



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

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ABSTRACT

This Part I paper describes the qualification of a new high performance hypromellose (hydroxypropyl methylcellulose, HPMC) capsule shell which contains no gelling agent and is dissolution friendly. The development history and the test results for a series of quality attributes including scanning electron microscopy, hygroscopicity, machineability, weight variation, powder leakage, mechanical strength, stability, cross-linking, animal and human pharmacokinetic results are reported. Comparisons to gelatin and HPMC capsule containing carrageenan showed the new HPMC capsule is superior in terms of mechanical strength, hygroscopicity and compatibility with a wide range of drugs. Specifically, the new HPMC capsule demonstrated improved weight variation, machineability and powder leakage than the HPMC capsule containing carrageenan. And the new capsule demonstrated a broader applicability than gelatin capsule for new drug development due to its inertness and compatibility for a wide range of excipients including those used for liquid fill formulations. In the second phase of qualification, disintegration and dissolution properties of the new HPMC were evaluated and reported in a Part II paper for 10 new clinical compounds with a variety of formulations optimized based on the biopharmaceutical classification system of solubility and permeability. Based on the superior performance, the new HPMC capsule is satisfactorily qualified and has since been used successfully for nearly 20 investigational new drug (IND) compounds.

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1. Introduction

Two-piece hard capsules are the dosage form of choice for clinical trial in the development of pharmaceutical products due to ease of blinding with placebo and comparative products. Capsules, due to ease of swallowing, are also very popular for nutritional and food supplements (nutraceutical) and Over-The-Counter (OTC) pharmaceutical products. The mad cow disease scare in 1990s triggered a FDA program to scrutinize the use of animal-derived materials in manufacture of pharmaceutical products (FDA BSE Testimony, 2003). Every FDA filing requires certification, which in turn requires suppliers properly certify that their animal-derived raw materials have minimum risk of bovine spongiform encephalopathy (BSE) and transmissible spongiform encephalopathy (TSE). Moreover, importation of clinical supplies into EU, Japan and South America

requires multiple steps in the certification of BSE/TSE free or the risk assessment for any animal-derived components (FDA Guidance, 1997a). The first step taken in Wyeth is to replace animal-derived excipients magnesium stearate and polysorbate 80 with vegetable grades and to use other sugars in place of lactose. The second step is to replace gelatin capsule shells with non-animal capsule shells for new products initially and then old products.

Gelatin is a good film-forming material suitable for capsule shell that dissolves readily in biological fluids at body temperature. Since James Murdock patented the two-part telescoping gelatin capsule in London in 1847, the process of dipping metal rods in molten gelatin solution remains the underlying principle for mass production. Gelatin was chosen as the main material due to its excellent gelatinizing characteristic including gelling, film-forming and surface active properties suitable to this manufacturing process. As a naturally occurring protein, gelatin is susceptible to hydrolysis to release amino acids and is inherently reactive toward many substances including aldehydes, reducing sugars, metal ions, plasticizers and preservatives (Rowe et al., 2003). In addition, gelatin

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is amphoteric and can interact with anionic and cationic polymeric materials (Cole et al., 1992). The other disadvantages of hard gelatin capsules (HGC) include shell brittleness after exposure to low humidity, and incompatibility with hygroscopic substances (Liebowitz et al., 1990). Moreover, upon storage in accelerated stability conditions such as 40 °C/75% RH, gelatin capsules undergo cross-linking reactions which reduce water solubility and retard disintegration of the shell and thus slow down the drug release (Brown et al., 1998). Many drugs and excipients can participate in the cross-linking reactions such as amine drugs (Schiff bases) and lactose, a reducing sugar. The authors have experienced frequent dissolution failures under accelerated conditions for gelatin capsules, which is not surprising since more than half of the pipeline compounds are basic, mostly with amine functional groups. The failed result triggers an investigation of formulation, manufacture, excipient and test methods including the addition of enzyme which can help digest the cross-linked gelatin. Gamma scintigraphy studies have been conducted in humans to confirm time and GI location of capsule rupture in vivo for stressed and non-stressed capsules (Digenis et al., 1994, 2000). A two-tier dissolution procedure that retests a cross-linked hard gelatin capsule with addition of gastric or intestinal enzymes was developed to verify the in vivo performance. As described in the USP <711> method (US Pharmacopeia XXXII, 2009), for hard or soft gelatin capsules and gelatin-coated tablets that do not conform to the dissolution specification, repeat the test as follows: "Where water or a medium with a pH of less than 6.8 is specified as the Medium in the individual monograph, the same Medium specified may be used with the addition of purified pepsin that results in an activity of 750,000 units or less per 1000 mL. For media with a pH of 6.8 or greater, pancreatin can be added to produce not more than 1750 USP units of protease activity per 1000 mL." A lot of times, the medium and method cannot accommodate the enzyme (i.e. because of surfactants), and a change of method followed by re-qualification is necessary. Because the extension of use period for clinical supplies for IND filings heavily depends on the shelf-life extrapolation using accelerated stability data, once the failure occurs, the program is delayed with crisis management. It is one of the reasons some firms prefer tablets even though tablets require additional encapsulation for blinding in clinical trials. In terms of risk management, HPMC shell is preferred to gelatin shells for new compound development.

Several materials have been examined as a substitute for gelatin over the years with little success. The cellulose ethers are the replacement materials most commonly mentioned in the literature. In early 1950s, HW Murphy of Elanco, a division of Eli Lilly & Company (Murphy, 1950) was granted an US patent for manufacturing hard capsules with cellulose ethers and two-piece methylcellulose capsules were produced. Manufacture of methylcellulose capsule was discontinued later upon discovery of its poor in vivo disintegration performance. Hypromellose quickly followed as an alternative with many patents granted on the manufacturing process including thermal gelation and a gelling system with additives. HPMC capsules have several distinct advantages over HGC. Besides no BSE/TSE risk, HPMC is a non-ionic polymer and the capsule has little compatibility issue with most drugs and excipients. The typical moisture content of HPMC capsules is 2–6% versus the 13–15% in HGC, and there is minimal impact on the brittleness of the HPMC capsules upon storage at low humidity (Missaghi and Fassihi, 2006).

Not until the rise of health conscious vegetarian sector of the nutraceuticals market in the USA, was popularity gained by the Vegicap®, an HPMC-based capsule patented by G S Technologies Inc. (now Catalent Pharma Solution) (Grosswald et al., 1997, 1998a,b). The dipping method of manufacture remains similar using a solution of HPMC. Since HPMC does not have enough

mechanical strength, the thickness of the capsule shells needs to be increased. To improve the grip and overcome the problem in stripping the dried films from the mould pins, a stripper jaw with dimples on the inner surface was developed. To prevent possible damage of the capsule shell wall due to liquefaction of the HPMC films, an induction heating system for the mould pins was used to maintain the correct temperature in the wet HPMC films until dry in order to maintain their shape. Since the cellulose film strength of hard capsules prepared by thermal or chemical gelling methods is much lower than the strength of a gelatin film, many gelling agents have been studied for HPMC capsule manufacture, including carrageenan, tamarind seed polysaccharide, pectin, curdlan, furcellaran and gellan gum. In the 1990s and early 2000s, several patents were granted to Shionogi Qualicaps Co. in Japan (Yamamoto et al., 1993, 1995, 1998; Matsuura and Tanjoh, 2003) on an HPMC gelling system using carrageenan and potassium chloride. Carrageenan is a linear sulphated polysaccharide extracted from red seaweeds. Carrageenan can form a double helix structure connecting two molecular chains in a three-dimensional structure, which results in a high gel strength and exhibits good gelling properties in combination with a potassium ion. Among the three known carrageenan types, kappa-carrageenan and iota-carrageenan have better gelation ability than lambda-carrageenan. By adding carrageenan and potassium chloride, the gelation of HPMC solution can be carried out at room temperature, therefore no special manufacturing apparatus and procedures are required and the most commonly known capsule manufacturing apparatus for immersion and molding of the conventional gelatin capsules can be used.

In early 2000, Capsugel (Cade et al., 2003), a division of Warner Lambert (later as Pfizer), developed a different HPMC gelling system and obtained an US patent for a HPMC capsule using gellan gum (hydrocolloids) as the gelling agent and either ethylenediamine tetra acetic acid (EDTA) or sodium citrate as a gelling promoter (sequestering agents). This product, Vcaps® Hypromellose, Shell 3, is successful in the OTC and nutraceutical markets. However, the slow dissolution of this Shell 3 in acidic buffer makes it difficult for formulation development for the highly regulated prescription drugs. Regulatory authorities worldwide require comparison of dissolution profiles in three pH's (pH 1.2, 4.5 and 6.8). Comparable results are required whenever there is a change in raw material, excipient, formulation, manufacture process, manufacture site (FDA Guidance, 1995, 1997b). Although Capsugel conducted a scintigraphy study demonstrating that slow acid dissolution translates into a slight delay in absorption in human which is not critical for most drugs (Cole et al., 2004), the regulatory burden is still high for life cycle management of any global pharmaceutical product. As a result, Wyeth selected Quali-V® Hypromellose-Carrageenan, Shell 1, to replace gelatin capsule shells for new product development and clinical supply manufacture in 2002. This HPMC Shell 1 has been used in Wyeth for over 100 clinical products for over 30 new chemical entities (NCE) between 2003 and 2006. The overall in vivo performance of these products in Shell 1 is judged comparable to those with gelatin capsules.

