Are your capsules vegetarian or nonvegetarian: An ethical and scientific justification

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Abstract:
Capsules are an important component of day to day health management. But recently an issue came up whether the capsule you are using is of vegetarian or non-vegetarian origin. Capsule shell can be divided into vegetarian and non-vegetarian origin on the basis of their origin. Gelatin capsule shell are typically of animal origin and HPMC or starch based shells are of vegetarian origin. CDSCO received one proposal to replace all non veg capsule with capsule of vegetarian origin. CDSCO has invited comments from different stakeholders regarding this. So, in this editorial, we are addressing different issues lying behind veg and non-veg capsules and scientific justification of the same.

Keywords:
Capsule, non-vegetarian, vegetarian

Gelatin Versus Non Gelatin Capsules: Scientific Perspectives

Capsule, a form of dosage form in medication, are common in our day-to-day health management. Capsules are made up of gelatin (hard or soft) and nongelatin shells generally derived from hydrolysis of collagen (acid, alkaline, enzymatic, or thermal hydrolysis) from animal origin or cellulose based. However, currently, an issue of vegetarian and nonvegetarian capsules is coming up. The Central Drugs Standard Control Organization (CDSCO) has invited comments from different stakeholders regarding this.

To address this issue, we need to understand that the needs and food habits vary from person to person and place to place. But, should we differentiate the nature of drugs as per their origin, for health management, which can have a serious impact on health/life? Therefore, in the present editorial, we will discuss their origin and properties in the scientific platform.

Veg versus non-veg capsule
Coming to origin, gelatin capsules are typically of animal origin. Being vegetarian, hydroxypropyl methylcellulose (HPMC) and starch capsule shells share religious and food preference advantage. The story started with a proposal received to the CDSCO to replace gelatin capsules with cellulose-based capsules. Further, the matter was referred to the Drugs Technical Advisory Board (DTAB) where it was found that the matter pertains not only to drugs but also to other products and hence the matter is beyond the scope of the DTAB, and the Ministry of Health may take a policy decision on this in consultation with other ministries regarding this. Members further felt that it also cannot be certified that the contents in the capsule are purely of vegetarian origin, as many chemicals or ingredients of manufacturing system are of nonvegetarian origin.1

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In another case by the Indian Soaps and Toiletries Makers Association versus Ozair Husain, (2013) 3 SCC 641-A,[2,3] the Supreme Court mentioned that, in terms of medical conditions, life of patient is of utmost importance. As many of the medical products are of nonvegetarian origin, choice cannot be left to individuals when it comes to community health. Again, categorizing nonlifesaving drugs only as vegetarian or nonvegetarian is also absurd as there is no fixed criteria to categorize drugs as lifesaving or nonlifesaving, as depending on patient’s condition, an ordinary drug may become lifesaving. Hence, vegetarian versus nonvegetarian distinction in case of drugs was rejected.[2,3]

Collagen specification and stability

Being scientific at cases, there are differences in both the categories of capsule which cater the different properties of ingredients. While preparing gelatin shells, collagens of mammals are preferred compared to collagen of lower animals due to more stability of the former. The stability of gelatin is highest between pH 4 and 7.[4,5]

Both hard and soft capsule shells can be prepared from gelatin. Presence of 12%–16% moisture is essential for maintaining the integrity of gelatin hard capsule shell. Plasticizers, especially nonvolatile plasticizers, are used in the manufacturing of soft shells. These plasticizers reduce interaction between protein molecules and allow retention of moisture by gelatin. Glycerol and sorbitol are used commonly, but sorbitol is associated with blooming (crystallization), when stored at low humid temperature. Hence, glycerol is blended with sorbitol. Polyethylene glycols (PEGs) can also be used.[4‑7]

Gelatin versus non-gelatin capsule: Kinetic comparison

The observations of Cole et al., 2004,[8] describe that there is very little difference between HPMC capsules and conventional hard gelatin shells’ in vivo and in vitro kinetic characteristics which is supported by Tulea et al., 2007.[9] Dissolution of both types of capsule shell was similar in water, whereas acidic environment (pH 1.2) and cations (K⁺/PO₄ buffer) hinder HPMC capsule shell opening. Despite difference, there was no significant difference observed in terms of pharmacokinetic parameters such as $C_{\text{max}}$ and area under the curve.[10] However, individuals fasted had lower mean disintegration time in case of gelatin capsules, compared to HPMC shells.[9]

