presented in Tables 6 and 7, and plotted in Figures 3 and 4. It appeared that the 40 mg granule with the 150 mg capsule shell had an average dissolution release of 88% at 20 min with 7.4% RSD for n = 6 samples. It was slower and more variable as compared to 96% release with 2.8% RSD from the original 40 mg capsules (40 mg granule in 40 mg capsule shell). The data clearly indicated that the problem followed the 150 mg shell. Nevertheless, the 150 mg granule with 40 mg capsule shell had an average dissolution release of 83% with 15.0% RSD at 20 min which was slightly faster and less variable as compared to 80% release with 19.4% RSD from the original 150 mg capsules (150 mg granule in 150 mg capsule shell). It was evident that the 150 mg shells had pronounced effect in slowing down the dissolution performance of the 40 mg formulation whereas the

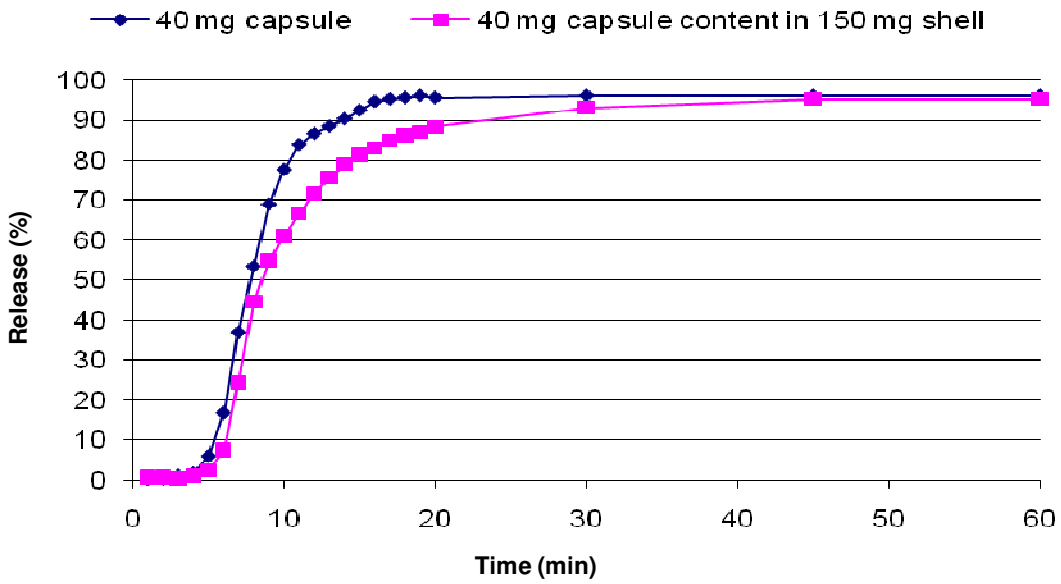

Figure 3. Dissolution profiles of 40 mg capsules (n = 6) and 40 mg granulation in 150 mg shells (n = 6).

