ALTERNATIVES FOR GELATIN IN THE PREPARATION OF CAPSULES

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Abstract:
In recent era, vegetable capsules are new approach which might be replacing the usage of gelatin or non vegetable capsules. Hydroxy propyl methyl cellulose (HPMC), starch, hydroxy propyl cellulose (HPC) etc are mainly used as alternatives for gelatin in the preparation of capsules. Among them (HPMC) is mainly used in manufacturing of such kind of capsule shell. HPMC is also used as viscolizing agent (thickening agent), coating polymer, bioadhesive, in solid dispersion to enhance solubility, binder in the process of granulation and in modified release formulations have been well documented. The aim of this review is to survey published literature on the vegetable capsule shells and resolve questions regarding their suitability as a replacement for hard gelatin capsules.

KEY WORDS: Vegetable capsule shell, Hydroxy propyl methyl cellulose (HPMC), Hypromellose, Quali-v

INTRODUCTION

Capsule is the most versatile of all dosage forms. Capsules are solid dosage forms in which one or more medicinal and inert ingredients are enclosed in a small shell or container usually made of gelatin.

There are two types of capsules, “hard” and “soft”. The hard capsule is also called “two pieces” as it consists of two pieces in the form of small cylinders closed at one end, the shorter piece is called the “cap” which fits over the open end of the longer piece, called the “body”. The soft gelatin capsule is also called as “one piece”. Capsules are available in many sizes to provide dosing flexibility. Unpleasant drug tastes and odors can be masked by the tasteless gelatin shell. The administration of liquid and solid drugs enclosed in hard gelatin capsules is one of the most frequently utilized dosage forms

ADVANTAGES OF CAPSULES:

- Capsules mask the taste and odor of unpleasant drugs and can be easily administered.
- They are attractive in appearance.
- They are slippery when moist and, hence, easy to swallow with a draught of water.
- As compared to tablets fewer adjuncts are required.
- The shells are physiologically inert and easily and quickly digested in the gastrointestinal tract.
- They are economical.
- They are easy to handle and carry.
- The shells can be opacified (with titanium dioxide) or colored, to give protection from light.
DISADVANTAGES OF CAPSULES:

- The drugs which are hygroscopic absorb water from the capsule shell making it brittle and hence are not suitable for filling into capsules.
- The concentrated solutions which require previous dilution are unsuitable for capsules because if administered as such lead to irritation of stomach.

ALTERNATIVES OF GELATIN:

Hard gelatin capsules have traditionally been made from gelatin using dipping process. Gelatin is very well-suited to this because it is an excellent film former and changes in liquid to solid at temperatures just above ambient \(^2\). The film produced is homogenous and very robust and gelatin capsules can readily withstand the mechanical stresses of the filling and packing operations. The primary drawback in the use of gelatin is that it contains water, which acts as a plastizer to a film. Thus, if they are not stored properly, their properties will change. When water is lost from the shells they become brittle and thus they are not suitable for hygroscopic materials. Moisture-labile substances cannot be filled in them.

HARD STARCH CAPSULES

Hard gelatin capsules have been used most widely. Recently, however, starch capsules have been used in various controlled-release products as well as in general use as demands for non-animal based products increase. Starch capsules are more easily coated than gelatin capsules. Gelatin shells may soften and solubilize when sprayed with aqueous dispersion of coatings and can become brittle during the drying stage. The higher bulk density of the starch capsule provides for a more uniform coating bed.

Starch capsules are manufactured by an injection molding process that yields exact dimensions and provides an excellent seal between “top” and “bottom.” The filling and sealing process is simultaneous, resulting in a finished product that is well-sealed, secure and relatively resistant to further manipulation.

Starch and HPMC are good candidates for making not only hard but also soft gelatin capsules. One of the limitations of using them is the initial high capital investment.

For certain markets there are customer requirements for a capsule of vegetable origin. Since from last century, people have been searching for gelatin alternatives. The primary problem to be overcome has been the need to obtain a system that gels in a manner similar to that of gelatin. So that the same manufacturing process and machines can be used. In 1950’s capsules of HPMC are produced by using a modified production process with heated mould pins or by the use of additives to make a true gelling system. Hard capsules made from HPMC have similar but different properties from gelatin capsules. Their primary advantage is that their moisture content is much lower and even if this is removed, they retain their mechanical strength \(^3\).