However, some issues of the HPMC Shell 1 have been observed during manufacturing and testing of the products. These capsules have large weight variation, leading to high product fill weight variation and high rejection rates. As a consequence a larger formulation fill weight is required to overcome the shell weight variation. Powder leakage is another issue that has been observed in products after shipment and during blister packaging. The presence of powder outside the capsule shells had lead to quality and safety concerns at clinical study sites in Japan and consequently batch rejection. Banding the joint of the cap and body with a HPMC band had subsequently been used to solve the leakage problem. Lastly the HPMC Shell 1 is less appealing in appearance because the colors are duller and less glossy than the gelatin capsules.

Table 1
Empty capsule shells.

Capsule shell	Hypromellose Shell 1	Hypromellose Shell 2	Hypromellose Shell 3	HGC shell
Brand name	Quali-V®	Vcaps Plus®	Vcaps®	Coni-Snap®
Gelling agent	Carrageenan	None	Gellan gum	None
Manufacturer	Qualicaps	Capsugel	Capsugel	Capsugel

In 2004, Wyeth and Capsugel established a partnership under a confidentiality agreement to develop a better capsule shell using new non-animal-derived materials for powder fill and/or liquid fill capsules. Since the gelling agent could affect in vitro dissolution and in vivo disintegration properties of HPMC capsules, Capsugel researchers went back to the “original” concept using only water and polymer as the ingredients. Indeed, the elimination of gelling agents gives a pH independent disintegration which performs in an ideal manner in vitro and in vivo under both fasted and fed conditions. Capsugel developed a new HPMC capsule, Vcaps Plus® (Hypromellose Shell 2), without a gelling agent or other ingredient in 2006. In late 2006, Wyeth and Capsugel agreed on a detailed plan of collaboration to evaluate this new Hypromellose Shell 2 using Wyeth new compounds. The evaluations started in 2006 focusing on physical, mechanical, processing, disintegration, and dissolution properties. Qualification of the new Shell 2 was completed in 2007 confirming the superior performance in several quality attributes including dissolution. Capsugel launched the product for Wyeth mid-2007 and the new Shell 2 has since been used successfully for over a dozen IND compounds. These comparative data among gelatin and the two HPMC capsules are summarized in two papers. The Part I publication herein focuses on comparison of the physical, mechanical and manufacture processing properties. The Part II publication will follow suit and concentrate on the comparative disintegration and dissolution of clinical products of ten (10) Wyeth new compounds encompassing various biopharmaceutical classification system solubilities and permeabilities.

2. Materials and methods

2.1. Empty capsule shells

Empty capsule shells are summarized in Table 1. The specific lots used in the studies are:

Hypromellose Shell 1: Size #0, Brown 4P, Lot# 115432A; Size #0EL, Brown 4P, Lot# 110442A.

Hypromellose Shell 2: Size #0, Natural Transparent, Lot# 90051731, 90075031, 70286611; Size #0, Swedish Orange, Lot# 70223231; Size #00, Natural Transparent, Lot# 90111351.

Hypromellose Shell 3: Size #00, Natural Transparent, Lot# 90111141.

Reference hypromellose capsules: Size #00, Lot# K720050.

Hard gelatin capsule: Size #1, Natural Transparent, Lot# 51017711; Size #0, Grey, Lot# 83610A; Size #0, Natural Transparent, Lot# 52087701, 52082141.

Capsugel hard gelatin LiCap® capsule: Size #0EL, Swedish Orange, Lot# 113349A.

2.2. Excipients and reference materials

Microcrystalline cellulose (Avicel PH 101), NF/EP Grade, FMC BioPolymer, Newark, DE.

Croscarmellose Sodium (AC-DI-SOL®), NF Grade, FMC BioPolymer, Newark, DE.

Magnesium stearate, NF/EP Vegetable Grade, Mallinckrodt Inc., St. Louis, MO.

Acetaminophen, Rhodia, Rhodapap Ref 042593.

Propylene glycol monocaprylate (Capryol® 90), Gattefosse, Saint-Priest, France.

Propylene glycol monolaurate (Lauroglycol® 90), Gattefosse, Saint-Priest, France.

Caprylocaproyl polyoxyl-8 glycerides (Labrasol®), Gattefosse, Saint-Priest, France.

Caprylic/capric glycerides (Imwitor® 742), Sasol, Westwood, NJ.

Caprylic/capric triglycerides (Miglyol® 812), Sasol, Westwood, NJ.

Glyceryl caprylate/caprate (Capmul® MCM), Abitec, Columbus, OH.

Polyoxyl 35 Castor Oil (Cremophor® EL), BASF, Florham Park, NJ.

Polysorbate 80, Spectrum Quality Products, Inc., NJ.

Phosal 53 MCT®, Lipoid LLC, Newark, NJ.

Super Refined® PEG 400, Croda, Inc., Edison, NJ.

2.3. Scanning electron microscopic (SEM)

Closed empty capsules were cut at the closure to expose the cross-section between the body and cap. All three types of shells are opaque, containing titanium dioxide plus colorant. Both cut and uncut capsules were sputter-coated with platinum vapor. The coated samples were analyzed using an ESEM Model Quanta 200 by FEI under high vacuum at a high voltage of 12.5 kV with a spot size of 3.5. The shell thickness was measured at 30 different points and the maximum gap between the body and cap was located and measured from the cross-sectioned samples. Photomicrographs of the surfaces of the three shell types were taken and compared for surface characteristics.

2.4. Hygroscopicity evaluation

Size 0 natural transparent Hypromellose Shell 2 and Capsugel natural transparent Coni-Snap® size 1 HGC shells were stored in closed desiccators at 22 °C and different relative humidity (RH) for 1 week. Because the HGC are expected to contain twice as much moisture, a smaller size capsule was selected for HGC than the hypromellose shell so that the weight loss ranges on LOD testing are similar between the two shells. The desiccators contained different saturated salt solutions to achieve different relative humidity values (Greenspan, 1977) as described in Table 2. After the capsules were stored at different conditions for 1 week, the equilibrated water content was measured using USP <731> Loss on drying test method. The capsules were dried overnight at 105 °C.

2.5. Mechanical strength evaluation

Resistance to breakage was tested using the Capsugel tube test method which consists of a 100 g weight dropping on an empty

Table 2
Desiccators to provide different relative humidity conditions.

	Relative humidity % @ temperature °C		
	From literature	Test results	Label
Lithium chloride	12–15% @ 20 °C	11.5% @ 21.0 °C	12% RH
Potassium acetate	20% @ 20 °C	23.2% @ 20.5 °C	23% RH
Calcium chloride	32% @ 20 °C	33% @ 20.5 °C	33% RH
Potassium carbonate	44% @ 20 °C	44.8% @ 20.2 °C	45% RH
Ammonium nitrate	65% @ 20 °C	66.2% @ 21 °C	66% RH

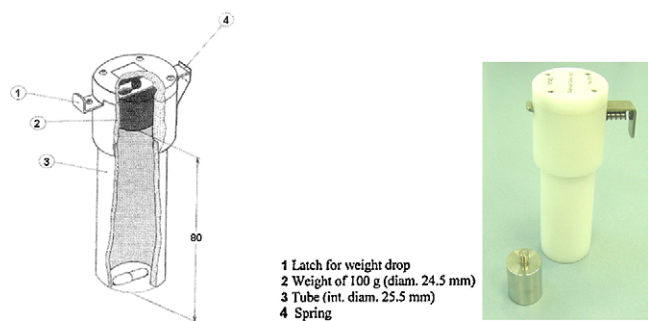


Fig. 1. Capsugel tube test.

capsule from a height of 8 cm (Fig. 1). The sample size is 50 capsules per test. The mechanical strength was evaluated after the capsules were stored at different conditions for 1 week using the tube test.

2.6. Capsule shell weight variation

Hypromellose Shell 2 was evaluated by comparing to the weights of Hypromellose Shell 1 as well as hard gelatin capsules, all in Size #0. The test was done with $n = 500$ using a Mocon ABPlus Automatic Balance.