Advantage of Hydroxypropyl methyl cellulose hard cells over gelatin shells

HPMC hard shells are less dependent on moisture content for integrity and thus cells are resistant to breakage even in dry conditions. HPMC shells contain low moisture at about 2%–6% and are less hygroscopic compared to their counterpart gelatin capsule shells.[4‑6] HPMC shells are less hygroscopic and subsequently moisture transfer to encapsulated material is low which are great advantages for the improved stability of the medicinal product in capsules.[6,7] Another advantage of HPMC shell is polar and hygroscopic solvents in the fill formulations are less likely to migrate to capsule shell or interact with shell material. Compared to gelatin, HPMC is a nonionic polymer and it has less compatibility changes with most encapsulated material and aldehyde impurities present therein.[4‑7]

One limitation of HPMC capsule shell is higher oxygen permeability due to looseness in its structure, which warrants caution for oxygen sensitive compounds. Inclusion of an anti-oxidant in the fill formulation or packaging the capsule into an oxygen-resistant configuration such as blister package with aluminum foil may prevent this oxidative damage.[4,5]

Non Gelatin capsule dosage form: Non gelatin hard capsule

Use of gelling agents such as carrageenan and Gellan gum delays HPMC cell dissolution. Improved HPMC versions are available which do not require a secondary gelling agent (e.g., VCaps). HPMC dissolution and disintegration time is usually longer than that of hard gelatin capsules. Gelling agents may interact with cations in dissociating medium such as potassium and calcium ions. However, dissolution of improved newer versions of HPMC capsules is independent of pH and the ionic nature of dissociating medium.[4,5,7]

Ideal properties of soft capsules are that they should be strong, more elastic, and fusible. These properties are ideally seen in gelatin which lack in nongelatin polymer
capsules. In experimental studies using amoxicillin as a model drug, gastrointestinal transit time and plasma amoxicillin concentration were found to be comparable between gelatin and starch-based capsules. Starch capsules have the advantage of superior finishing and can be easily coated for preparation of modified release forms. Coating is easy in case of starch capsule owing to its smooth seal and bulk density.\cite{4,5}

Other options are starch polyvinyl alcohol (PVA)-based capsules. Compared to soft gelatin capsules, water migration is less in starch-PVA-based preparations and hence, subsequent less drug crystallization. Another advantage is the surface of starch-PVA capsules is more rough and hence more resistant to mechanical deformation and more amenable to coating process.\cite{4,5}

### Different Issues Related to Gelatin versus Non-gelatin Capsules

#### Microbial growth

Gelatin contains all essential elements with the exception of tryptophan and cysteine. Tryptophan is essential for bacterial growth, and lack of tryptophan prevents microbial growth. At ideal packaging and storage conditions, both gelatin and nongelatin capsules are comparable in terms of microbial growth.\cite{4,5}

#### Fragility

Moisture range outside 12%–16% in hard gelatin shell can be detrimental to the shell. Moisture content is especially useful in this regard. Maintenance of hard gelatin capsule shell integrity requires presence of 12%–16% of moisture. If the moisture content decreases, the capsule shell becomes brittle and it is more prone to breakage. On the other hand, a capsule shell deforms and becomes sticky in the presence of high moisture content.\cite{4,5}

#### Aging

Again, on exposure to stress and aging, cross-linking of gelatin occurs and ultimately leads to reduced solubility of gelatin. Acetylation, use of masking agents (e.g., succinic acid), use of excipients with low aldehyde content or anti-oxidants (to minimize the formation of aldehydes), and use of excipients containing abundant number of amino groups (e.g., glycine) can be used to slow down the aging process.\cite{4,5}

#### Tolerance of the capsule shell toward fill composition

Low molecular weight PEGs in the fill formulation (<300) can diffuse into the gelatin shell and act as plasticizer which limits their use. Hard gelatin capsules are less compatible with PEG of molecular weight <4000 as they decreases the moisture from the capsule shell and make it brittle. They are generally compatible with PEG of molecular weight >4000.\cite{4,5}

#### Tolerance of the fill formulation toward shell water content

The order of relative stability against crystallization and or hydrostatic degeneration among different capsule shell material is HPMC capsule > hard gelatin > soft gelatin capsule.\cite{4,5}