VEGETABLE CAPSULE SHELL

In recent era, vegetable capsules are new approach which might be replacing the
usage of gelatin or nonvegetable capsules. Hydroxy propyl methyl cellulose (HPMC) is mainly used in manufacturing of such kind of capsule shell. HPMC is also used as viscolizing agent (thickening agent), coating polymer, bioadhesive, in solid dispersion to enhance solubility, binder in the process of granulation and in modified release formulations have been well documented. The aim of this review is to survey published literature on the vegetable capsule shells and resolve questions regarding their suitability as a replacement for hard gelatin capsules.

Vegetable capsule shell is mostly prepared from the hydroxy propyl methylcellulose (HPMC), 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.

1. As a coating polymer
2. As a bioadhesive
3. Thickening agent in controlled release systems
4. In solid dispersion to enhance drug solubility
5. As a bioadhesive.
6. as a binder.

The material is described as a white to slightly off-white powder or granules, practically insoluble in hot water, in acetone, in dehydrated ethanol and in chloroform, but dissolves in cold water giving a colloidal solution owing to the reversible thermal gelation property. HPMC is available in different type of groups with limits on methoxy and hydroxy propoxy groups. These groups affect many of the HPMC properties such as gelation temperature, viscosity, flexibility and hydration [4]. The word-capsule origin from the Latin capsula, which means small box. Capsules are either hard (two-piece) or soft (one-piece) and are used to encapsulate pharmaceutical formulations [5]. The two-piece capsule is made of a cap-piece that slips over one side open body-piece forming closed cylindrical object [6]. The most common route of administration of capsules is orally but capsules for inhalation such as Spiriva HandiHaler, vaginal such as Gyno-Daktarin and rectal administrations are all possible [7].

Most of pharmaceutical capsules available in market are made of gelatin, several HPMC capsules for powdered herbs and dietary supplements have been available in recent years. 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) have encouraged the search for gelatin replacement. Religious, cultural and personal issues may affect patients preference towards the medications presented in capsule dosage forms. HPMC capsules are good alternative of gelatin capsules due to its vegetable source [8].

Here is the structure of HPMC (Hypermellose):

\[
\text{R = H or CH}_3 \text{ or CH}_2\text{CH(OH)CH}_3
\]
The first vegetable capsule which is made of HPMC was produced in 1989 by G S Technologies Inc. with trade name Vegicaps. For gelatin capsule alternative, the first patent registered was in 1950 by H W Murphy of Eli Lilly and Company for methyl cellulose which did not last long in the market because of in vivo disintegration delay. Several attempts were made to improve it. The production of vegetable capsules is by thermal gelation and a gelling system used to lower thermal gelation temperature of HPMC \cite{9}. The manufacturing technique remains similar to that of hard gelatin capsules and involves the use of pins dipping into HPMC solution. There are different types of HPMC capsules which may have different in vitro and in vivo performances among themselves and in comparison to hard gelatin capsules \cite{10}.

Vegicaps soft capsules are alternative animal free capsules. The shell is made from seaweed extract and gluten free starch and contains no modified sugars and artificial colors. Advantages of it is that it is free of all animal derivates-no pork or beef content, easy to swallow, soft, natural, perception of a healthier product and low shell odor.

![Fig 1: EMPTY VEGETABLE CAPSULE SHELLS](image)

<table>
<thead>
<tr>
<th>Table 1: DIFFERENCE BETWEEN VEGCAPS AND GELCAPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegcaps</td>
</tr>
<tr>
<td>100% vegetarian</td>
</tr>
<tr>
<td>HPMC or Hydroxy propyl methyl cellulose is used.</td>
</tr>
<tr>
<td>GRAS listed in FDA</td>
</tr>
<tr>
<td>Kosher certified</td>
</tr>
<tr>
<td>Suitable for cultural, religious and vegetarian dietary requirements.</td>
</tr>
<tr>
<td>Stability over wide range of temperature and humidity.</td>
</tr>
<tr>
<td>Perfect for hygroscopic preparations.</td>
</tr>
<tr>
<td>Compatible with capsule filling machines, all sizes available.</td>
</tr>
<tr>
<td>Doesn’t support bacterial growth.</td>
</tr>
</tbody>
</table>
Table 2: DIFFERENCE BETWEEN VEGCAPS AND TABLETS