2.7. Machineability evaluation

A small scale and slow speed IN-CAP capsule filling machine made by Dott. Bonapace & Co. was first used to assess the machineability of Swedish orange Hypromellose Shell 2, Hypromellose Shell 1 and hard gelatin capsule. 245 mg of microcrystalline cellulose powder were filled into the capsules under standard operation conditions. The performance of capsule shells was evaluated on the fill weight variation and capsule rejection rates.

The machineability of Hypromellose Shell 2 was further evaluated in an encapsulation process using a Bosch H&K 400 encapsulation machine at a speed of 20,000 capsules per hour with Size #0 dosing disc of 15.0 mm thickness and 19-17-12-12-9 tamping pin settings. 250 mg of a placebo blend containing 96.5% microcrystalline cellulose, 3.0% croscarmellose sodium and 0.5% magnesium stearate were filled into the capsules. The encapsulation was performed at 22 °C and 41% relative humidity. The filled capsule weights of individual and average of 10 capsules were tested throughout the encapsulation process. All powder-filled capsules were inspected on a capsule polisher for powder leakage and the capsule locking mechanism was also checked after encapsulation.

Capsule filling machine (CFM) trials at high speeds with Size 00 Hypromellose Shell 2 were performed on a Bosch GKF 1500 filling machine with powder filling and the performance is compared with other existing commercially available hypromellose capsules from Capsugel and a reference shell. A combined sample of 18,000 capsules from three different cartons of each type was used and a nominal CFM speed of 90,000 capsules per hour was used during the trials. Additional encapsulation trials were performed on Bosch GKF 1500 filling machine with the same capsule to evaluate the impact of filling machine speeds.

Trials at high speeds without powder filling were performed with Size 0 Hypromellose Shell 2 on Bosch GKF 2500, IMA Z40 and MG2 Planeta filling machines. A combined sample of 5000 capsules from two different cartons was used and nominal CFM speeds of 120,000 capsules per hour for Bosch 2500, 40,000 capsules per hour for IMA Z40 and 100,000 capsules per hour for MG2 Planeta were used during the trial runs.

2.8. Blistering and carding evaluation

Hypromellose Shell 2 capsules filled with placebo powder using Bosch machine were further blister-packed with Uhlmann UPS thermoforming machine. The sealing temperature was 150 °C and the forming temperature was between 120 and 135 °C. The blister-packing process was performed at 20.9 °C and 42.8% relative humidity.

The blisters were sealed into paper cards using Zed 15-DLX Shuttle Blister Sealer Machine. The carding process was performed at 21.7 °C and 32.4% relative humidity. The sealing time is from 4 to 6 s with an average of 5.3 s. The sealing temperature is from 90 to 135 °C with an average of 119 °C.

2.9. Transport simulation test

Hypromellose Shell 2, Hypromellose-Carrageenan Shell 1 and Capsugel hard gelatin capsules filled with Avicel PH101 were evaluated in a seal integrity test for assessing the powder leak risk during transportation. Fifty powder-filled capsules of each type were packed in 100 cm³ HDPE bottles. The bottles were shaken for 2 h on an arm wrist shaker at 600 osc/min. The capsules were visually inspected for powder leakage after shaking.

2.10. Short term stability at high temperature

Hypromellose Shell 2 capsules (about 200) were filled into glass bottles to the full capacity. The glass bottles were heated at different temperatures (up to 90 °C) for 24 h in an oven. The glass bottles are kept at room temperature for at least 5 h before opening. The capsules were evaluated on visual, dissolution and resistance to breakage tests.

2.11. Formaldehyde challenge test for cross-linking potential

Hypromellose Shell 2 Size 0 capsules were filled with acetaminophen (APAP) and lactose spiked with formaldehyde (HCHO) at 25 ppm. The filled capsules were stored at room temperature in closed HDPE bottles. After 1 week storage, the capsules were emptied and filled with APAP at a fill weight 380 mg (± 10 mg). The capsules were tested as per the acetaminophen capsules USP monograph for Acetaminophen Capsules – Dissolution Test <711> with water and USP apparatus II (paddle, 50 rpm) on a sample size of $n = 6$. The level of cross-linking is assessed by comparing the dissolution results.

2.12. Liquid fill compatibility

Four capsules of each of three types were filled with 0.5 g of each of 10 excipients without banding or sealing and placed vertically in 8 mL clear glass screw cap vials. The filled capsules were stored at 40 °C/75% RH and visually monitored weekly for leakage, cracking and any change in capsule shape. The aged capsules filled with different liquid/semisolid excipients were visually examined against empty capsules for shape change (swelling or shrinkage), and leakage of fill formulation. The number of capsules with leakage, sweating, swelling or shrinkage are reported as number of leak/sweat/swell/shrink out of 4 capsules tested such as 1-leak, 2-swell, etc.

2.13. Animal pharmacokinetic data

Animal tests were conducted as single-dose studies of oral capsule formulations using groups of 4 male beagle dogs. Dosing was done after an overnight fast and, for groups of fed dogs, 30 min after standard chow. Blood samples were drawn up to 24 or 30 h after

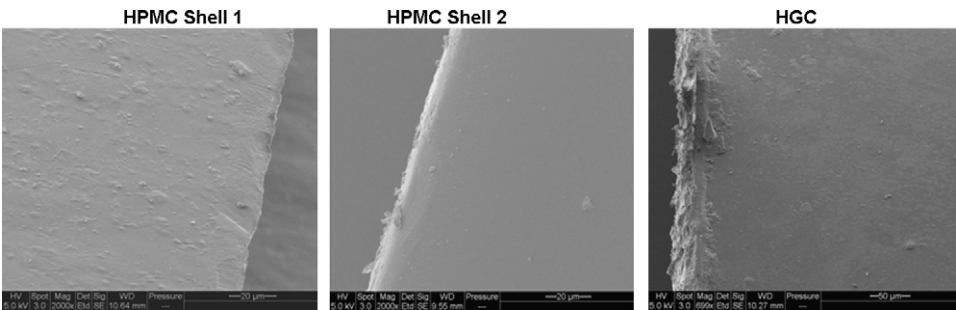


Fig. 2. Scanning electron photomicrographs of the three types of capsule shell surfaces.

dosing; plasma was separated and analyzed for drug content with a validated LC/MS/MS method.

2.14. Human data

The human data are reported from a randomized double-blind sequential-group GCP trial of ascending single doses of oral capsule formulations in healthy volunteers. Groups of six subjects received a single dose after an overnight fast of at least 10 h, and with the fed study, subjects were dosed 5 min after a FDA high-fat meal in a cross-over design. Blood samples were collected up to 72 h post-dose, plasma separated and analyzed for drug content with a validated LC/MS/MS method.

3. Results and discussion

3.1. Comparison of shell thickness and joint gap by scanning electron microscope

The scanning electron photomicrographs of shell surfaces across-the three types are presented in Fig. 2. Hypromellose Shell 2 has a clean edge and very smooth surfaces compared to the other two capsules. The maximum gap between the body and cap as well as the measurement of shell thickness at the closure cross-section is summarized in Table 3. The scanning electron photomicrographs are presented in Fig. 3. HGC has the thickest shell followed by Hypromellose Shell 2 and Hypromellose Shell 1. The shell thickness variations (RSD) are similar. Hypromellose Shell 1 has a large

gap between the body and cap, twice as much as the gap for the gelatin capsule. Hypromellose Shell 2 has slightly larger gap than gelatin but much smaller than Hypromellose Shell 1. An improvement in the powder leakage quality attribute can be expected from the new Hypromellose Shell 2 capsule shell and is shown in the blister carding and seal integrity test section. In fact, no powder leakage has been observed since the replacement of the Hypromellose Shell 1 by Hypromellose Shell 2 in the past 18 months. The evenness and smoothness of the HPMC film contribute significantly to the higher quality performance of the Hypromellose Shell 2. The observed difference in the joint cap correlated well with the leakage rates reported the simulated shipping studies in Section 3.7.

3.2. Hygroscopicity and equilibrium moisture content

The moisture content of Hypromellose Shell 2 and hard gelatin capsules after 1 week storage at different relative humidity are summarized in Fig. 4. Hypromellose Shell 2 capsules have lower average moisture contents of 6% at 50% RH, compared to 14% for gelatin capsules. The gelatin capsule has a 3-fold higher moisture content and is more hygroscopic than the HPMC capsule.

3.3. Mechanical strength evaluation

Due to the nature of the hydrophilic polymers used for the manufacture of hard capsules (gelatin, hypromellose, Pullulan) it is important to consider this parameter as a function of the water equilibrium (Kontny and Muslki, 1989). Hard capsules mechanical

Table 3
SEM analysis of three capsule shells.

