A REVIEW: MANUFACTURING OF CAPSULE SHELL FROM NATURAL SOURCES

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ABSTRACT: Use of natural polymers is increasing day by day in pharmaceutical preparation. The capsule shell can be made from the natural, semisynthetic polymers or others, because from last decades capsule shells are made from gelatin which is obtained from animal sources etc. By the use of ionotropic gelation technique, potential sago starch mixture etc hard capsule shell can be prepared from vegetarian sources. The aim of this review article to provide information regarding the manufacturing of capsule shell from plant based material.

Key words: Capsule, gelatin, ionotropic gelation, polymers.

INTRODUCTION:

Capsules:
The word capsule derived from the Latin Capsula, meaning a small box. In current English usage it is applied to many different objects, ranging from flowers to spacecraft.

In Pharmacy, the word is used to describe an edible package made from gelatin or other suitable material which is filled with medicines to produce unit dosage, mainly for oral use.

One of the two oral solid dosage forms most commonly used is tablet and capsule. They are unit dosage forms in which one usual dose of the drug has been accurately placed.

Capsule shell contains two parts: cap and body. Body is larger than the cap.

Capsules are solid dosage forms in which drug substances are enclosed within a hard or soft soluble shell generally formed from gelatin. Capsules may be classified as either hard or soft depending on the nature of the capsule shell. The capsule shells of both hard and soft capsule are made up of gelatin blends and may contain excipients.

Gelatin:

Gelatin is still the major component used for capsules and replacement polymer systems need to have the same basic properties. Gelatin possesses five basic properties that make it suitable for the manufacture of capsules:

1. It is non toxic, widely used in foodstuffs, and is acceptable for use worldwide.
2. It is readily soluble in biological fluids at body temperature.
3. It is a good film forming material producing a strong flexible film. The wall thickness of a hard gelatin capsule is about 100µm
Solutions of high concentration, e.g. 40%w/v are mobile at 50°C. Other biological polymers, such as agar, are not.

A solution in water undergoes a reversible change from a sol to gel at temperatures only a few degrees above ambient. This is in contrast to other films formed on dosage forms, where either volatile solvents or large quantities of heat are required to cause this change of state. E.g. tablet film coating. These types of films are formed by spraying and have a structure that could be described as formed of overlapping plates, whereas the gelatin films are homogeneous in structure, which gives them strength.

Gelatin is still the major component used for capsules. Gelatin is a substance of natural origin that does not occur as such in nature. Gelatin is a heterogeneous product derived by hydrolytic extraction of animal collagen, a natural protein, which occurs in the skin, bones and connective tissue of the animals. There are two main types of gelatin i.e. Type A and type B. Type A gelatin is derived from an acid precursor and exhibits an isoelectric pH 9, whereas type B gelatin is from an alkali-treated precursor and has its isoelectric pH 4.7. The acid process takes about 7 to 10 days and is used mainly for porcine skins because they require less pretreatment than bones. The basic process takes about 10 times as long and is used mainly for bovine bones. The bones must first be decalcified by washing in acid to give a soft sponge-like material, called ossein, and calcium phosphates are produced as a by-product. The ossein is then soaked in lime for several weeks. After hydrolysis, the gelatin is extracted from the treated material using hot water. The first extract contains the gelatin with the highest physical properties, and as the temperature is raised, the quality falls. The resulting weak solution of gelatin is concentrated in a series of evaporators and then chilled to form gel. This gel is then extruded to form strands, which are then dried in a fluidized bed system. The dried material is graded and then blended to meet the various specifications required. Although capsules may be made from either type of gelatin.

The properties of gelatin that are most important to capsule manufacturers are the bloom strength and viscosity. The bloom strength is a measure of gel rigidity. It is determined by preparing a standard gel (6.66% w/v) and maturing it at 10°C. It is defined as the load in grams required to push a standard plunger 4mm into the gel. The gelatin used in hard capsule manufacture is of a higher bloom strength (200-250 g) than that used for soft capsules (150 g) because a more rigid film is required for the manufacturing process.

Advantages of gelatin capsule shells:

1. They are elegant.
2. Ease of use.
3. Provide a smooth, tasteless shell for the drug.
4. Economical.
5. Their ability to hide their contents from sights and to mask.
Disadvantages:

1. The main disadvantages of capsule shells are vegetarian and dietary restrictions.
2. Problems related to religious beliefs.
3. The water instability of gelatin.
4. Major disadvantage of capsules over tablets is their higher cost.