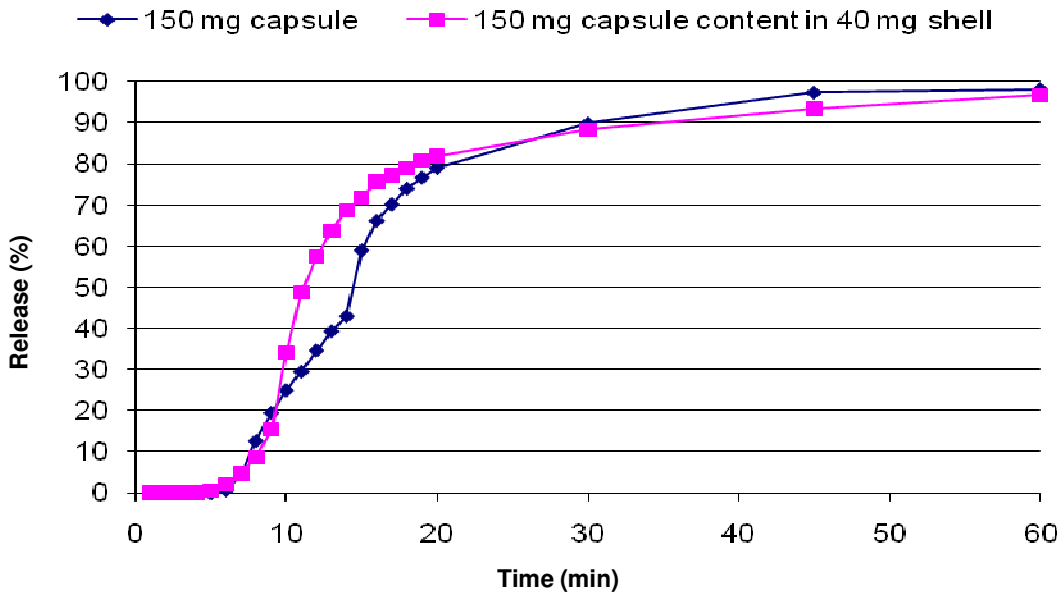

Figure 4. Dissolution profiles of 150 mg capsules (n = 6) and 150 mg granulation in 40 mg shells (n = 6).

40 mg shells only slightly improved the rate and consistency of the drug release of the 150 mg formulation. Among all the capsules that were tested, one original 150 mg capsule failed S1 dissolution specification of NLT 80% at 30 min and a couple of filled capsules with 150 mg granule in 40 mg capsule shells were just above 80% border line which indicated that the dissolution performance of the intermittent, inconsistent batch was affected by multiple factors rather than the 150 mg shells alone.

Effect of moisture content in HPMC shells on dissolution

Unlike its counterpart gelatin capsules, HPMC capsules do not undergo cross-linking under high temperature and high moisture (Digenis et al., 1994; Gold et al., 2011). The effect of moisture content in capsule shells on capsule dissolution has not been widely reported and studied in literatures; therefore, an experiment to probe the effect of shell moisture level on disintegration and dis-

Table 8. Effect of moisture content in capsule shells on dissolution.

Sampling point (min)	Mean % Release		% RSD	
	Original (4.07%)	Dried (1.46%)	Original (4.07%)	Dried (1.46%)
10	25	49	49.8	58.2
20	88	96	16.5	5.7
30	98	100	6.9	0.5
45	99	101	1.4	0.6
60	100	102	1.3	0.5

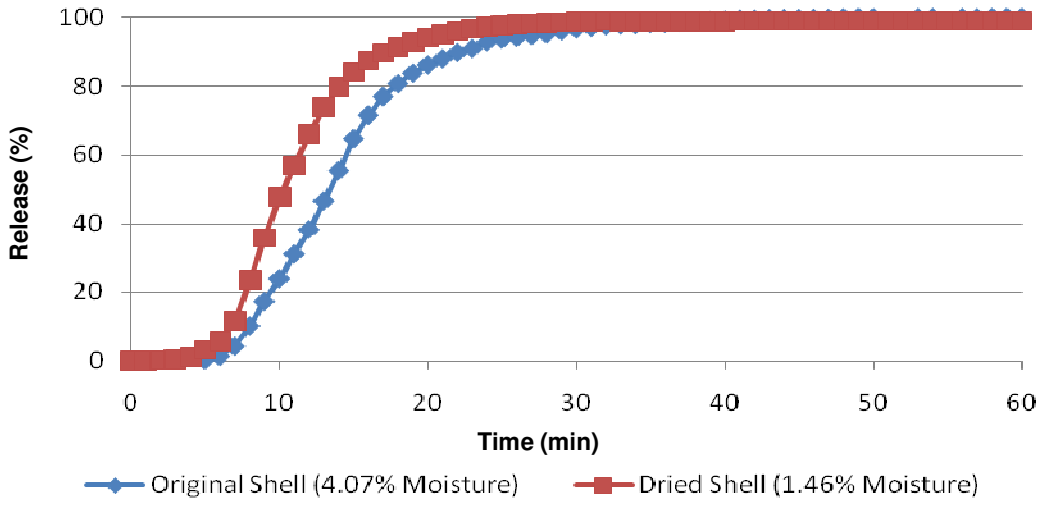

Figure 5. Effect of moisture content in HPMC capsule shells on dissolution (n = 6).