	Hypromellose Shell 1	Hypromellose Shell 2	HGC capsule
Average shell thickness (μm)	102.77	103.94	108.79
RSD (%)	0.05	0.09	0.11
Measurements (#)	30	40	47
Max gap (μm)	132.14	88.77	66.86
Shell surface	Rough edge, relatively smooth surface	Clean edge, very smooth surface,	Rough edge, relatively smooth surface

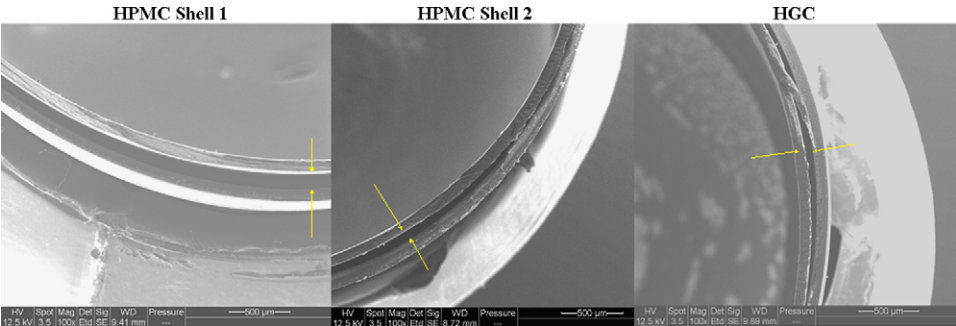


Fig. 3. Scanning electron photomicrographs of the cross-sections at the closure between the body and cap of the three types of capsules.

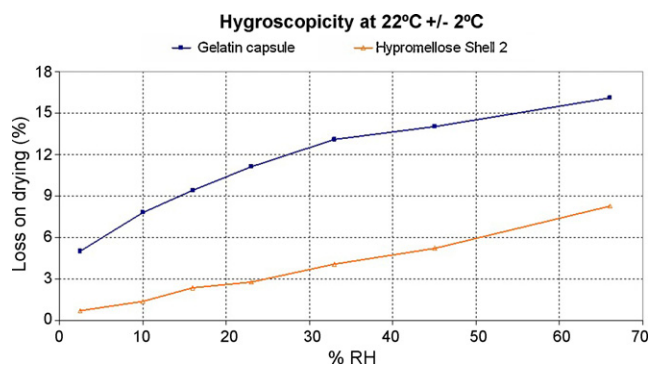


Fig. 4. Equilibrated moisture content of Capsugel HGC and Hypromellose Shell 2 after 1 week storage at different RH.

properties have been evaluated using various techniques in the literature. For our studies we selected the “tube test” (Cadé and Madit, 1996) as the most appropriate method to simulate the stress the capsules may be exposed to during the filling and packaging operations or when “de-blistered”.

Fig. 5 compares the resistance to breakage as a function of storage relative humidity (RH) between gelatin and Hypromellose Shell 2 capsules. At higher humidities, Hypromellose Shell 2 showed similar resistance to breakage as HGC. At lower humidities, gelatin capsules become brittle and exhibit higher breakage rates. Hypromellose Shell 2 capsules are less affected, maintain their elasticity, and resist breakage at low moisture levels. Similar results have been reported for Hypromellose Shell 1 (Ogura et al., 1998).

Based on these data, the specifications for moisture content are 2–7% for Hypromellose Shell 2 corresponding to 10–60% RH storage conditions. Whereas the specifications for moisture content are 13–16% for gelatin capsules corresponding to storage at 35–65% RH. Since the climate in North American and Europe frequently falls below 35% RH except in summer time, it is not uncommon for gelatin capsule shells to dry out and become fragile after storage in uncontrolled humidity warehouses. It is why gelatin capsules need to be stored in controlled environments such as air conditioned rooms.

3.4. Capsule shell weight variation

The manufacture of capsule products typically utilizes a dosing station to form a powder plug which is then inserted into the cap-

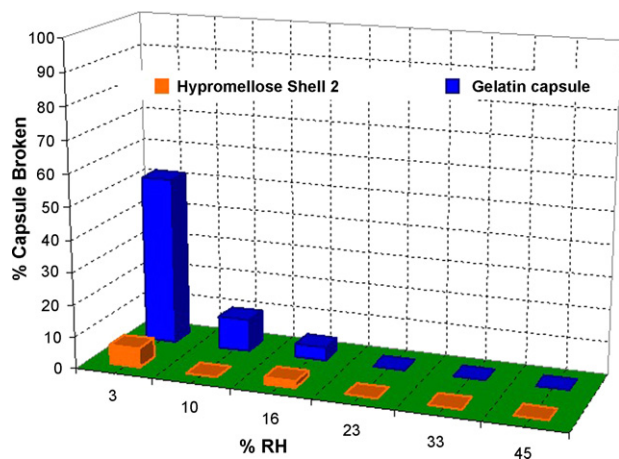


Fig. 5. Comparison of gelatin capsule and Hypromellose Shell 2 resistance to breakage as a function of the equilibrated storage conditions with relative varying relative humidity (RH).

Table 4

Average weights and tolerances of three types of capsule shells.

Size	Mean capsule weight (mg)		
	Hypromellose Shell 1 ^a	Hypromellose Shell 2	HGC
0el	105	107 ± 9	107 ± 7
0	90	96 ± 8	96 ± 6
1	70	76 ± 8	76 ± 5
2	60	62 ± 7	61 ± 4
3	46	47 ± 6	48 ± 3

^a Tolerance reported to vary by ±10%.

sule body followed by closure with the cap. The filled capsules are weight-checked and sorted to remove under or over weight capsules. If the variability of the capsule shell is high, some capsules may be rejected during weight sorting even though the powder fill weights are accurate. Conversely, under or over filled capsules may be accepted with heavier or lighter shells. A narrow weight range for the capsule shells is necessary to ensure that the product does not have a high rejection rate of good product and to give an accurate reflection of the product fill weight uniformity. Hypromellose Shell 1 had been shown to have a relatively large weight variation, making it difficult to achieve weight uniformity, especially for low fill weight formulations where this effect of shell weight variability is exaggerated. As a consequence, formulations were necessarily diluted with more filler in order to have a higher fill weight to minimize the impact of shell weight variation on the total weight.

Table 4 gives the average weights and tolerances that have been reported for hypromellose and hard gelatin capsule shells (Capsugel, 2007, 2009). Hypromellose Shell 1 is reported to vary by ±10% from the target value (Qualicaps, 2005) and the vendor can provide pre-sorted shells with tighter weight tolerances at a cost. Fig. 6 shows the frequency of the three types of Size #0 capsule shell weights. Table 5 gives the acceptable rates within target criteria for 500 Size #0 capsule shells. Similar variability were seen with capsule shell Size #0el. Size #0 and #0el were the primary sizes used in clinical supplies and therefore evaluated in this qualification study.

Hard gelatin capsules showed the tightest weight variation, followed by Hypromellose Shell 2, then Hypromellose Shell 1. All of Hypromellose Shell 2 capsules fell within ±10% of mean and near 98% fell within ±7.5%. Hypromellose Shell 1, on the other hand, had over 21% outside the ±7.5% limit and 10.8% of the shells outside the ±10% limit, with some individual capsules being 15% outside the average. Thus the Hypromellose Shell 2 will provide better control of capsule fill weight, and thus product uniformity, than Hypromellose Shell 1. The tighter shell weight variation will also result in a lower rejection rate during weight sorting with a higher product yield.

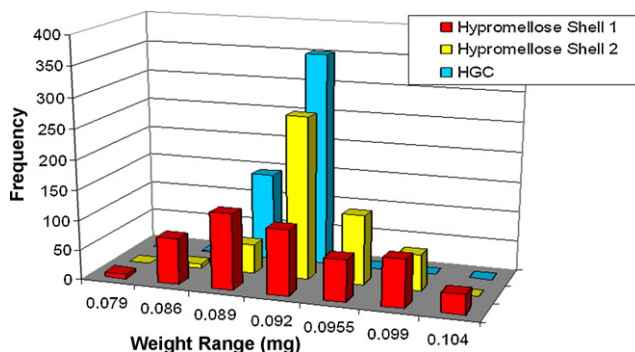


Fig. 6. Size #0 capsule shell weight distributions.

Table 5
Capsule weight variation.

Criteria (\pm target)	Acceptable rate (%)		
	Hypromellose Shell 2 Size #0	Hypromellose Shell 1 Size #0	Capsugel HGC Size #0
5.0%	85.2%	53.2%	100%
7.5%	97.8%	78.4%	100%
10.0%	100.0%	89.2%	100%
Average wt. (mg)	94.5	92.7	92.0
Maximum wt. (mg)	102.6	107	95.2
Minimum wt. (mg)	85.5	79	87.5
RSD	3.29%	6.45%	1.44%

3.5. Machineability evaluation

Throughout the encapsulation process on IN-CAP capsule filling machine, the targeted amount of microcrystalline cellulose powder was filled into Hypromellose Shell 2, Hypromellose Shell 1 and hard gelatin capsules. The fill weight variation is very small for all three types of capsule shells with a fill weight check ranging from 239 to 248 mg around a target of 245 mg. The number of rejected capsules at capsule opening station, capsule filling station and capsule closing station were compared and showed some difference among the three shells. The rejected capsules include split capsule caps and bodies, unclosed capsules and capsules with dimples and creases. The capsule rejection results are summarized in Table 6. HGC performed best with 0.2% rejected, followed by Hypromellose Shell 2 at 2.4% rejected and Hypromellose Shell 1 at 4.2% rejected. The main rejection occurred at the capsule closing station indicates ease of closing plays a very important role in the machineability.

