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### Review Article

## Vegetable Capsule Shell: Types and Regulation

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### Abstract

Typical gelatin sourced capsule shells have been used for almost a century in the pharmaceutical field. Gelatin is largely derived from cows, pigs and other animals. In the recent time to satisfy the religious belief, cultural and personal issues towards non-veg capsules shell and patients' preference towards the medications contains only vegetarian source and increasing demand of vegan food research on vegetable source of capsule shell increase. Hydroxypropyl methyl cellulose (HPMC) is primary material studied and used in manufacturing of vegetable capsule shell. This review covers published literature and discussion regarding alternate option of gelatin capsules shell as vegetable capsule shells.

**Keywords:** Gelatin, Vegetable Capsule, Hydroxy Propyl Methyl Cellulose Capsules, Monograph, Regulatory criteria

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## 1. Introduction

### Capsule

Capsules were first patented for use in 1830 by Joseph Gerard Auguste Dublanc and Francois Achille. The first patented capsules were made from soft gelatine. In 1846 Jules Lehuby obtained a patent for two-piece hard capsules, such as those that are in use today. (1) Among the all-dosage form capsules are the most versatile dosage forms because they are chemically and physically stable, easy to administer, attractive and can be easily compounded. The capsule can be easily customized with respect to needs of individual patient regarding dosing ingredients and also, minimize the number of dosage form to be taken by patient by incorporating more than one drugs. Some examples are tablet and powder mixture in single capsule or tablet in capsule dosage forms, etc. The gelatin is still extensively used as capsule shell material for the manufacturing of empty hard capsule shell and soft capsule shell. (2)

### Gelatin

Gelatin is derived mostly from collagen by thermal denaturing with the aid of diluted acid or alkali. The composition of Gelatin is a mixture of water-soluble proteins (84-90 percent), mineral salts (1-2 percent), and water (8-15 percent). These proteins contain a significant amount of the amino acids: glycine, proline,

hydroxyproline, glutamic acid, alanine, arginine, aspartic acid, and lysine; in addition to other amino acids in smaller amounts. Gelatin is varying in its chemical and its physical properties depending on the source of the collagen and the manner of extraction. These two types can be differentiated by their isoelectric points (4.8-5.0 for Type B and 7.0-9.0 for Type A) and by their viscosity building and film forming characteristics. (3)

There are two types of gelatin:

Type A: derived from pork skin by hydrolysis with an acid

Type B: derived from bones and animal skin by hydrolysis with an alkaline solution. (4)

But due to its animal origin and cross-linking property other vegetarian source material that meets the dietary and cultural needs of vegetarian patients and also comply with the regulatory requirement same as gelatin needs to be invented hence various non-animal origin materials such as hydroxyl propyl methyl cellulose (HPMC), Pullulan, starch, poly vinyl alcohol copolymer assessed as a capsule shell material. (2)

Also, the stringent regulatory requirements which encourage searching for gelatin alternative is drug incompatibilities of some drugs with gelatin capsules shell, strict regulation regarding use of animal derived

gelatin such as absence of transmissible spongiform encephalopathy (TSE). As gelatin is from animal connective tissue, bone, skin, and sinew there had been great concern over about its susceptibility to pass the infection to men. There had been some research and studies that show some faint possibility of its being transmitted. Therefore, the vegetarian capsules coming to scene. Finally, more in-depth studies are needed about gelatin capsules and the vegetarian capsules are 100% safe. (4)

## 2. Vegetarian Capsules

Religious, cultural and personal issues may affect patients' preference towards the medications presented in capsule dosage forms. Mostly Hydroxyl propyl methyl cellulose (HPMC) is used to prepare vegetable capsule shell and general term used for HPMC is Hypromellose. The naturally occurring polymer cellulose has been modified to produce Hypromellose which is considered safe for normal consumption, in human. HPMC is 100% plant fiber and is derived from not only tree cellulose, but also from vegetable and plant fiber. HPMC comes under GRAS i.e. generally recognized As Safe by FDA. HPMC derived capsules can meet all requirements of current USP and FCC (Food Chemical Codex). (4) Hydroxyl propyl methyl cellulose (HPMC) capsules are good alternative of gelatin capsules due to its vegetable source. 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 patient registered was in 1950 by H W Murphy of Eli Lilly.

The production of vegetable capsules is by thermal gelation and a gelling system used to lower thermal gelation temperature of HPMC. 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. Vegicaps soft capsules are an alternative animal free capsule. 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 derivatives-no pork or beef content, easy to swallow, soft, natural, perception of a healthier product and low shell odor. (5)



**Figure 1.** Empty Vegetable Capsule Shell (5)

In this review among all types vegetable capsule shell more emphasis given on hydroxy propyl methyl

cellulose (HPMC) capsule shell considering more work and innovation has been done on HPMC capsule shell.