<table>
<thead>
<tr>
<th>Without Preservatives</th>
<th>Preservatives are to be added</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ideal for hygroscopic preparations.</td>
<td>Not ideal</td>
</tr>
<tr>
<td>Fast dissolving ensuring better bioavailability.</td>
<td>Delay in dissolving.</td>
</tr>
<tr>
<td>Free from irritants, inactive binders, Colors.</td>
<td>They are to be added.</td>
</tr>
</tbody>
</table>

Table 2: Empty HPMC capsules and their manufacturers

<table>
<thead>
<tr>
<th>Capsule shell brand name</th>
<th>Manufacturer</th>
<th>Registered year in USA</th>
<th>Gelling aid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quali-V</td>
<td>Shionogi Qualicaps</td>
<td>July, 2002</td>
<td>Carrageenan</td>
</tr>
<tr>
<td>Vcaps Plus</td>
<td>Capsugel (A division of Pfizer)</td>
<td>-</td>
<td>None</td>
</tr>
<tr>
<td>Vcaps</td>
<td>Capsugel (A division of Pfizer)</td>
<td>April, 2003</td>
<td>Gellan gum</td>
</tr>
<tr>
<td>Vegi Caps</td>
<td>G S Technologies Inc. (now R.P. Scherer Technologies ownership))</td>
<td>May, 1989</td>
<td>None</td>
</tr>
<tr>
<td>Embo Caps –Vg</td>
<td>Suheung Capsule Co., Ltd</td>
<td>-</td>
<td>Pectin and glycerin</td>
</tr>
<tr>
<td>Capstech’s HPMC Capsule</td>
<td>Baotou Capstech Co., Ltd</td>
<td>-</td>
<td>None</td>
</tr>
<tr>
<td>Natural Plant Capsule</td>
<td>Zhejiang LinFeng Capsules Co. Ltd</td>
<td>-</td>
<td>Carrageenan</td>
</tr>
</tbody>
</table>

MANUFACTURING OF VEGETABLE CAPSULES AND TYPES:

The detailed about the empty HPMC capsules and their manufacturer are listed below. Hard gelatin and HPMC capsules are produced by using similar equipments developed by Eli Lilly.

The manufacturing of HPMC based capsules requires some modification to the molding machine or to the formulation of the shell materials. HPMC gelling from solution occurs when the temperature is increased while it is converted to its original solution as the temperature is decreased, unlike gelatin solution. It 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. The pins, the temperature of the
pins must be further maintained post-dip to facilitate gelation until the films dry out in the kilns [11-13]. Because HPMC shell walls are much weaker than gelatin made shells, removal of the capsule from the pins and subsequent handling and filling are difficult. 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 [14].

Non-ionic cellulose derivates such as hydroxy propyl cellulose (HPC) have been used in controlled-release formulations and as film coatings. In a previous study, different viscosity grades of HPC were used as the material for film coatings, and the drug release lag time was prolonged with increasing viscosity grade in both the in vivo dissolution test and the in vivo bioavailability study. Polyethylene oxide (PEO) is a water-soluble macromolecular polymer and has been used in formulations of controlled-release products. In this study, we attempted to use both HPC and PEO as capsule shell materials. Previously, we described the application of a heat-melting method for the manufacture of hard capsules from hydroxy propyl cellulose (HPC) or polyethylene oxide (PEO).

**PREPARATION OF THE HPC CAPSULE SHELLS:**

PEO (200K) and HPC (80K, 100K, and 370K) were melted by heating them to above their respective melting temperatures. Hard HPC or PEO capsule shells were prepared by the same melting method for which we previously had been granted a US Patent. The apparatus used in this study consisted of two major parts, as shown in Fig. 2.