The second machineability evaluation of Hypromellose Shell 2 was on a Bosch H&K 400 encapsulation machine. The experience with Hypromellose Shell 1 used in manufacturing over the last few years had been troubling, especially on the capsule separation and movement during the encapsulation process. The filled Shell 2 capsules were weight-checked individually and as an average of 10 capsules throughout the encapsulation process. The weights were within the specified range, which is $\pm 7.5\%$ of the target fill weight. The powder leakage test performed on a capsule polisher did not find any leaking capsule. The locking system of the filled capsules was checked by pinching the filled capsules and no capsule disengagement was observed. The machine trial on the clinical supply production equipment is deemed superior for the new Shell 2 to the old Shell 1.

Capsule filling machine (CFM) trials with powder filling was performed on a Bosch GKF 1500 filling machine to compare the three shells: Size 00 Natural Transparent Hypromellose Shell 2 against Hypromellose Shell 3 and a reference shell. The performance at rectification, opening, filling, closing and ejection stages were evaluated. The CFM performance is determined by the ability to run the CFM at the same target speeds as for HGC and to run the tested capsules without creating more CFM stops or product losses than in normal when using gelatin capsules. Table 7 summarizes the rejection rates in three categories: % Defect, % Miss, and %Non Sep. The rejection criteria for the three categories are defined as below:

Table 6
Machineability evaluation on IN-CAP (Size #0).

Evaluating area	Capsule rejected (%)		
	Hypromellose Shell 1	Hypromellose Shell 2	Gelatin capsule
Capsule opening station	0.1	0	0
Capsule filling station	0.4	0	0
Capsule closing station	3.7	2.4	0.2
Total capsule lost	4.2	2.4	0.2

- % Defect includes inspection rejects for all possible reasons combined.
- % Miss are for those that do not make it into the filling machine segment causing empty segments due to poor capsule glide, capsules sticking in the magazine, poor rectification and horizontal finger alignment.
- %Non Sep are for those non-opening (capsule not separating from the body) on the filling machine.

The above machine run is at a nominal speed of 90,000 capsules per hour. The new Shell 2 showed the lowest total reject rate at 6.1%. The machine speed was further varied to a range of 60,000–120,000 capsules per hour to evaluate the impact of speed on encapsulation machine for the new Shell 2. The results were summarized Table 8. The reject rates actually improved a little from 7.6% to 4.3% when the machine speed was increased from 60,000 to 120,000. The reject rate at 90,000 was reproducible at 6.7% compared to the previous run at 6.1%.

The capsule filling machine trial was further expanded to three other high speed machines—Bosch GKF 2500, IMA Z40 and MG2 Planeta using both natural and opaque Size 0 Hypromellose Shell 2. The trial was performed without powder filling to evaluate the performance at rectification, opening, filling, closing and ejection. The number of capsules that do not make it into the filling machine segment causing empty segments due to poor capsule glide, capsules sticking in the magazine, poor rectification and horizontal finger alignment (% non-rectified) and the number of capsules rejected due to non-opening (capsule not separating from the body) on the filling machine (% non-separation) are summarized in Table 9. Both natural and opaque capsule Shell 2 performed exceedingly well with no rejects except on MG2 Planeta showing 0.1% non-separating for the opaque shell.

During the on-going collection of CFM performance data in commercial settings and from the above performed CFM trials, the new Hypromellose Shell 2 capsules have received very positive comments from floor operators. The operators working on high-speed equipment commented on the clarity, smooth and shiny

Table 7
Performance on Bosch GKF 1500 Filling machine at 90,000 capsule per hour (Size #00 Natural Hypromellose Shell 2 Capsule).

	% Defect	% Miss	% Non Sep	% Total
Hypromellose Shell 2	1.5	1.2	3.4	6.1
Reference shell	4.6	3.9	0.2	8.7
Hypromellose Shell 3	8.4	1.6	31.8	41.8

Table 8
Impact of machine speed on Bosch GKF 1500 (Size #00 Natural Hypromellose Shell 2).

Speed capsules/HR	% Defect	% Miss	% Non Sep	% Total
60,000	1.9	2.0	3.7	7.6
90,000	1.7	3.0	2.0	6.7
120,000	1.0	1.0	2.3	4.3

Table 9

Test results on different types of high speed encapsulation machine (Size 0 Hypromellose Shell 2).

	% Non-rectified		% Non-separation	
	Nat	Opaque	Nat	Opaque
IMA Z40	0.0	0.0	0.0	0.0
Bosch 2500	0.0	0.0	0.0	0.0
MG2 Planeta	0.0	0.0	0.0	0.1

appearance, as well as a cleaner finish and observed much less exterior product clinging to the capsule shell. Performance trials on high speed Bosch, MG, IMA as well as semi-automatic machine clearly indicate that the new Shell 2 with no gelling agent are superior to the existing gellan gum and carrageenan shells in the market. Since Shell 2 is of a different polymer, some machine-specific set-ups are required for optimum encapsulation efficiency. In many cases, no adjustments are needed when switching to Hypromellose Shell 2 capsules. But sometimes, optimization of CFM performance is achieved through minor adjustments such as vacuum settings or slight enlargement of diameters, and fine tunings of CFM settings to optimize the performance, especially with larger size capsules. This is however not typical for Hypromellose Shell 2 capsules, as the same adjustment is sometimes encountered with HGC as well, depending on the brand and type filling machine.

Continuous improvement of machineability for this new HPMC capsule shell is expected in future to match the performance of gelatin capsule that has been perfected over the long use history for the past 50 years.

3.6. Blistering and carding evaluation

Powder leakage is an important issue that has been observed during blister packaging for Hypromellose Shell 1. The presence of powder outside the capsule shells had lead to quality and safety concerns at clinical study sites in Japan and consequently

Hypromellose Shell 1 batch rejection. Therefore, the absence of powder leakage during blistering and carding operation is an important criteria for the qualification of Hypromellose Shell 2. 19,040 placebo powder-filled Hypromellose Shell 2 capsules were blister-packed on 680 blister strips with 28 capsules in each blister. There was no powder leaking in the blister upon visual inspection. 20 capsules were found with damages prior to the blistering process.

The blisters were then carded which are the primary packaging choice for both commercial and clinical supplies. Blister carding is a process in which a blister strip is placed on a paper card and seal using heat and pressure. The evaluation of Shell 2 capsules under blister carding process runs very well. 255-Carded blisters were made with Zed 15-DLX Shuttle Blister Sealer Machine. All carded blisters were visually inspected and there was no powder leakage found.

3.7. Simulated transportation test

Simulated transportation test showed no powder leakage for the powder-filled Hypromellose Shell 2 and gelatin shells, whereas powder-filled Hypromellose Shell 1 had a 6% leak rate around the joint of capsule body and cap. The 100 cm³ HDPE bottles packed with the powder-filled hypromellose capsules were then shipped from UK to Japan using standard DHL shipping and powder leakage was found for Shell 1 but not for Shell 2 verifying the simulated transportation test results. The replacement of Shell 1 with Shell 2 helped to resolve the quality issue of powder leakage for Japan clinical supplies.

3.8. Short term stability at high temperature

After storage in the closed glass bottle and heated at seven temperatures up to 90 °C for 24 h, Hypromellose Shell 2 capsules showed more resistance and less discoloration than hard gelatin capsules to high temperature. Capsule performance on disinte-

Table 10

Stability evaluations after heated for 24 h in closed glass bottles.

