AN ALTERNATIVE TO GELATIN CAPSULE SHELL – A REVIEW

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ABSTRACT
The non-animal components of the hypromellose capsule formulation are accepted for pharmaceutical use in all major global markets. Using a proprietary manufacturing process that eliminates the addition of gelling agents, HPMC capsules expand the range of capsule applications. In recent era, vegetable capsules are new approach which might be replacing the usage of gelatin or non-vegetable capsules. Hypromellose is mainly used in manufacturing of such kind of capsule shell. Despite the great advantages of gelatin capsules, gelatin has numerous drawbacks that limit its utilization for capsules. The animal source of gelatin can be a quandary for certain consumers such as vegetarians or vegans and religious or ethnic groups. Since unmodified gelatin is prone to cross linking when in contact with aldehydes, solubility problems might be expected with certain fill formulations. The non-gelatin capsule shells are made up of such as Starch, HPMC, PVA, and Alginate. The main objective to write this review is to assess published literature on the vegetable capsule shells and steadfastness objections regarding their appropriateness as a substitute for hard gelatin capsules.

Key words: - Gelatin, Vegetable capsule shell, Hypromellose, HPMC, Dissolution, Alginate capsule shell.

INTRODUCTION

With an elegant high gloss surface, hypromellose capsules appear identical to gelatin, and use a similar array of colorants including globally-approved iron oxide pigments. With no animal derived components, a wider array of global dietary needs and preferences are met. Capsules are solid dosage forms in which the drug is enclosed within either a hard or soft soluble container or shell. The shells are usually formed from gelatin however; they also may be made from starch or other suitable substances. [1] The gelatin capsule shell may be soft or hard depending on their formulation. Capsules are intended to be swallowed whole by the patient. [2]

In the manufacture of pharmaceuticals, encapsulation refers to a range of techniques used to enclose medicines in a relatively stable shell known as a capsule, allowing them to, for example, be taken orally or be used as suppositories. The two main types of capsules are hard shelled capsules and soft shelled capsules. Both of these classes of capsules are made from aqueous solutions of gelling agents like:

✔ Animal protein mainly gelatin;
✔ Plant polysaccharides or their derivatives like carrageenans and modified forms of starch and cellulose.
Vegetable capsule shell is mainly manufactured from the hydroxypropyl methylcellulose most commonly known as hypromellose. It is produced by synthetic modification of the naturally occurring polymer cellulose and is considered safe for normal consumption, in human as a coating polymer, as a bioadhesive, thickening agent in controlled release systems, in solid dispersion to enhance drug solubility, as a bioadhesive, and as a binder. The cross linking of gelatin and drug incompatibilities and the strict regulations regarding the use of animal derived gelatin requiring the absence of bovine spongiform encephalopathy (BSE)/ transmissible spongiform encephalopathy (TSE) have encouraged the search for gelatin replacement. Religious, cultural and personal issues may affect patients’ preference towards the medications presented in capsule dosage forms. [3] The production of HPMC capsules are by thermal gelation and a gelling system used to lower thermal gelation temperature of HPMC. The production technique remains similar to that of hard gelatin capsules and involves the use of pins dipping into HPMC solution, although the machinery may require some modifications such as the use of heated pins. The HPMC capsules patented are not all the same and differ mainly in whether a gelling system is used and in the type of gelling system. [4]

**Hypromellose capsules:**
Hypromellose (INN), short for hydroxypropyl methylcellulose (HPMC), is a semi synthetic, inert, viscoelastic polymer used as an ophthalmic lubricant, as well as an excipient and controlled-delivery component in oral medicaments, found in a variety of commercial products. [5]

<table>
<thead>
<tr>
<th>Table 1: Product details</th>
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<tbody>
<tr>
<td><strong>Other names</strong></td>
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<tr>
<td><strong>CAS number</strong></td>
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<tr>
<td><strong>Chem Spider</strong></td>
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<tr>
<td><strong>UNII</strong></td>
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<tr>
<td><strong>Molecular formula</strong></td>
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<td><strong>Molar mass</strong></td>
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**Properties of Hypromellose:**

**Well Suited for Moisture-Sensitive Formulations:** With low moisture content, HPMC capsule applications include:
- Formulations that contain hygroscopic materials, including dry powder inhalers.
- Formulations with active ingredients that are moisture sensitive.