solution of the high strength formulation were conducted. The experimental details involved drying adequate amount of shells (~4.1% moisture) in a 45°C oven for 12 h. Both dried and un-dried shells were filled with HDL granules and dissolutions were performed on n = 6 capsules made with these shells. The comparison data generated from the two types of capsules demonstrating that capsules with un-dried shells exhibited a slower and variable dissolution at early sampling-points whereas a faster and consistent dissolution was obtained for capsules with dried shells Table 8 and Figure 5. Visual observation on the dissolution process that was conducted simultaneously at the time indicated that the capsules with un-dried shells did not disintegrate readily when compared with that of the capsules with dried shells.

It appears that the manufacturer suggested specification for moisture content 4 to 6%) in HPMC shell has its merit. Appropriately hydrated shell can prevent water penetration more effectively than its dried counterpart. From protecting product quality and stability perspective, it is beneficial that the capsule shells do not uptake moisture easily; however, it provides challenges for *in vitro* dissolution especially when water penetration and disintegration of capsule shells are the rate-limiting steps. In such event, perhaps formulation with more effective disintegrant could help to improve dissolution rate.

Surface dissolution of HPMC capsule shells

To help visualize the dissolution process of HPMC shells, a ActiPix SDI 300 UV area imaging system was used to enable the quantitative imaging of the surface erosion and dissolution for shells with various moisture contents. pH 6.8 sodium phosphate buffer was employed for the study. Two sets of images at 7 min time-point for a piece of dried shell (moisture undetermined, shells with 4.1% moisture were dried under 45°C for 12 h) and a piece of un-dried shell (4.1% moisture) that show the 254 nm absorbance images of areas containing shell and flowing dissolution medium Figures 6 and 7. The swell of shells from the exposure surface was significantly different between the two types of shells. The swell rate and swell size were calculated based on the surface dissolution process recorded by the SDI 300 software. The results demonstrated that the dried shell swells about four times faster than the un-dried shell (0.0405 mm/min versus 0.0093 mm/min). The dried shell had about two times the swell size as the un-dried shell at 7 min time-point. The

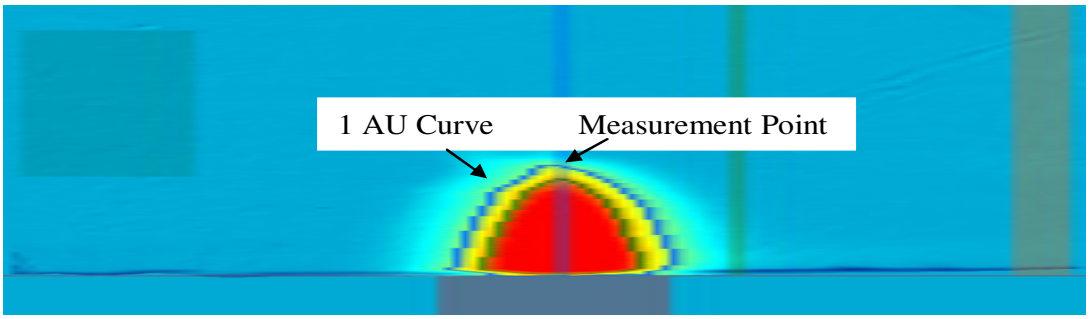

Figure 6. Surface dissolution imaging of dried shell.