Visual Evaluation							
Temperature	Room conditions	40 °C	50°C	60°C	70°C	80°C	90°C
HGC Capsules	No change		Slight color change	Capsuled deformed, sticking together and partly molten			
Hypromellose Shell 2	No change	Slight color change			Capsules more brownish with salting out		
Disintegration and dissolution							
Temperature	Room conditions	40 °C	50°C	60°C	70°C	80°C	90°C
HGC Capsules	No change			Test not applicable as capsules are deformed, sticking together and partly molten			
Hypromellose Shell 2	No change						
Mechanical Property Assessment (tube test)							
Temperature	Room conditions	40 °C	50°C	60°C	70°C	80°C	90°C
HGC Capsules	No change			Test not applicable as capsules are deformed, sticking together and partly molten			
Hypromellose Shell 2	No change						

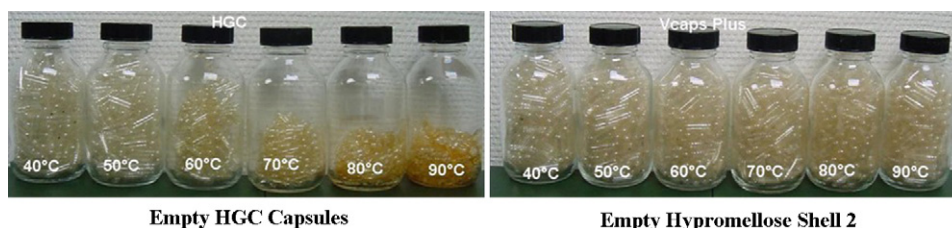


Fig. 7. Visual evaluation after heated for 24 h in closed glass bottles.

gration and dissolution were then tested using three media: pH 1.2 USP buffer, demineralized water and pH 6.8 USP buffer. Resistance to breakage was tested using the Capsugel “tube test” method which consists of a 100 g weight dropped on an empty capsule ($n = 50$) from a height of 8 cm. Hypromellose Shell 2 capsules are not affected by short term exposure to high temperature and maintain their elasticity. The evaluation results on visual test, disintegration and dissolution, as well as mechanical property assessment are compared in Table 10 and Fig. 7. Overall, Hypromellose Shell 2 exhibits a significantly better short term stability at high temperature than hard gelatin capsules.

3.9. Formaldehyde cross-linking challenge test

Incompatibility of gelatin capsules with lactose is well known and it is originated from the trace of a stabilizer, hexamethylenetetramine, which decomposes into formaldehyde (Digenis et al., 1994) which cross-links with gelatin. With the recent development of the liquid capsule formulations, there is a growing concern as some of the excipients used such as fats, polyethylene glycols and its ethers, aliphatic alcohols or phenols, polyoxylenated glycerides, polysorbates and esters of unsaturated fatty acids can undergo auto oxidation to form aldehydes (Nassar et al., 2004; Doelker and Vial-Bernasconi, 1988; Chafetz et al., 1984).

Cross-linking susceptibility of capsules is compared using lactose spiked with 25 ppm formaldehyde (HCHO), a known cross-linking agent. After 1 week storage at room temperature, dissolution of acetaminophen from the Hypromellose Shell 2 is unchanged while gelatin shell observed significant dissolution slow down. The dissolution profiles are presented in Fig. 8.

3.10. Liquid fill excipient compatibility

It is generally recognized that nowadays, the discovery pipeline has much less BCS Class 1 compounds with high solubility and high permeability. It is estimated that about 40% clinical pipeline compounds can benefit from formulation manipulation to improve human PK performance (Ku, 2008a). The author has previously

reported (Ku, 2008b) that 15% of Wyeth oral clinical products from 2003 to 2008 utilized liquid capsules in order to optimize dose linearity and reduce PK variability in human. Therefore it is critical to evaluate Hypromellose Shell 2 for compatibility of those excipients used commonly for solubilized formulations in capsules.

Compatibility with 10 commonly used excipients was compared between HGC and Hypromellose Shell 2. The excipients were selected based on in-house data accumulated over the past 10 years in that their long term room temperature compatibility was demonstrated when used at not more than 40% in HGC. The selected excipients encompass the three functionality classes as surfactant, cosurfactant, or solvent that are commonly present in liquid fill formulations. The filled capsules were stressed at 40 °C/75% RH for up to 7 weeks beyond the stable period for most excipients with HGC. The capsules were visually examined against empty capsules for shape change (swelling or shrinkage) and leakage of fill formulation. Table 11 summarizes the results for HGC in a descending order of compatibility (top is most compatible and bottom is least compatible). All excipients passed visual inspection after 3 weeks storage at 40 °C/75% RH. Severe swelling was observed for Capmul[®] MCM and Labrasol[®] after 4 and 5 weeks respectively. The Phosal[®]

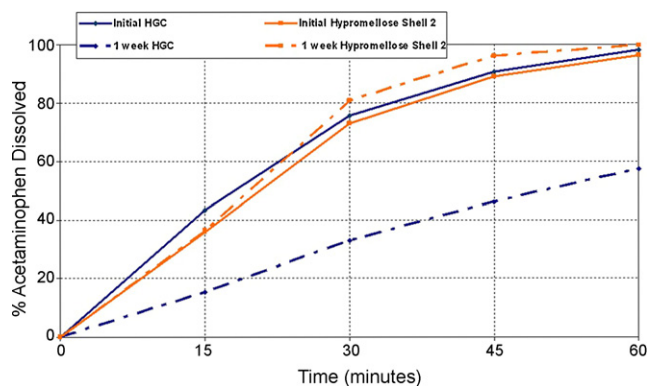


Fig. 8. Dissolution of APAP in HGC and Hypromellose Shell 2 after 1 week exposure to lactose spiked with formaldehyde.

Table 11
Compatibility of excipients in HGC (LiCap[®]) capsule.

Excipient	Functionality	Visual observation ^a						
		1 Week	2 Weeks	3 Weeks	4 Weeks	5 Weeks	6 Weeks	7 Weeks
Polyethylene glycol 400	Solvent	c	c	c	c	c	c	c
Caprylic/capric triglyceride	Solvent	c	c	c	1-leak	2-leak	2-leak	2-leak
Propylene glycol monocaprylate 90% (Type II)	Cosurfactant	c	c	c	c	2-leak	2-leak	2-leak
Propylene glycol monolaurate (Type II)	Cosurfactant	c	c	c	1-leak	1-leak	1-leak	1-leak
Mono- and di-glycerides (Imwitor 742 [®])	Cosurfactant	c	c	c	c	1-swell	1-swell	1-leak 1-shrink
Mono- and di-glycerides (Capmul MCM [®])	Cosurfactant	c	c	c	3-swell	3-swell	4-swell	4-swell
Caprylocaproyl polyoxyglycerides	Surfactant	c	c	c	c	2-swell	4-swell	4-swell
Lecithin in caprylic/capric triglycerides/alcohol	Solvent	c	c	c	c	c	c	c
Polysorbate 80	Surfactant	c	c	c	c	1-shrink	1-shrink	1-shrink
Polyoxyl 35 Castor Oil	Surfactant	c	c	c	1-iaK 1-shrink	i-iaK 1-shrink	i-iaK 1-shrink	i-iaK 1-shrink

c—compatible.

^a Number of leak/sweat/swell/shrink out of 4 capsules.

Table 12
Compatibility of excipients in Hypromellose Shell 2.

Excipient	Functionality	Visual observation ^a						
		1 Week	2 Weeks	3 Weeks	4 Weeks	5 Weeks	6 Weeks	7 Weeks
Polyethylene glycol 400	Solubilizer	c	c	c	1-shrink	2-shrink	2-shrink	2-sweat 1-shrink
Caprylic/capric triglyceride	Oily vehicle, solubilizer	c	c	c	c	c	c	c
Propylene glycol monocaprylate 90% (Type II)	Oily vehicle, solubilizer	1-leak	1-leak	1-leak	1-leak	1-leak	1-leak	1-leak
Propylene glycol monolaurate (Type II)	Oily vehicle, solubilizer	c	c	c	c	c	c	c
Mono- and di-glycerides (Inwitor 742®)	Oily vehicle, solubilizer	1-leak	1-leak	1-leak	1-leak	1-leak	1-leak	1-leak
Mono- and di-glycerides (Capmul MCM®)	Oily vehicle, solubilizer	c	c	c	c	1-leak	1-leak	1-leak
Caprylocaproyl polyoxylglycerides	Oily vehicle, solubilizer	c	c	c	c	c	c	c
Lecithin in caprylic/capric triglycerides, alcohol, glyceryl stearate, oleic acid and ascorbyl palmitate (Phosal 53 MCT®)	Oily vehicle, solubilizer	c	c	c	c	c	c	c
Polysorbate 80	Surfactant	c	c	c	c	c	c	c
Polyoxyl 35 Castor Oil	Surfactant	c	c	c	c	c	c	c

c—compatible.

^a Number of leak/sweat/swell/shrink out of 4 capsules.

53 MCT was found to be the most compatible excipient in the HGCs. Table 12 summarizes the data for Hypromellose Shell 2. Eight of ten excipients showed compatibility for at least 3 weeks and 6 of 10 for the full 7 weeks at 40 °C/75% RH. Sweating and shrinkage were observed with Super Refined® PEG 400 after 7 weeks. Leaking was also observed in the capsules filled with Capryol® 90, Inwitor® 742 and Capmul® MCM which have lower molecular weight.