1. A mold, which contains an opening shaped as a capsule cap, and
2. A capsule-forming pestle also shaped as a capsule cap or a capsule body, but its diameter was slightly smaller than the mold opening. Both the mold and the capsule-forming pestle were made of stainless steel. A hard capsule shell was prepared by the following procedures. About 60 mg of HPC or PEO was added to the opening of the mold; the diameter of the opening of the mold corresponds with intended capsule shell size. The mold and a capsule-forming pestle with a diameter equal to the internal diameter of a no. 2 capsule shell were heated. The pestle was inserted into the mold while the polymer was in a melted condition, with pressure so that the melted polymer was evenly coated onto the pestle. The pestle was withdrawn from the mold, by a pulling device connected to the pestle.

3. After the capsule-forming composition had cooled on the pestle, the dried capsule was removed from the pestle [15].

**Fig. 2: Capsule-forming devices.** (1) Mold; (2) pestle of the capsule cap and body; (3) pestle coated with polymer.
MARKETED PRODUCTS

Table 4: The HPMC capsule shells have found popularity for their use with nutraceuticals and over-the-counter (OTC) formulations

<table>
<thead>
<tr>
<th>Product</th>
<th>Nature of the Formulation</th>
<th>Manufacturing Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Damiana Herb 300mg</td>
<td>Pure powdered herbs (Damiana turnera aphrodisiaca)</td>
<td>Bio-Health Ltd., UK</td>
</tr>
<tr>
<td>Thera Veda’s Ajay- Allergy Support Formula</td>
<td>Vegetable extracts and powders</td>
<td>Organix South, USA</td>
</tr>
<tr>
<td>Natren Life Start 2</td>
<td>Bacteria, vitamin C, potato powders and whole goat milk</td>
<td>NATREN, Inc., USA</td>
</tr>
<tr>
<td>Colocolar (in VegiCap)</td>
<td>Flax seeds, slippery elm and other herbs</td>
<td>Higher Nature Ltd., UK</td>
</tr>
<tr>
<td>Jarro-Dophilus EPS</td>
<td>8 probiotic species and ascorbic acid</td>
<td>Jarrow Formulas, USA</td>
</tr>
<tr>
<td>Culturelle HS Capsules</td>
<td>80 mg lactobacillus GG (L. rhamnosus GG) Vegetarian Formula</td>
<td>Kirkman Labs, USA</td>
</tr>
<tr>
<td>Align Daily Probiotic Supplement Capsules</td>
<td>Bifidobacterium infantis</td>
<td>Procter and Gamble, USA</td>
</tr>
<tr>
<td>Sportlegs Supplement</td>
<td>Vitamin D, calcium and magnesium</td>
<td>Sportlegs, USA</td>
</tr>
<tr>
<td>Planetary Herbals Cinnamon Extract</td>
<td>Cinnamomum aromaticum 300 mg, bark extract 10:1 yielding 8% flavonoids, cinnamomum aromaticum bark 100 mg</td>
<td>Planetary Herbals, USA</td>
</tr>
<tr>
<td>Ex-Tox II</td>
<td>Folic acid, cilantro powder (leaf), ethylenediamine tetra acetic acid, N-Acetyl L-cysteine, fulvic (humic) acid, Rlipoic acid (K-RALA), L-methionine</td>
<td>Progressive Labs, USA</td>
</tr>
</tbody>
</table>

EVALUATION OF VEGETABLE CAPSULE [16]

(1) In-vitro disintegration and dissolution

Vegetable 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. The shell dissolution properties of hard gelatin capsules, gelatin/PEG capsules and HPMCcarr capsules were compared independent of their capsule content. Different dissolution media and storage conditions were used. The capsule shells disintegration/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. The HPMCcarr
capsules disintegrate slowly than the Gelatin and gelatin/PEG capsules. This delay in the HPMC capsule disintegration was especially notable in mixed phosphate buffer of pH 6.8. In water at 37 °C following storage at ambient room conditions (19±1°C, 35-40% RH) HPMCcarr capsules disintegrated in approximately 4 minutes. The influence of the composition of test fluids on dissolution from HPMCcarr capsules (Quali-V) in comparison to the hard gelatin capsule was studied. The results were in agreement with another study showing significant retarding effect of potassium and/or calcium ions in the dissolution medium, while the effect of pH was minimal on dissolution. HPMC capsules in an acidic pH (0.1 N HCl), the dissolution of the capsules formulations were retarded in comparison to hard gelatin capsules at earlier times and therefore delaying the time of complete drug dissolution. 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. Because the gut concentration of potassium is low, then justication is the change of dissolution medium to neutral tribasic sodium phosphate which resulted in complete and less variable drug release. In this medium 100% of the drug was released for both types of capsule within 15-20 minutes, however, there was a lag time of approximately 4 minutes before the drug release from HPMCcarr capsules, unlike gelatin capsules in which the release was immediate.