## 3. Types of Vegetarian Capsule shell

1. Hydroxy Propyl Methyl Cellulose (HPMC) Capsule shell
2. Pullulan Capsule shell
3. Starch Capsule shell
4. Polyvinyl alcohol (PVA) Capsule shell
5. Alginate Capsule shell

### a) Hydroxy Propyl Methyl Cellulose (HPMC) Capsule Shell

HPMC vegetarian capsules (vegetarian capsules) are made of natural polymers and fibers and may be stated to as polymer capsules. These polymer capsules may also function as time-delayed release capsules because they have the ability to delay drug release from the capsule shell. These empty shells are filled with active pharmaceutical ingredients in dry form or liquid form. If it is filled with powder, then it is called a dry filled capsule and if it is filled with liquid or semi-solid, it may be called a liquid filled capsule. Also, its machine friendly design ensures smooth encapsulation on semi-automatic and automatic filling machines.



**Figure 2.** Filled Vegetable Capsule Shell (6)

Furthermore, these HPMC vegetarian capsules are attractive, all-natural solid dosage forms that retain all the advantages of hard gel capsules; they are easy to swallow, effectively mask taste and odor, and allow product visibility. Hydroxy propyl methyl cellulose (HPMC) has thus become a successful alternative material for two-piece, hard gelatin capsules, all over the world. Due to advantages and key features these HPMC capsules offer a significant advantage over other solid dosage forms. (6-7)

### Characteristics of HPMC Capsules (4)

- Made from non-animal materials than Gelatin capsule.
- Lower water vapor permeability
- Low static electricity and light protected.
- No Millard reaction with fillings.
- Not substrate for protease.
- Chemical inactivity and solubility at room temperature.
- In these type of capsules powder, tablet, granules, pellets, liquids and semisolids are filled

### Advantages of Vegetable Empty Capsule with its implication (8)

- Low moisture content of vegetable empty capsules make it suitable for filling with hygroscopic and moisture sensitive drug powders as well as nutraceutical herbal powders.
- Superior stabilities when compared with conventional gelatin or modified starch capsules and does not generate any interaction with its fillers to form cross-linking reactions.
- Easy and ambient storage required and broad range relative humidity. It is stable at high temperature and does not crack even under zero percent relative humidity. It has long shelf life.
- High filling rate and the specification of vegetable empty capsules is similar to all sizes of conventional gelatin. There is no need to alter the filler machine to meet the filling requirement.

#### Development in HPMC capsule

QUALI-V®, developed by Shionogi Qualicaps, is the first HPMC capsule developed for eventual use in pharmaceutical products. The features of QUALI-V are summarized as following.



**Figure 3.** Quali-V® by Qualicaps

#### Features

- 100% vegetable origin and Preservative free
- Gelatin equivalent dissolution profile
- Chemically and thermally stable
- Moisture content 4-6% less than gelatin capsule (13-16%), hence less chances of microbial contamination.
- Less brittle even in low humidity ( $\leq 1\%$  moisture content)
- Fast dissolution (No change in dissolution profile under stress conditions) and soluble in water at room temperature
- Lower water vapor permeability than gelatin capsule (Gelatin>PEG-Gelatin>HPMC)
- Provide protection from light and oxygen (3, 9)

#### Challenges (9)

- High manufacturing cost. As day-by-day usage of vegetarian capsules shell increases cost can be made down further. (4)
- Less resistant to indentation
- Lower tensile strength than gelatin shells, which results in processing problem.
- Limitation in automatic filing machine specifically for size #00 HPMC capsule, defects include dimpled bodies, spilt caps, improperly closed caps and large number of capsules that did not open for filling observed.



**Figure 4.** HPMC Capsules (Hypromellose), QUALI-V® (3)

#### b). Pullulan Capsules Shell (9-10)

It is listed as a new authorized Food Additive “E 1204 Pullulan” via Environment European Commission (EEC) Directive 2006/52/EC. Pullulan is produced from starch by the fungus *Aureobasidium pullulans* by fermentation process with sugars

#### Features

- Water soluble polysaccharide which is derived by bacterial fermentation from corn starch.
- They are odorless, tasteless, and completely biodegradable.
- Relatively low water content (10-15%), than gelatin, low toxicity.
- Chemically inert and does not react or cross link with contents of the capsule therefore, it exhibits high stability over storage such as mechanical and dissolution properties.
- Because pullulan offers the best oxygen barrier of all the plant-based products, these capsules can help mask pungent odors from ingredients and enhance the protection of sensitive ingredients. Hence, Pullulan capsules are the best choice for material susceptible to oxidation.