Six out of ten excipients were found compatible with the HPMC capsules and did not show any leakage or capsule changes for the full 7 weeks at 40 °C/75% RH. In particular, two of the four excipients that are not compatible showed leakage in the first week. It is theorized that these excipients may have a molecular size smaller than the pore size of the HPMC film matrix. In contrast, only two solvents (PEG 400 and Phosal® 53 MCT) were found compatible with the hard gelatin capsules. None of the surfactants are compatible. Furthermore the leakage was accompanied by shrinkage or swelling and did not occur until after at least 3 weeks. It is theorized that gelatin as a protein may slowly be denatured by excipients with good surfactancy resulting in swelling or shrinkage followed by leakage from the enlarged pore size.

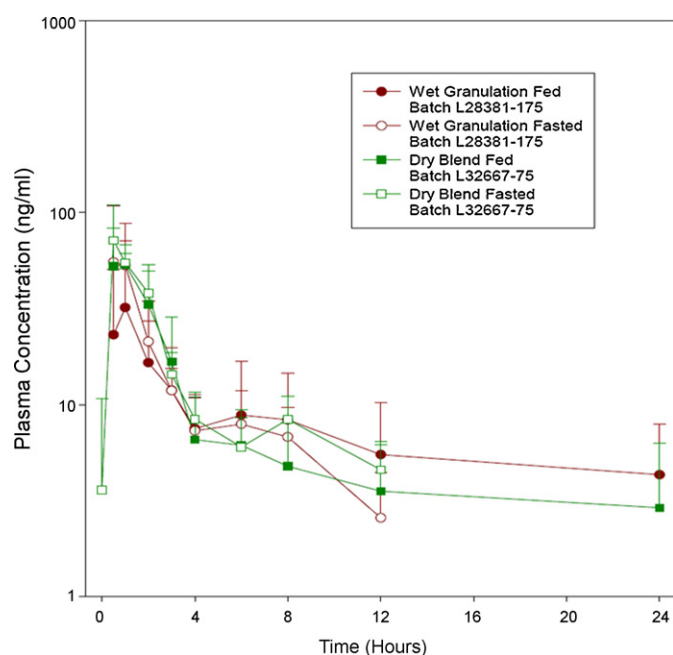


Fig. 9. Dog PK profile of Compound 1 encapsulated in Size #0 Hypromellose Shell 1.

The results from this study show that certain excipients have better compatibility with gelatin and others with HPMC capsules. This study suggests matching of formulation with capsule shell materials is critical for long term physical stability. A wider selection of excipients may be possible through choice selection of more than one type of capsule shells. It is advisable to screen excipients and their combination for capsule shell compatibility prior to finalization of liquid fill formulations.

3.11. In vivo evaluation

Cole et al. (2004) described slow disintegration *in vitro* for hypromellose capsules using gellan gum as the gelling agent. The slow down is caused by ionic interactions between the acidic and phosphate buffers and the gellan gum which exerts its gelling action by expanding the glycoprotein helical chains. As a consequence, a human scintigraphic study using Ibuprofen, a BCS Class 2 compound, was carried out to examine if the disintegration differences would reproduce *in vivo*. The result showed a significant difference in the *in vivo* disintegration times but not in esophageal transit. The initial and the complete disintegration times were 28 and 41 min for the hypromellose shell 3 and 8 and 14 min for the gelatin shells respectively. In spite of these differences from the scintigraphy, there was no significant difference in the pharmacokinetic parameters for the two shells. Nevertheless, the slow disintegration for the hypromellose shell 3 may be detrimental for those products requiring fast absorption and fast onset of therapeutic effects.

Comparatively, Tuleu et al. (2007) reported rapid disintegration of the hypromellose shell 1 based shells matching that of gelatin shells in a human scintigraphic study. The disintegration times were 7 and 9 min for the gelatin and Hypromellose Shell 1, respectively. This is why the Hypromellose Shell 1 was selected to replace the gelatin shell for all new Wyeth clinical lead compounds in 2002. The *in vivo* performance in animal and human for Shell 1 were satisfactory for >30 compounds from 2002 to 2007. Therefore the change from Shell 1 to Shell 2 is not for *in vivo* but for *in vitro* overall quality improvement in dissolution and manufacture. After the change over from Shell 1 to Shell 2, the *in vivo* animal and human data are compared retrospectively to ensure no change in the *in vivo* performance. This retrospective comparison between an old Compound 1 using Shell 1 and a new Compound 2 using Shell 2 are presented below.

3.12. Animal data

Animal testing of immediate-release formulations using Hypromellose capsule shells reflected a rapid T_{max} , indicating that

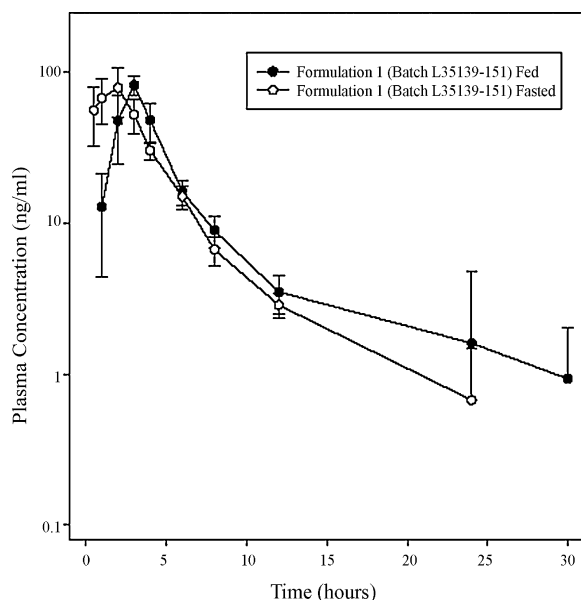


Fig. 10. Dog PK profile of Compound 2 encapsulated in Size #0 Hypromellose Shell 2.

the dissolution of the capsule shell was not rate-limiting for absorption. Fig. 9 shows the dog PK profile for Compound 1 encapsulated in Hypromellose Shell 1 across two different immediate-release formulations optimized for the wet granulation and dry blend processes. The plasma profiles yielded a T_{max} of less than 1 h in the fasted state and slightly longer, as expected, when given with food. Fig. 10 likewise shows a short T_{max} for an immediate-release formulation of Compound 2 given to dogs, reflecting rapid in vivo dissolution of Hypromellose Shell 2.

3.13. Human data

Fig. 11 shows human dose escalating data for an immediate-release formulation of Compound 1 filled in Hypromellose Shell 1. The median T_{max} of approximately 1 h in the absence of food reflects the rapid disintegration of the hypromellose capsule shell. Fig. 12 shows human dose escalating data for an immediate-release formulation of Compound 2 filled in Hypromellose Shell 2. Again, the median T_{max} of approximately 1 h in the absence of food indicates a rapid disintegration of the shell. Thus, both Hypromellose Shells 1 and 2 yield a comparable quick in vivo plasma profile in both animals and humans.

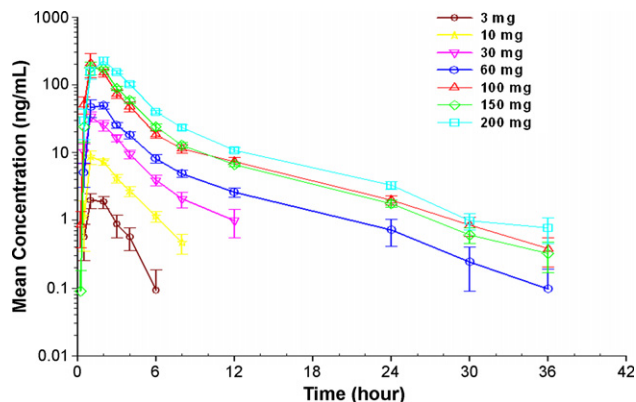


Fig. 11. Human PK profile of Compound 1 encapsulated in Size #0 Hypromellose Shell 1.

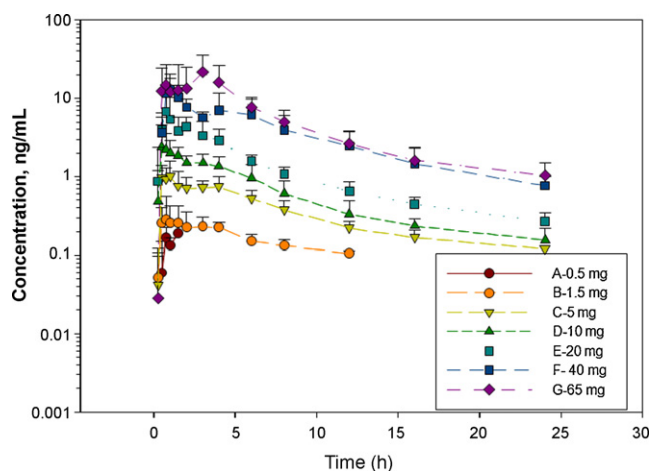


Fig. 12. Human PK profile of Compound 2 encapsulated in Size #0 Hypromellose Shell 2.