**Excellent Machinability & Mechanical Stability:**
- An exclusive capsule design coupled with an elastic polymer structure enables high machine efficiencies.
- Extensive field testing on a wide array of capsule filling and blister packaging equipment confirms robust commercial performance.
- HPMC capsule shells are not affected by moisture. Even in low humidity environments, they maintain their elasticity and ability to resist mechanical breakage.
Resistant to Cross-Linking:
With a well-characterized and stable polymer structure, HPMC capsules offer reduced potential for cross-linking. And unlike gelatin, they will not cross-link with aldehydes.

**Globally Accepted Formulation:** The non-animal components of the HPMC capsule formulation are accepted for pharmaceutical use in all major global markets.

- TSE certification is not required, reducing the resources required for regulatory filings and international shipping and customs documentation.

### Table 2: Literature review of HPMC based capsules

<table>
<thead>
<tr>
<th>S.No</th>
<th>Name of researchers/company</th>
<th>Workdone</th>
</tr>
</thead>
<tbody>
<tr>
<td>01.</td>
<td>U.S. Pat. Nos. 5,264,223 and 5,431,917 registered for Yamamoto et al.</td>
<td>Capsules can be produced by the use of HPMC with the gelatinizing agent such as carrageenan (HPMCcarr) and auxiliary for gelation is a water-soluble compound containing potassium ion. [6,7]</td>
</tr>
<tr>
<td>02.</td>
<td>Yang of Suheung Capsule Co., Ltd., a Korean based company, had patented cellulose capsules using mixed solution of pectin and glycerin.</td>
<td>Manufacture are to add the mixed solution of pectin and glycerin to the HPMC solution followed by the addition of small amount of glacial acetic acid, calcium gluconate, and sucrose fatty acid ester.[8]</td>
</tr>
<tr>
<td>03.</td>
<td>Warner-Lambert Company (now with Capsugel that later became part of Pfizer).</td>
<td>documented the preparation of HPMC capsules with hydrocolloids such as gellan gum (HPMCgell) and sequestering agents (such as ethylenediaminetetraacetic acid, sodium citrate, Citric acid and their combinations). Gellan gum is a water-soluble polysaccharide produced by the bacteria <em>Sphingomonas elodea</em>. 5% of the capsule shell materials comprised of approximately equal proportions of both the hydrocolloid and the sequestering agent.[9]</td>
</tr>
</tbody>
</table>
Table 3: Availability of product in the market of HPMC based shell

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Product name</th>
<th>Formulation type</th>
</tr>
</thead>
<tbody>
<tr>
<td>01.</td>
<td>Ex-Tox II</td>
<td>Folic acid, cilantro powder (leaf), ethylenediamine tetraacetic acid, N-Acetyl L-cysteine, fulvic (humic) acid, Rlipoic acid (K-RALA), L-methionine</td>
</tr>
<tr>
<td>02.</td>
<td>Align Daily Probiotic Supplement Capsules</td>
<td>Bifidobacterium infantis</td>
</tr>
<tr>
<td>03.</td>
<td>Planetary Herbals Cinnamon Extract</td>
<td>Cinnamomum aromaticum 300 mg, bark extract 10:1 yielding 8% flavonoids, cinnamomum aromaticum bark 100 mg</td>
</tr>
<tr>
<td>04.</td>
<td>Natren Life Start 2</td>
<td>Bacteria, vitamin C, potato powders and whole goat milk</td>
</tr>
<tr>
<td>05.</td>
<td>Damiana Herb 300mg</td>
<td>Pure powdered herbs (<em>Damiana turnera aphrodisiaca</em>)</td>
</tr>
</tbody>
</table>

