Review Article

Vegetable Capsule Shell

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ABSTRACT
In recent era, vegetable capsules are new approach which might be replace the usage of gelatin or non-vegetable capsules. Hydroxypropyl 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.

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

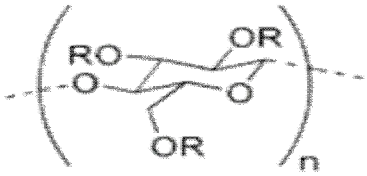
INTRODUCTION

Vegetable capsule shell is mostly prepared from the hydroxypropyl 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) and as a binder. The material is described as a white to slightly offwhite 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 hydroxypropoxy groups. These groups affects many of the HPMC properties such as gelation temperature, viscosity, flexibility and hydration[1].

The word-capsule origin from the latin capsula, which means a small box[2]. Capsules are either hard (two-piece) or soft (one-piece) and are used to encapsulate pharmaceutical formulations[3]. The two-piece capsule is made of a cap-piece that slips over one side open body-piece forming closed cylindrical object[4]. The most common route of administration of capsules is orally but capsules for inhalation[5] such as Spiriva HandiHaler, vaginal[6] 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 crosslinking 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 is good alternative of gelatin capsules due to its vegetable source[1].

Here is the structure of HPMC (Hypromellose):



R = H or CH_3 or $CH_2CH(OH)CH_3$

The first vegetable capsule which is made of HPMC were 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 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 are by thermal gelation and a gelling system used to lower thermal gelation temperature of HPMC[8]. 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[1].

Vegicaps soft capsules are an 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[16].

EMPTY VEGETABLE CAPSULE SHELL

DIFFERENCE BETWEEN VEGCAPS AND GELCAPS

Vegcaps	Gelatin Capsules
100% vegetarian	Animal derived - cows, bovine product
HPMC or Hydroxypropylmethyl cellulose is used.	Gelatin is used.
GRAS listed in FDA	GRAS listed in FDA
Kosher certified	Kosher certified
Suitable for cultural, religious and vegetarian dietary requirements.	Not suitable for vegetarian requirements
Stability over wide range of temperature and humidity.	Not that much stable.
Perfect for hygroscopic preparations.	Not suitable.
Compatible with capsule filling machines, all sizes available.	Same compatibility.
Doesn't support bacterial growth.	Under good storing conditions, it doesn't support bacterial growth.
DEFFERENCE BETWEEN VEGCAPS AND TABLETS	
Vegcaps	**Tablets**
Without Preservatives.	Preservatives are to be added.
Ideal for hygroscopic preparations.	Not ideal.
Fast dissolving ensuring better bioavailability.	Delay in dissolving.
Free from irritants, inactive binders, colors.	They are to be added.

GRAS-Generally recognized as safe by FDA [18]

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.[9]

Empty HPMC capsules and their manufacturers

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

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[10-13].

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. The following gelling agents were experimented: tamarind seed polysaccharide, carrageenan, pectin, curdlan, gellan gum and furcellaran. Shionogi Qualicaps Co. (Japan) was able to produce HPMCcarr capsule using the standard machinery for the hard gelatin capsule by using HPMC gelling system containing carrageenan as a gelling aid (kappa- and iota- carrageenans are preferred) and potassium chloride as gelation promoter. The company has a Quali-V registered trademark. European patent EP0592130 claims that HPMC with higher whiteness, lower equilibrium moisture content and better film properties and compatibility with drugs could be produced by exposing the materials to ultraviolet light in the wavelength range of at least 200 nm[14]. The claim indicates that at the wavelength 253.7 nm, the preferred conditions for ultraviolet radiation are a spacing of about 10 cm for about 10 hours.

An invention of Warner-Lambert Company (now with Capsugel that later became part ofPfizer) have 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 5% of the capsule shell materials comprised of approximately equal proportions of both the hydrocolloid and the sequestering agent. The claim shows that these capsules would have films that are less brittle (unlike those produced with carrageenans), no poor disintegration in vivo and the film transparency is retained[15].

MARKETED PRODUCTS

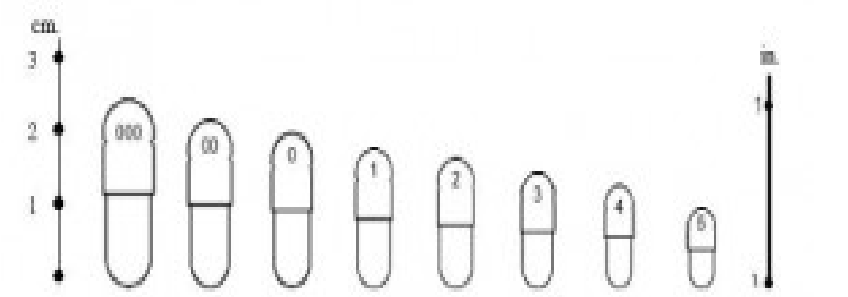
The HPMC capsule shells have found popularity for their use with nutraceuticals and over-the-counter (OTC) formulations.