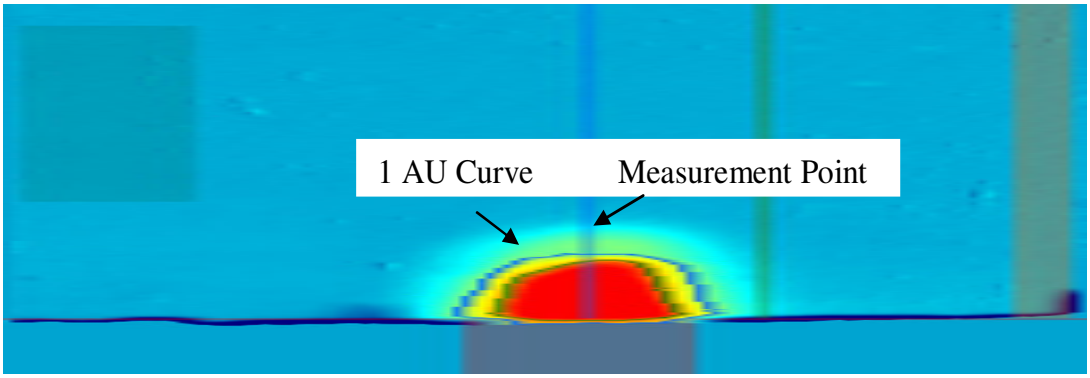

Figure 7. Surface dissolution imaging of un-dried shell.

swell height as a function of the time, indicated that medium penetration through the hydrated shell (un-dried shell) is slower when compared with the dehydrated shell (dried shell). This finding supported the hypothesis that was reported in the literature (Moawia, 2010) and our investigation in effect of moisture content in HPMC shells on dissolution on the effect of moisture content in HPMC shells on capsule dissolution.

Hydrodynamics evaluation: Effect of capsule landing positions on dissolution

The effect of capsule landing positions on the dissolution performance of the intermittent inconsistent batch was studied, because dissolution variations and robustness of the dissolution method are often affected by the insufficient hydrodynamics in dissolution vessels (Lozano et al., 1994). It had been observed in previous dissolution testing that chunks of granules with pieces of shell sometimes remained at the bottom “dead zone” of the vessels for a prolonged period of time. The effect of the “dead zone” on the HPMC capsule dissolution was unknown and worth to study. Dissolutions for capsules that landed at three positions (Figure 9) were performed with n = 2 capsules being dropped at the center, near center and off center locations prior to the start of the dissolution. The percent drug release as a function of time was generated by the UV fiber optics software at 1 min interval for a total of 60 min, with a simultaneous visual observation collected by the analyst. It was observed that the center capsules started to rupture at the shoulder of both ends and the capsule content gradually dispersed into the solution with the pile located at the “dead zone” last to disperse. In one of the two centered capsules, un-dissolved shell fragments were found above and below the capsule content at the “dead zone” area which prevented the drug from dispersing into medium for a prolonged period of time. Examination of the dissolution profile of this capsule revealed a 66% release at 30 min which would have failed the dissolution specification. A summary of the result in Table 9 illustrated the dissolution profiles of three sets of capsules landed at various locations. Capsules landed at the center had the slowest disintegration/dissolution rate at 15 min time-point when compared with capsules that landed near or off center. Based on the study results, it was concluded that the intermittent failure in S1 specification for the high strength batch could partially due to the artifact of un-dissolved shell fragment hinder the release of the capsule content when the capsules landed close or at the “dead zone”. Similar observation was reported in literature that during the dissolution of shell 1 in pH 4.5 acetate buffer, fragments of the shell may sometimes trap the powder against the bottom of the vessel, hindering fast and complete release of the drug (Sherry et al., 2010).