Capsule size:

Empty gelatin capsules are manufactured in various lengths, diameter, and capacities. The size selected for use is determined by the amount of fill material to be encapsulated. The bulk density and compressibility of the fill will largely determine to what extent it may be packed into a capsule shell.

For human use empty capsules ranging in size from 000 (the largest) to 5 (the smallest) are commercially available. Larger capsules are available for veterinary use.

<table>
<thead>
<tr>
<th>Capsule No.</th>
<th>000</th>
<th>00</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capacity to accommodate in (mg)</td>
<td>950</td>
<td>600</td>
<td>450</td>
<td>300</td>
<td>250</td>
<td>200</td>
<td>150</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 1: Capsule size chart

Development the formulation and selection of capsule size:

The goal is to prepare a capsule with accurate dosage, good bioavailability, easy to fill and production, stability and elegance.

In dry formulation the active and inactive components must be blended thoroughly to ensure a uniform powder. This can be achieved by size reduction, and effective blending.

A diluent as filler may be added to the formulation to produce the proper capsule fill volume. Lactose, microcrystalline cellulose and starch are commonly used diluents. Apart from providing bulk these materials provide cohesion to the powders.

Disintegrating agents are also added in the formulation to facilitate the breakup and distribution of the capsule content.
Ionotropic gelation method:

It is based on the ability of polyelectrolytes to cross link in presence of counter ions to form hydrogel beads. It is also called the gelisphere. Gelispheres are spherical crosslinked hydrophilic polymeric entities capable of extensive gelation and swelling in gastric fluids. The release of drug is controlled by polymer relaxation.

The beads are produced by dropping a drug loaded polymeric solution into the aqueous solution of polyvalent cation. The cations diffuse into drug loaded polymeric drops, forming a three dimensional lattice of ionically crosslinked moiety.

Fig. 1: It shows the basic technique of Gelispheres preparation

In Ionotropic gelation technique, there has been a growing interest in the use of natural polymers as drug carriers due to their biocompatibility and biodegradability. The natural or semisynthetic polymers i.e. Alginates, Gellan gum, Chitosan, Pectin and Carboxymethyl cellulose are widely used for the encapsulation of drug by this technique.

In ionotropic gelation method natural polymers are used. These natural polyelectrolytes contain certain anions /cations on their chemical structure, these anions /cations form mesh like structure by combining with the counter ions and induce gelation by cross linking. In spite of having a property of coating on the drug core these natural polymers also act as release rate retardant.
Polyelectrolytes used in ionotropic gelation:

<table>
<thead>
<tr>
<th>Natural polymers</th>
<th>Synthetic polymers/monomers</th>
<th>Multivalent cations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chitosan</td>
<td>Hydroxyethyl Methacrylate(HEMA))</td>
<td>Calcium (Ca⁺)</td>
</tr>
<tr>
<td>Alginate</td>
<td>N-(2-Hydroxy propyl)methacrylate (HPMA)</td>
<td>Potassium (k⁺)</td>
</tr>
<tr>
<td>Dextran</td>
<td>Vinyl acetate</td>
<td>Ferric (Fe⁺)</td>
</tr>
<tr>
<td>Collagen</td>
<td>Acrylic acid</td>
<td>Barium (BA⁺)</td>
</tr>
<tr>
<td>Gelatin</td>
<td>Methacrylic acid</td>
<td>Sodium (Na⁺)</td>
</tr>
<tr>
<td>Hyaluronic acid</td>
<td>N-isopropylacrylamide(NIPAMM)</td>
<td>Magnesium (Mg⁺²)</td>
</tr>
<tr>
<td>Fibrin</td>
<td>Polyethylene diacrylate/dimethacrylate</td>
<td>Glycol Zinc (Zn⁺²)</td>
</tr>
</tbody>
</table>

Ionotropic gelation technique, use of polymers is increasing as drug carriers due to bioavailability and biodegradability. The natural or semisynthetic polymers are alginate, chitosan, pectin, carboxymethylcellulose are widely used. These natural polyelectrolytes contain cations/anions that form a mesh like structure by combining with the counter ion to induce gelation by cross linking 14.