#### The real issue: Transmissible spongiform encephalopathy

The first regulatory alert was issued by the US-Food and Drug Administration (FDA) in November 1992, in which the US-FDA alerted dietary supplement manufacturers regarding the concern about transmissible spongiform encephalopathies (TSEs). The manufacturers were directed to gather information regarding any ovine or bovine material and to ensure that these materials are not from bovine spongiform encephalopathy (BSE)-endemic countries.\cite{10,11}

In December 17, 1993, the US-FDA recommended manufacturers not to use bovine-derived materials from cattle resided or originated from BSE countries and issued direction regarding the identification of origin of bovine-derived materials, to maintain traceable record of each lot of bovine-derived material and country of origination of the materials.\cite{10,11}

#### Precautions

Skin-derived gelatin has less risk than bone-derived gelatin and specially bone of vertebral column and skull, where the chance of contamination is highest. Documentation of source and traceability of record is must. Gelatin processors should ensure that slaughterhouses that supply bovine bones for gelatin production remove heads, spines, and spinal cords as the first procedure following slaughter.\cite{10,11}

Raw materials should not be collected from cattle that show signs of neurological disease. BSE-free country (BSE-related standards of the Office International des Epizooties) is preferable, but can also be collected from non-BSE countries if the cattle come from BSE-free herds and if the slaughterhouse removes the heads, spines, and spinal cords directly after slaughter. Use of alkaline hydrolysis further reduces the risk of TSE. The raw materials can be further processed to make the risk even lower.\cite{10,11}

#### Plasticizer issues

Use of plasticizers shares many problems such as phase separation and consequent migration of plasticizer to the surface of capsule. Oxygen permeability and loss of volatile fill components can be minimized by the use of nonglycerol plasticizers or substituting a portion of
glycerol with higher polyol plasticizer and maintaining low shell moisture content; protecting the capsule against high humid conditions,[4,7]

**Manufacturing and price**

Gelatin capsules are being used worldwide for the past 100 years with known safety and toxicity profile. Gelatin is easily available from hydrolysis of collagen whereas manufacturing of HPMC is a synthetic process. Raw materials for gelatin are readily available in the market which can fulfill the requirement of industries in India whereas raw materials for non-gelatin are quite less available and hence they are four times costlier than their gelatin counterpart. Moreover, most of the vegetable capsule shell technologies are in patent period, contributing to the cost component of these capsule shells.[12]

**Conclusive Remarks**

Food habits vary from person to person and place to place. Religion is the vital source of such variation. Jainism people are vegetarian but they do not take some vegetarian foods such as potato, carrot, onion, and garlic which are grown below earth. All the different cultures have their own beliefs and habits. Therefore, we must remember that medicine should not be treated as food articles and is independent of these thoughts or boundaries to save life of patients. We can see that both gelatin and nongelatin capsules are comparable in toxicity. However, lower moisture content, low hygroscopicity, physical stability, stability in different ranges of temperature and humidity are advantages that favor the use of nongelatin capsules. But, to keep in mind is that gelatin is an age-old technology with proven safety record. Manufacturing easiness, easily available raw material, and low cost are advantages of gelatin capsules.

Regarding the vegetarian versus nonvegetarian issue, defining vegetarian is a difficult issue, with special reference to variation among different religious beliefs present. Many a times, manufacturing of drugs requires different reagents of animal origin. Again, different drug products are also of nonvegetarian origin, for example, hormonal products, heparin, insulin, antiserum, and human cell line-derived products. Involvement of all these complicated issues makes determination of vegetarian and nonvegetarian capsules complicated. Again, this will create chaos between patients and doctors regarding the prescription of vegetarian versus nonvegetarian capsules. Scientific and manufacturing advantages can guide in this issue. On the ethical basis, representation says that gelatin-based capsules should be allowed to be marketed without any additional labeling.

“Some members also pointed out that HPMC – a type of cellulose capsules – is basically of synthetic origin and as such cannot be considered as purely of vegetarian origin as in the case of food preparations,” the minutes noted. The DTAB’s decision is in line with the 2013 Supreme Court decision which stated that cosmetics and drugs cannot be treated at par with food articles, when it comes to labeling them with a brown or a green mark to distinguish the vegetarian and nonvegetarian ingredients and hence, we are with the decision of the Supreme Court.

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