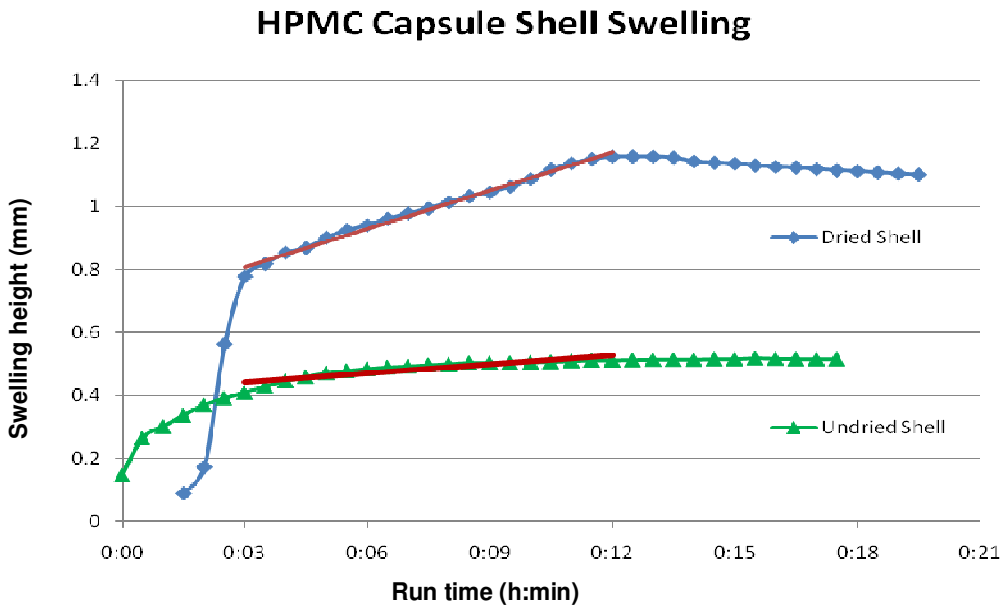

Figure 8. Swelling of HPMC capsule shell.

Table 9. Effect of capsule landing positions on dissolution.

Sampling point (min)	Release (%)					
	Center	Center	Near center	Near center	Off center	Off center
5	0	0	0	1	0	1
10	12	22	19	32	45	21
15	30	32	48	66	64	77
20	70	48	62	73	99	93
30	99	**67**	86	86	100	101
45	103	87	102	95	101	102
60	105	100	102	103	104	103

Figures in bold represent result which would fail the proposed specification of 75% (Q)+5% at stage I.

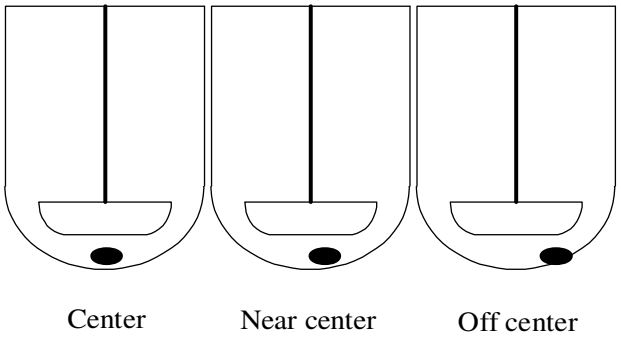

Figure 9. Capsule landing positions.

Conclusions

Here, a unique case where the same lot of HPMC shells stored in different storage conditions yielded substantially different *in vitro* dissolution release for a BCS Class III compound was presented. The root cause of the intermittent, inconsistent dissolution of the high strength batch was determined to be the higher moisture content in the HPMC shells. It appears that HPMC shells with manufacture specified moisture content would not readily uptake moisture which is a desirable element from protecting product stability and quality perspective. However, it posts challenges for the dissolution method development as shells with 4 to 6% moisture would not dissolve in dissolution media readily. To enhance the dissolution performance of the HPMC formulations, one could consider employing super-disintegrant to improve the disintegration capacity of the formulation. Another important factor that should be considered from method development perspective is to ensure adequate hydrodynamics in dissolution vessel and deaeration of dissolution medium. In our case, justification of higher

agitation speed that is beyond the compendia condition is appropriate as it would not only improve the shell disintegration thus improve the overall dissolution rate, but also reduce the effect of “dead zone” and minimize the chance of drug being trapped by shell fragments.

With the aim of fully understanding the effect of dissolution sink, apparatus, agitation, hydrodynamics, medium deaeration and effect of shell moisture content on dissolution, we are able to identify the root cause of the intermittent and inconsistent dissolution of the high strength batch and minimize the occurrences of S2 or S3 testing. With the inherent moisture content in the HPMC shells, achieving adequate hydrodynamics in dissolution vessel is vital in order to reduce intermittent dissolution failure and dissolution variations for capsule formulation with HPMC shells.

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