**Capsule Size Information**

HPMC capsules are available in similar physical dimensions of sizes and shell weights as that of hard gelatin capsules. Gelatin capsules are the main stream in the production for most capsule manufacturing companies and because their production has been standardized over long period, they are available in wider range of sizes. Ex. Capsugel company (A Pfizer division) produces Coni Snap hard gelatin capsules in the standard sizes from 000 to 5 with elongated sizes (have capacities approximately 10% more than the standard ones) for capsules 00, 0, 1 and 2, while the same company produces V-caps Plus HPMC capsules with sizes from 00 to 4 with elongated capsules for size 0. The cross sectional part of the capsule joints has been evaluated under electron microscope for three types of capsule shell. The examination intended to measure the maximum observed gap between the body and the cap. The relationships between wet film dimensions, dip sequences, and the physicochemical properties of the dip solutions in the manufacture of hard-shell capsules were studied. In the dipping process for making hard-shell HPMC capsules, the effects of solution concentration are more important than pin temperature. It is difficult to predict wet film thickness in a hot-pin, cold solution dipping process. [10, 11]

Figure 1: Empty capsule shell of HPMC
Hardness of capsules:
In a test examining the effect of humidity on the mechanical properties of both HPMC and gelatin capsules, it was found that both types of capsules softened, especially above 60% of relative humidity, with gelatin capsules exhibiting in general higher stiffness and hardness values compared to the HPMC capsules. In another study it was found that at ambient conditions, capsules made from gelatin were harder and stronger but less elastic compared with HPMC counterparts. [12, 13]

Manufacturing of HPMC capsules:
HPMC based soft capsules, which are available as alternative to soft gelatin capsules. Hard gelatin and HPMC capsules are manufactured using similar equipments developed by Eli Lilly. In hard gelatin capsule manufacturing, pins (molds for making the capsules) at 22°C are dipped in a dip pan or pot that holds a fixed quantity of gelatin at a constant temperature, between 45° and 55°C. The level of solution is maintained automatically by a feed from the holding hopper. Once the molds are dipped a film will be formed on them by gelling since they are at lower temperature. The slowly withdrawn pins from the dipping pan are rotated to maintain uniform film thickness, where they are passed through a series of drying kilns at controlled temperature and humidity. The dried films (shells) are stripped of the pins, cut to the correct length and the two pieces (cap and body) are joined together. The pins are then cleaned and lubricated to start the next cycle. The manufacture of HPMC based capsules necessitates some modification to the molding machine or to the formulation of the shell materials. HPMC gelling from solution occurs when the temperature is raised while it is converted to its original solution as the temperature is lowered, unlike gelatin solution. This means that the pins immersed in the dip pan containing the HPMC solution must be of higher temperature (70°C) in order for the film to be formed. To avoid liquefaction of the films formed on the pins, the temperature of the pins must be further maintained post-dip to facilitate gelation until the films dry out in the kilns. Because HPMC shell walls are much weaker than gelatin made shells, removal of the capsule from the pins and subsequent handling and filling are in jeopardy. To overcome these problems, three approaches were adapted. These approaches were to use a stripper jaw with depressions on the inner surface, increase the formed HPMC film thickness and the use of gelling agents. The following gelling agents were experimented: tamarind seed polysaccharide, carrageenan, pectin, curdlan, gellan gum and furcellaran. [14, 15]

Effects of Ambient Conditions:
The use of capsules as means for rapid disintegration in the oral cavity was experimented. HPMC shell exhibits significantly better short term stability at high temperature than hard gelatin capsules on visual test, disintegration and dissolution, as well as mechanical property assessment. When they were stored at different relative humidity (RH), the HPMC capsules exhibited lower moisture contents compared to gelatin capsules. [16]
**In-vitro disintegration:**
Donauer and Löbenberg have called in a min review the USP to specify how to carry out the disintegration test with HPMC capsules. That is because the dissolution behaviors of HPMC and gelatin capsules have to be different in dissolution media. Moreover, HPMC capsules are not all the same as they may or may not contain a gelling agent and the gelling agents used are not all the same.[17]

**In-vitro dissolution:**
Different dissolution media and storage conditions were used. The capsule shells dissolution time was determined as the time for enough parts of the suspended capsule to dissolve, permitting steel ball bearing filled into the capsule to fall free. Capsules were placed in media of different temperature (between 10º and 55º C) in order to simulate taking the capsules with cold, warm or hot drinks. The dissolution media in the glass beaker at different temperatures were brought back to 37º C with the controlled temperature of the surrounding water bath. Gelatin and gelatin/PEG capsules disintegrated rapidly and faster than the HPMC carr capsules in the different media following storage at different conditions when tested at temperature \( \geq 37º \) C. This delay in the HPMC capsule disintegration was especially notable in mixed phosphate buffer of pH 6.8. The delay at pH 6.8 is inherent for the HPMC shells. Honkanen showed that when ibuprofen formulation in HPMCCarr capsules tested for drug release in a neutral potassium phosphate buffer, it was incomplete and highly variable compared with the gelatin capsules and attributed this to the presence of potassium ions (K+) in the dissolution medium that causes the capsule shell to form a membrane around the filling. [18, 19]