**Figure 5.** Plantcaps® Capsules by Capsogel (11)

#### Challenges

- More sensitive than gelatin or HPMC to low moisture conditions.
- This sensitivity causes increase in shell brittleness at low water content. (12)
- Higher manufacturing losses.
- A poorer quality and higher costs.

#### c). Starch Capsule Shell (9, 13)

Starch capsules represent the direct alternative to hard gelatin capsules and made from potato starch. Starch capsules manufactured by the injection molding technique developed by Capsugel (Capill®) 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. Different size capsules are manufactured (number 0, 1, 2, 3, 4) by changing the mold.

#### Features

- Suitable for enteric coating
- Tamper evident
- Ready for filling immediately following manufacturing.
- Offer greater resistance to humidity and heat than gelatin and allow easy filling as they are non-static.
- Dissolution is independent of pH.
- Good surface finish.

#### Challenges

- Use of plain starch capsule have limited use in targeted delivery in lower part of digestive system.
- Hence, enteric coated starch capsule shell can provide targeted delivery but that can increase cost considerably.

#### d). Polyvinyl alcohol (PVA) Capsule (9)

##### Features

- Water soluble
- Less hygroscopic than gelatin
- Oxygen permeability through PVA copolymer is significantly less than through gelatin and HPMC capsule

##### Challenges

- Softened by surrounding moisture.
- Lower hardness and if try to increase hardness with other co-polymer then decreases the polymer solubility.

#### e). Alginate capsule (13)

Utilizing alginate for capsule shell provides a unique seamless, enteric, vegetarian alternative to gelatin soft capsules in one unit process for pharmaceutical and nutraceutical applications.

##### Features

- Smaller Capsule - seamless thinner capsule shell, allowing for capsules 30% smaller than traditional gelatin for a given fill volume can increase patient compliance.
- Superior elegance provides high shell transparency
- Sugar and gluten free
- Manufacture of capsules easier and favourable unit cost.

#### 4. Components used in HPMC Capsule Shell Manufacturing (7)

In addition of the below discussed basic components, HPMC capsule shell may also contain gelling agents, gelling aids and other additives such as, humectants, surfactants, dispersing agents, gliding agents, lubricating agents, flavouring agents, antimicrobial agents, sweetening agents, opacifying agents as per the need. (14)

##### a). Hydroxypropyl methylcellulose (HPMC) or Hypromellose

Hydroxypropyl methylcellulose (HPMC) belongs to the group of cellulose ethers in which hydroxyl groups have been substituted with one or more of the three hydroxyl groups present in the cellulose ring. Hypromellose is a solid, and is a slightly off-white to beige powder in appearance, which forms colloids when dissolved in water. This non-toxic ingredient is combustible and can react vigorously with oxidizing agents. HPMC is a hydrophilic (water soluble), biodegradable, and biocompatible polymer having a wide range of applications in drug delivery, dyes, paints, cosmetics, adhesives, coatings, agriculture, and textiles.

##### b). Plasticizer

Plasticizers are added to reduce the rigidity of the polymer and make it more pliable. Most commonly used plasticizers are sorbitol and glycerine.

##### c). Water

Water quantity varies depending on storage conditions and what type of material to be filled in the capsule.

##### d). Opacifiers

Opacifiers generally provide guard against light and photodegradation. Also, also play a role in concealing the contents used in the filling of capsule shells. The Titanium dioxide mostly used as an Opacifier in capsules shell.

##### e). Colorants

Coloring agents can impart various colors according to the need to hard gelatin capsules. They are mostly used to improve patient compliance and also can be further selected to complement the disease being treated. Colorants used must be approved in the respective county in which capsules going to be market and also fulfil their regulatory requirements.

#### 5. Comparison of gelatin capsule between vegetarian capsules

General comparison of gelatin capsule between vegetarian capsule and properties described in article gives idea about the selection of the capsule shell for dosage form development. (9) In this section also details of manufacturer are provided for different types of vegetarian capsule shell.