**NATURAL POLYMERS USED IN IONOTROPIC GELATION TECHNIQUE:**

**Alginate:**

It is a non-toxic, biodegradable, naturally occurring polysaccharide obtained from marine brown algae, certain species of bacteria. Sodium alginate is a sodium salt of alginic acid a natural polysaccharide and a linear polymer composed of 1,4-linked β-D Mannuronic acid (M) and α-D-glucouronic acid (G) residues in varying proportions and arrangements 2. Sodium alginate is soluble in water and forms a reticulated structure which can be cross-linked with divalent or polyvalent cations to form insoluble meshwork. Calcium and zinc cations have been reported for cross-linking of acid groups of alginate. Alginic acid is insoluble in water thereforie sodium alginate is used 2, 16, 17 and14.
**Gellan gum:**

It is bacterial exopolysaccharide prepared commercially by aerobic submerged fermentation of Sphingomonas Elodea. For gelation a concentrated solution is prepared by dissolving in warm water. When the temperature is decreased the chain undergoes a conformational transition from random coils to double helices (co helix transition) \(^{18}\).

**Chitosan:**

It is natural, nontoxic, bioabsorbable, poly(aminosaccharide). It is a biopolymer used in the preparation of polyelectrolyte complex products. It is also chitin deacetylation product \(^{2}\).

E.g: chitosan-alginate complex.

**Carboxymethylcellulose:**

Cellulose is a plant product. On carboxymethylation of cellulose it forms carboxymethylcellulose. Carboxylic group of CMC interacts with multivalent cation metal ions to form ionotrop gel which is stabilized by electrostatic interaction. Interaction between the metal group and –OH group of the polymer produces good stability. It is used as a stabilizer in various pharmaceutical preparations. It is non toxic \(^{19}\).

**Pectin:**

It is non toxic, inexpensive. Polysaccharide extracted from orange peel or apple pomaces. It is used as food additives, thickening agent and gelling agent. It is a polymer of D-galacturonic acid with 1-4 linkages. In the presence of calcium ions it forms gel \(^{19}\).

**Factors affecting ionotropic gelation method:**

1. Polymer and electrolyte concentration:

It has a major effect on formulation. Both should be calculated in the ratio depending on the number of crosslinking units. Percent entrapment efficiency varies depending on the type of electrolytes and concentration of polymer

2. Temperature:

It affects the size of beads and time required for cross linking.

3. pH OF cross linking solution:

It is very important during formulation to show the speed of reaction and size of the bead.

4. Gas forming agent:
Gas forming agent such as calcium carbonate, sodium carbonate are added to produce porous structure in gelisphere. It majorly affect the size of bead and causes irregular shape.

**Advances in ionotropic gelation**:  

1. Ionotropic pregelation/polyelectrolyte complexation technique: It increases the permeability; by addition of oppositely charged another ion increases the mechanical strength.  
2. Ionotropic gelation under high voltage electrostatic field: It is used mainly to prepare protein loaded chitosan microsphere.  
3. Emulsion internal ionotropic gelation: Incorporation of oil phase and emulsifier.  
4. Ionotropic gelation followed by coacervation.  
5. Alginate-Poly(ethylene glycol) Hybrid gelisphere.  
7. Ionotropic gelation followed by compression.  

Capsule shells made from sago starch/carrageenan blends can be used as hard capsule material. Combination of sago starch/carrageenan homogeneous, translucent and smooth films. From the article it was illustrated that it is a suitable alternative for gelatin as hard capsule material. The capsule shell was made from the alginate-chitosan by tripolyphosphate cross link method. The capsule shell has good physical properties so it can be used as a drug delivery. Use of HPMC in the production of capsule shells, replacing the animal derived gelatin in conventional two piece capsules.

**Conclusion:**  

It is conclude that by use of natural and semisynthetic polymers the plant based capsule shell can be prepared by the use of ionotropic gelation technique and by using various concentration of polymer ratio. The prepared capsule shell can be used for encapsulating drug molecules for extended or sustained drug delivery system or others. It is best suitable alternative for gelatin as a hard capsule. Currently the only available source is HPMC capsule which cost three times compared to gelatin. Therefore by use of natural or semisynthetic polymers capsule shell can be prepared.
References:


9. Gelatin capsule have technical advantage over HPMC capsule:PHD chamber.