**In-vivo evaluation:**
**Oesophageal Sticking Tendency:**
Perkins and colleagues have compared the oesophageal transit of radiolabelled enteric coated tablets with similar sized and shaped gelatin capsules when administered with 50 ml of water while sitting on two separate occasions, using a population of elderly healthy volunteers (n = 23). Honkanen et al. (41) have recommended that both HPMC capsules as well as gelatin capsules be taken with a sufficient amount of water (150–200 ml) in an upright position and maintaining the upright position for several minutes since they found that HPMC capsules had a tendency to attach to the oesophagus.[20, 21]

**Coating of HPMC capsules:**
Enteric and colonic delivery of HPMC capsules were claimed by using coating materials of different pH solubility (at 5.5 and above and at 7 and above for enteric and colonic delivery respectively). The comparison between the coating of gelatin capsules and HPMC capsules showed that the later coating was straight forward, while gelatin capsules were not suitable for direct coating when Eudragit L and S 12.5 (acrylic polymers) was used because of insufficient film adhesion to the smooth capsule surface and the brittleness of formed films. Because HPMC capsule shell surface is rougher compared to gelatin capsules as examined by scanning electron microscope, this may provide good adhesion to the coating. [22, 23]

**In-vitro - In vivo correlation:**
For hard gelatin capsules, for the in vitro testing to correlate with in vivo evaluation, it has been suggested that dissolution experiment is carried out in two stages, one representing gastric medium (pepsin at pH 1.2) and the other representing the intestinal medium (pancreatin at pH 7.2) (43). El-Malah and his colleagues indicated that the composition of the dissolution medium
influences the disintegration time of the HPMC capsules, however, drug release delay in vitro may not be correlated in vivo. [24]

**Alginate Capsules:**
Utilizing a novel patented process based on one of FMC core Biopolymers (alginate) this technology provides a unique seamless, enteric, vegetarian alternative to gelatin soft capsules in one unit process for pharmaceutical and nutraceutical applications.

**Advantages:** [25]
- Globally acceptable regulatory compliance with Vegetarian (gelatin-free)
- Capsules easier to swallow:
- Smaller Capsule: Seamless thinner capsule shell, allowing for capsules 30% smaller than traditional gelatin for a given fill volume
- No Fish Burps: Naturally enteric providing superior gastro resistant and enteric release properties to film coated alternatives
- Superior elegance - high shell transparency
- Sugar and gluten free
- Manufacture of capsules easier:
- Favourable unit cost - process does not produce waste ribbon as seen in traditional rotary die processes and eliminates need/cost of enteric film coating maximizing production efficiency
- Process designed to provide oxidation protection
- QbD development philosophy
- Patented product and process enables product life cycle enhancement.

**Manufacturing of alginate capsules:**
Steps involved in alginate capsule shell formation:-
- Extrude formation of Emulsion.
- Introduce emulsion fragments into alginate bath.
- CaCl₂ diffuses through the emulsion and react with sodium alginate at the interface.
- The capsule shell wall is formed with the same thickness all around.
- Washing and drying.
- Dry capsule with transparent shell and transparent core.

![Figure 3: Alginate capsule shell manufacturing process](image)
CONCLUSION

These published literatures are form scientists affiliated for their own premises and companies and so there may have overemphasized the potential of HPMC capsules over gelatin one. Two important areas where improvements have to be achieved in order to qualify the HPMC capsules ahead of gelatin capsules are in their machineability and in the in vitro and in vivo disintegration/dissolution performances. It may be costly for the pharmaceutical industry to reformulate their products to make use of HPMC capsules as the profit achieved might not be weighing out the cost. However, for new capsule products, HPMC capsules should become an option. Except for HPMC, alginate capsule shell, starch capsule shell PVA copolymer capsule shells are also in the development process to replace the gelatin capsule shell.

REFERENCES