**Table 1.** Comparison of gelatin capsule between vegetarian capsules (9)

Gelatin Capsule	Vegetarian Capsule
Animal bone, skin used	Plant material used
Considered for non-vegetarian people	Considered for vegetarian people
Moisture content (13-15%)	Low moisture content (2-7%)
Cross linking of gelatin with aldehyde	No cross linking
Allergy due to cow and bovine product	No allergy in patient
Not for kidney and liver disease patient	For kidney and liver disease patient
Not for moisture sensitive and hygroscopic ingredient	Ideal for moisture sensitive and hygroscopic ingredient
Contains preservative	Preservative free
BSE (mad cow disease) and TSE (Transmissible spongiform encephalopathy) to humans	No risk of BSE and TSE

**Table 2.** Manufacturer of Vegetable Capsule Shell (5, 9)

Brand Name of Capsule Shell	Manufacturer
HPMC Capsule Shell	
Quali-V	Shionogi Qualicaps
Vcaps Plus	Capsugel (A division of Pfizer)
Vcaps	Capsugel (A division of Pfizer)
VegiCaps (Natural Plant Capsule)	R.P. Scherer Technologies Zhejiang LinFeng Capsules Co. Ltd.
Embo Caps –Vg	Suheunge Capsule Co.Ltd.
Capstech's HPMC Capsule	Baotou Capstech Co., Ltd
Natural Plant Capsule	Zhejiang LinFeng Capsules Co. Ltd.
Pullulan Capsule Shell	
NP Caps	Capsugel Health Care Ltd
Daula	Pharma (Nanjing) Co.Ltd
Guangsheng	Shanxi Gaungsheng Medicinal Capsule Co.Ltd

## 6. Discussion

### Challenges

The other side of use of vegetarian capsule is to also consider challenges to adopt and used of vegetable capsules shell widely across the world. The first is cost factor which is somewhat more than gelatin capsule shell. As day-by-day usage of vegetarian capsules shell increases cost can be made down further. Another challenge is to improvements have to be made in order to qualify the HPMC capsules ahead of gelatin capsules are in their machineability and in the in vitro and in vivo disintegration and dissolution performances. And at last, by solving all the issues need to get approval from the regulatory authority. (5)

### Regulatory requirements in various countries

In the recent time there is increase demand of non-gelatin alternative capsule shell manufacturer of finished product formulation needs to change their already approved products form gelatin capsules to non-gelatin capsule shell. To do this change there are numbers of effort require to reformulate the existing product and also need to file the supplement or variation application to the respective regulatory authority to get approval. In USA, Prior approval supplement (PAS) need to be filed as per MANUAL OF POLICIES AND PROCEDURES (MAPP 5016.6) published by Center for Drug Evaluation and Research. (15)

**Table 3.** Status of Pharmacopeial Monograph for Vegetarian Capsules Shell in Different Region

Sr. No.	Name of Pharmacopeia	Status of monograph	Remarks
1	Indian Pharmacopoeia (IP)	Monograph published	Published in AMENDMENT LIST -004 to the 7 <sup>th</sup> edition of Indian Pharmacopoeia 2014 which was published on 28-November-2016. (14)
2	United State Pharmacopoeia (USP)	Draft monograph published	A new draft USP monograph for Hard Hypromellose Capsule shells (HPMC or veggie capsules) has been proposed in Pharmacopeial Forum (PF) 42(4) and again, proposed in PF 44 (5) on 02-March-2020 and still it is not official in USP. (16)
3	European Pharmacopoeia (Ph.Eur.)	No monograph published	Not yet published
4	British Pharmacopoeia (BP)	No monograph published	Not yet published

5	Japanes Pharmacopoeia (JP)	No monograph published	Not yet published
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### Evaluation tests for vegetable capsules (14,16)

It is always important to set the quality parameters for the evaluation of capsule shell which will ultimately impact final performance of the dosage form. Below parameters describe the test used for evaluation of the vegetable capsule shell.

- Description
- Identification
- Odour
- Average weight
- Weight variation
- Disintegration test
- Moisture permeation test
- Loss on drying
- Microbial contamination test
- Elemental impurity test
- Content uniformity of filled capsules
- Dissolution test of filled capsules

### 7. Conclusion

Religious, cultural and personal issues may affect patients' preference towards the medications presented in capsule dosage forms. (4) The population called vegetarians or vegans and religious or ethnic groups (Hindus, Jews and Muslims, etc.) who follows dietary laws that prohibit the use of certain animal have problem with the animal derived gelatin products. Also, there is high risk of TSE, having CJD or Creutzfeldt - Jakob disease by using gelatin capsules. For such instances vegetarian capsules are definitely a better option. 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. (13) This review article throws the light on the different types of polymers from vegetarian sources that can be used as an alternative to the gelatin capsule in pharmaceuticals as well as food industries and also these polymers can overcome the demerits associated with the gelatin. (17)

To summaries, it may be concluded that none of the gelatin free capsule concepts is fully implemented in industry yet. Nevertheless, capsules based on plant-derived or synthetic polymers are an interesting line extension to gelatin capsules with the potential to gain a market share for certain niche products considering they are made from materials obtained from plant sources, which are an additional bonus in today's regulatory climate.

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### Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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