4. Conclusions

This Part I paper describes the qualification of a new high performance hypromellose (hydroxypropyl methylcellulose, HPMC) capsule shell which contains no gelling agent and is dissolution friendly. The development history and the test results for a series of quality attributes including scanning electron microscopy, hygroscopicity, machineability, weight variation, powder leakage, mechanical strength, stability, cross-linking, animal and human pharmacokinetic results are reported. Comparisons to gelatin and HPMC capsule containing carrageenan showed the new HPMC capsule is superior in terms of mechanical strength, hygroscopicity and compatibility with a wide range of drugs. Specifically, the new HPMC capsule demonstrated improved weight variation, machineability and powder leakage than the HPMC capsule containing carrageenan. And the new capsule demonstrated a broader applicability than gelatin capsule for new drug development due to its inertness and compatibility for a wide range of excipients including those used for liquid fill formulations. Based on the superior performance, the new HPMC capsule is satisfactorily qualified and has since been used successfully for nearly 20 investigational new drug (IND) compounds. There is no powder leakage from the new Shell 2 capsules found in the 2 years which is a critical improvement in clinical supply quality.

During the 6 years (2002–2007) of using Hypromellose Shell 1 for over 30 IND compounds, it is not without dissolution problems. It exhibits slow dissolution in medium with divalent cations and potassium ion but disintegrates quickly in acid due to the negative charge retention on the sulphate groups of carrageenan. With careful selection of dissolution buffer species and concentrations, a pH independent dissolution profile may be achieved for some compounds. Since Hypromellose Shell 2 contains no gelling agent and is therefore more inert toward ionic species and buffers. In the second phase of qualification, disintegration and dissolution properties of the new HPMC capsule were evaluated and reported in a Part II paper for 10 new clinical compounds with a variety of formulations optimized based on the biopharmaceutical classification system of solubility and permeability.

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References

- Brown, J., Madit, N., Cole, E.T., Wilding, I.R., Cade, D., 1998. Effect of cross-linking on the in vivo disintegration of hard gelatin capsules. *Pharm. Res.* 15, 1026–1030.
- Cadé, D., Madit, N., 1996. Liquid filling in hard capsules—preliminary steps. *Bulletin Technique Gattefossé*, 15–20.
- Cade, D., Scott, R., He, X., 2003. Polymer film compositions for capsules. US Patent No. 6,517,865 B2, February.
- Capsugel, 2007. Technical Reference File, Vcaps® Plus Two-Piece Capsules, Version 1.2.
- Capsugel, 2009. Coni-Snap Capsules (Link: <http://www.capsugel.com/products/conisnap.chart.php>).
- Chafetz, L., Hong, W.H., Tsilifonis, D.C., Taylor, A.K., Philip, J., 1984. Decrease in the rate of capsule dissolution due to formaldehyde from polysorbate 80 auto oxidation. *J. Pharm. Sci.* 73, 1186–1187.
- Cole, E.T., Scott, R.A., Cade, D., Connor, A.L., Wilding, I.R., 2004. In vitro and in vivo pharmacoscintigraphic evaluation of ibuprofen hypromellose and gelatin capsules. *Pharm. Res.* 21, 793–798.
- Cole, S.K., Story, M.J., Attwood, D., Laudanski, T., Robertson, J., Barnwell, S.G., 1992. Studies using a non-ionic surfactant-containing drug delivery system designed for hard gelatin capsule compatibility. *Int. J. Pharm.* 88, 211–220.
- Digenis, G.A., Gold, T.B., Shah, V.P., 1994. Cross-linking of gelatin capsules and its relevant to their in-vivo performance. *J. Pharm. Sci.* 83, 915–921.
- Digenis, G.A., Sandefer, E.P., Page, R.C., Doll, W.J., Gold, T.B., Darwazeh, N.B., 2000. Bioequivalence study of stressed and nonstressed hard gelatin capsules using amoxicillin as a drug marker and gamma scintigraphy to confirm time and GI location of in vivo capsule rupture. *Pharm. Res.* 17, 572–582.
- Doelker, E., Vial-Bernasconi, A.C., 1988. Interactions contenant-contenu au sein des capsules gélatineuses et évaluation critique de leurs effets sur la biodisponibilité des principes actifs S.T.P Pharma, vol. 4, pp. 298–306.
- FDA BSE Testimony, 2003. US Food and Drug Administration (FDA) Bovine Spongiform Encephalopathy (BSE) Testimony (Link: <http://www.fda.gov/NewsEvents/Testimony/ucm161943.htm>).
- FDA Guidance, 1995. Guidance for Industry, Immediate Release Solid Oral Dosage Forms Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (SUPAC-IR). U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER).
- FDA Guidance, 1997a. Guidance for Industry: The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated Products for Human Use, Food and Drug Administration (Link: <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125182.htm>).
- FDA Guidance, 1997b. Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER).
- Greenspan, L., 1977. Humidity fixed points of binary saturated aqueous solutions. *J. Res. Natl. Bur. Stand.* 81A, 89–96.
- Grosswald, R.R., Anderson, J.B., Andrew, C.S., 1997. Method of manufacture of pharmaceutical cellulose capsules. US Patent No. 5,698,155, December.
- Grosswald, R.R., Anderson, J.B., Andrew, C.S., 1998. Apparatus for the manufacture of pharmaceutical cellulose capsules. US Patent No. 5,750,157, May.
- Grosswald, R.R., Anderson, J.B., Andrew, C.S., 1998. Method for the manufacture of pharmaceutical cellulose capsules. US Patent No. 5,656,036, May.
- Kontny, M.J., Muslki, C.A., 1989. Gelatin capsules as a function of relative humidity at room temperature. *Int. J. Pharm.* 54, 79–85.
- Ku, M.S., 2008a. Use of the biopharmaceutical classification system in early drug development. *AAPS J.* 10, 208–212.
- Ku, M.S., 2008b. Early formulation development approaches: Wyeth perspective. In: AAPS First-in-Human Formulation Strategy Symposia Presentation, AAPS Annual Meeting, Atlanta, GA.
- Liebowitz, S.M., Vadino, W.A., Ambrosio, T.J., 1990. Determination of hard gelatin capsule brittleness using a motorized compression test stand. *Drug Dev. Ind. Pharm.* 16, 995–1010.
- Matsuura, S., Tanjoh, M., 2003. Hard capsule formed of cellulose ether film with a specific content of methoxyl and hydroxypropoxyl groups. US Patent No. 6,649,180 B1, November.
- Missaghi, S., Fassihi, R., 2006. Evaluation and composition of physicochemical characteristics of gelatin and hypromellose capsules. *Drug Dev. Ind. Pharm.* 32, 829–838.
- Murphy, H.W., 1950. Methyl cellulose capsules and process of manufacture. US Patent No. 2,526,683, October.
- Nassar, M.N., Nesarikar, V.N., Lozano, R., Parker, W.L., Huang, Y., Palaniswamy, V., Xu, W., Khaselev, N., 2004. Influence of formaldehyde impurity in the polysorbates 80 and PEG-300 on the stability of a parenteral formulation of BMS-204352: identification and control of the degradation product. *Pharm. Dev. Tech.* 9, 189–195.
- Ogura, T., Furuya, T., Matsuura, S., 1998. HPMC capsules—an alternative to gelatin. *Pharm. Tech. Eur.* 10, 32–42.
- Qualicaps, 2005. Quali-V® Hypromellose Capsules Handbook.
- Rowe, R.C., Sheskey, P.S., Weller, P.J., 2003. Handbook of Pharmaceutical Excipients, 5th ed. Pharmaceutical Press (London, UK) and the American Pharmacists Association (Washington DC, USA).
- Tuleu, C., Khela, M.K., Evans, D.F., Jones, B.E., Nagat, S., Basit, A.W., 2007. A scintigraphic investigation of the disintegration behavior of capsules in fasting subjects: a comparison of hypromellose capsules containing carrageenan as a gelling agent and standard gelatin capsules. *Eur. J. Pharm. Sci.* 30, 251–255.
- US Pharmacopeia XXXII, 2009. US Pharmacopeial Convention, Rockville, MD, USP32/NF 27, USP<711> Dissolution, pp 263–271.
- Yamamoto, T., Abe, K., Matsuura, S., 1993. Hard capsule for pharmaceutical drugs and method for producing the same. US Patent No. 5,264,223, November.
- Yamamoto, T., Abe, K., Matsuura, S., 1995. Hard capsule for pharmaceutical drugs and method for producing the same. U.S. Patent No. 5,439,917, 11 July.
- Yamamoto, T., Matsuura, S., Akai, K., 1998. Capsule shell. US Patent No. 5,756,123, 26 May.