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

CAPSULE SIZE INFORMATION

Vegetable capsules of HPMC are available in different dimensions of sizes and shell weights. For example Capsugel company (division of Pfizer) produces Vcaps Plus HPMC capsules with sizes from 00 to 4 with elongated capsules for size 0. Quali-V capsules are available in sizes from size 0 to 4 with elongated size 0 only and the empty shells weights varied by ± 10% according to the Qualicaps Group company website, but not exceeding 8% for Vcaps Plus according to the Capsugel company website. If the variations in the capsule shell weights are large, this may result in several filled capsules being rejected from the batch during weight sorting, even though the filled weights are accurate.

Our capsule shells are certified by the Soil Association to be GMO free and suitable for use in organic products. We tend to use size zero caps. You can see the relative size of the different capsules in the graphic below[19]



[20]

Size Specification

Size	Length,cap	Length, body	wall thickness,cap	wall thickness, body	Average weight	Limited weight(mg)
00	11.9±0.4mm	20.4±0.4mm	0.115±0.015mm	0.110±0.015mm	125±6mg	Averageweight ±12
0	11.0±0.4mm	18.5±0.4mm	0.110±0.015mm	0.105±0.015mm	98±5mg	Averageweight ±9
1	9.9±0.4mm	16.5±0.4mm	0.105±0.015mm	0.100±0.015mm	75±4mg	Averageweight ±7
2	8.9±0.4mm	15.3±0.4mm	0.100±0.015mm	0.095±0.015mm	60±4mg	Averageweight ±6
3	8.1±0.4mm	13.6±0.4mm	0.095±0.015mm	0.095±0.015mm	52±4mg	Averageweight ±5
4	7.1±0.4mm	12.1±0.4mm	0.095±0.015mm	0.095±0.015mm	40±4mg	Averageweight ±4

EVALUATION OF VEGETABLE CAPSULE

(1) In-vitro disintegration and dissolution

USP only mentions the testing of gelatin capsules, so that Donauer and Löbenberg have called in a min review the USP to specify how to carry out the disintegration test with HPMC capsules. This is because the dissolution behaviors of HPMC and gelatin capsules have to be different in dissolution media. Moreover, 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 º 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. Stein and Bindra who used HPMC capsules from Shionogi for their formulations found that 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.

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. Because the gut concentration of potassium is low, she justified 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, radiolabelled formulations, containing different viscosity grades of HPMC powder (HPMC K100 and HPMC K4M) filed in HPMCcarr capsules size 0 from Shionogi Qualicaps were tested in 6 healthy volunteers with one week wash-out period between the two administrations to examine the fate of the capsules in the GIT[1].

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 (Figure 1). 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[1].

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). 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.

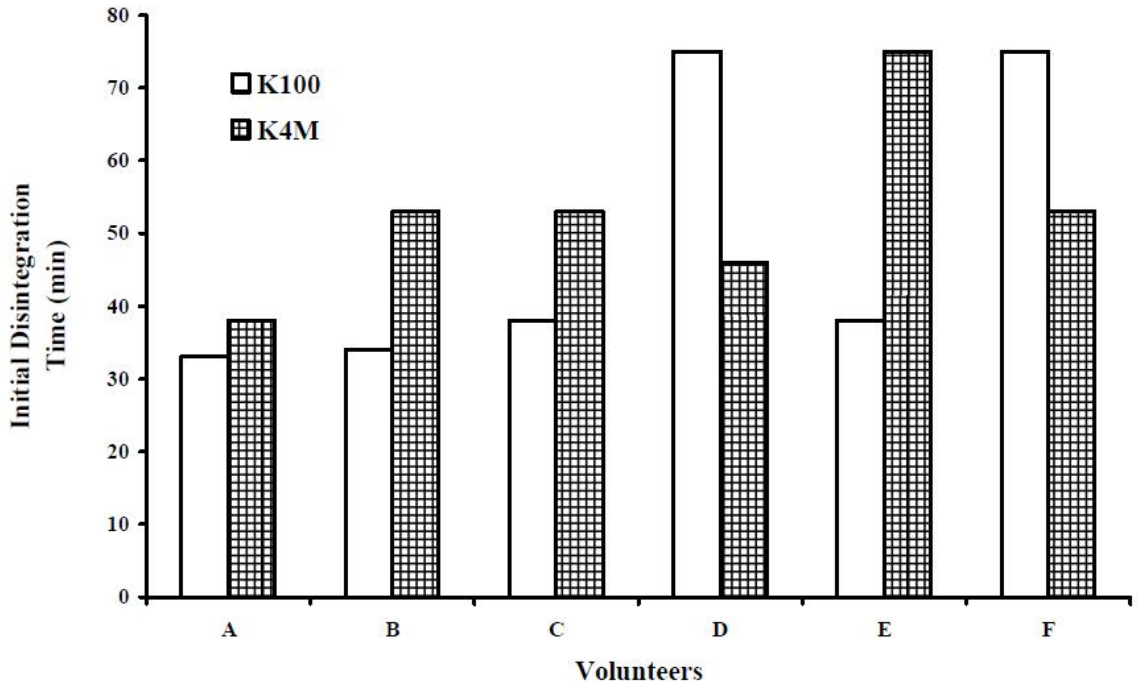


Fig. 1: In vivo initial disintegration time (minutes) for the HPMC capsules in 6 healthy volunteers filled with two different prolonged formulations containing different viscosity grades of HPMC powder (HPMC K100 and HPMC K4M). Graph was generated from data published by Honkanen and colleagues

CONCLUSION

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. 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. 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.

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