(2) In Vivo Disintegration and Dissolution
Two prolonged release, radio labelled formulations, containing different viscosity grades of HPMC powder (HPMC K100 and HPMC K4M) filed in HPMCcarr capsules Qualicaps were tested in 6 healthy volunteers with one week washout period between the two administrations to examine the fate of the capsules in the GIT. The initial disintegration times for the capsules were measured as the midpoint of the time interval between the last image of the capsule with clear outlines and visually undetectable spreading of the radioactivity and the time of first detection of spreading radiation. It was found that in 4 occasions out of 12, the capsules were lodged in the oesophagus for 22–143 min. For the two formulations the initial disintegration time ranged from 33 to 75 minutes with no significant difference at the 5% level. (All of the administered capsules started the disintegration in the small intestine except for two which started in the oesophagus region at 75 minutes for each of the two formulations.

In vitro-in vivo correlation
Unlike hard gelatin capsules, HPMC capsules may have low correlation between the in vitro dissolution/disintegration and the in vivo performance. The reason for this was explained on the basis of interaction between the medium and the HPMC capsule gelling systems. It was suggested that dissolution/disintegration testing specifications should be different from that of hard gelatin capsules to reflect in vivo
performance. 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). 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.

**Fig. 3:** In vivo initial disintegration time (minutes) for the HPMC capsules in 6 healthy volunteers filled with two different prolonged formulations containing different viscosity grades of HPMC powder (HPMC K100 and HPMC K4M).

**DISCUSSION:**
The well known capsule manufacturer are thinking that now a day vegetable capsules give tough competition to gelatin capsules in market but it required some modification or improvement. Two important areas where improvements have to be achieved in order to qualify the HPMC capsules ahead of gelatin capsules are in their machine ability and in the in vitro and in vivo disintegration/dissolution performances. The main area where HPMC capsules can have better prospect compared to gelatin capsules is the dietary sensitivities in certain markets and in wider patients’ preferences. The main advantage of HPMC capsules over gelatin capsules could be because of their vegetable source which has wider customer acceptance. Fish based gelatin capsules are also available in the market (EMBO CAPS-Fish from Suheung Capsule Co., Ltd). The fish gelatin solution from which the shells are produced contains mixed solution of pectin and glycerin as gelling agent and a small quantity of calcium glycolate, sucrose fatty acid esters, glacial acetic acid as additive. These capsules may offer alternative to people with concern from gelatin produced from bovine and/or porcine collagen of bones and skin. Another reported advantage of HPMC capsules over gelatin capsules is related to the difference in moisture content of the shells. Because HPMC shells contain significantly less moisture compared to hard gelatin capsules by almost one third, it is compatible with hygroscopic materials. While HPMC shells physical strength tolerates wide range of environmental conditions, hard gelatin capsules readily becomes brittle and unusable in low humidity. One offered solution to this problem is to add PEG 4000 to the gelatin. As such the brittleness of the capsules will be minimized and encapsulation of hygroscopic materials becomes possible.

It may be expensive for the pharmaceutical industry to reformulate their products to make use of HPMC capsules as the benefits achieved might not be weighing out the cost. However, for new capsule products, HPMC capsules should become an option. Currently marketed products using HPMC capsules filled with herbal formulations benefit from flexible regulations over this category of
supplements. Such regulations are expected to be tougher in the future which may lead to the number of HPMC capsule products to become static. PEO and low-molecular-weight HPC capsules might prove to be useful alternatives to their gelatin counterpart.

REFERENCES: