Vegetarian substitutes for gelatin soft capsules

This article provides an overview of the current state of materials and technology used to produce vegetarian soft capsules and discusses applications, processing, and suitable products for these alternatives to soft gelatin capsules.

Soft capsules, also called softgels, are one of the most widely used solid oral dosage forms, particularly in the nutraceutical market. Traditional softgels are made from gelatin, but interest in vegetarian alternatives to gelatin soft capsules (GSCs) is growing.

The materials used to make vegetarian soft capsules (VSCs) have very different properties than gelatin. The first commercially viable VSCs appeared on the market around 2001 and were developed for encapsulating oils.
and suspensions for dietary and cosmetic products [1]. The capsules were made from carrageenan-modified starch (C-MS), and the encapsulation equipment subjected the capsules to a curing step, in which the capsules passed through a band of hot air. Later machines included die rolls designed to increase the thickness of the seal and prevent the capsule contents from leaking.

The industry has made continuous improvements to the materials, equipment, and processes involved in their manufacture. As a result, vegetarian soft capsules can now be produced using the same type of mixing and encapsulation equipment used for GSCs at similar encapsulation speeds.

**VSC market**

VSC products are currently available in the nutraceutical and cosmetics markets as well as a few products in the pharmaceutical market. VSCs currently constitute approximately 10 to 15 percent of the nutraceutical soft capsule market in terms of revenue, and their use is expected to continue to grow due to increasingly competitive material prices and optimized processing technology as well as expansion into the pharmaceutical market.

The primary market for VSCs includes consumers who demand vegetarian capsules for cultural, religious, or dietary reasons. VSCs can also be beneficial in applications where gelatin is not a suitable capsule polymer, such as high-temperature encapsulation or products with high-pH fill content. Manufacturers are also looking to VSC polymers as alternatives to gelatin because gelatin is derived from animals, is prone to price fluctuations, and has a relatively large carbon footprint.

VSCs have faced some concerns from consumers interested in "clean label" products—defined as products containing only unprocessed or unmodified ingredients—since starches are chemically modified materials. Also, carrageenan suffered from a long period of concerns that it was carcinogenic, causing many food producers, especially in the US, to stop using it in their products. However, the FDA considers carrageenan a generally recognized as safe (GRAS) material.

**VSC materials**

The most common gelatin substitutes used to make VSCs are carrageenan, modified starch, and alginate. Table 1 summarizes the market and sourcing challenges for each.

**Carrageenan.** The global market for carrageenan is approximately 60 to 70 kilotonnes per year, with an expected compound annual growth rate (CAGR) of 4 to 5 percent [2]. Seventy to 80 percent of the carrageenan produced is used in the food industry for its gelling, thickening, and stabilizing properties, while less than 10 percent is used by the pharmaceutical industry. Pharmaceutical applications, particularly soft capsules, are still considered a niche segment.

As previously mentioned, the first VSCs consisted of a blend of carrageenan and modified starch (hydroxypropyl starch), and most nutraceutical VSCs currently on the market still use carrageenan-based formulations.

**Vegetarian soft capsules can now be produced using the same type of mixing and encapsulation equipment used for gelatin soft capsules at similar encapsulation speeds.**

**Table 1**

<table>
<thead>
<tr>
<th>Material</th>
<th>Global market in 2018 (kilotonnes)</th>
<th>Pharma usage</th>
<th>Major pharma suppliers*</th>
<th>Average price ($/kg)</th>
<th>Raw material</th>
<th>Sourcing challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrageenan</td>
<td>60-70</td>
<td>7% VSC: 500 tonnes</td>
<td>~10-12</td>
<td>11-12</td>
<td>Red seaweeds</td>
<td>Limited supply base and concerns with feedstock availability may occur due to climate change. Currently, no supply issue with feedstock in major producing regions.</td>
</tr>
<tr>
<td>Alginate</td>
<td>40</td>
<td>8-10% GSC: unknown</td>
<td>~2-4</td>
<td>12-14</td>
<td>Brown seaweed</td>
<td>Highly consolidated supply base and high entry cost for new suppliers.</td>
</tr>
<tr>
<td>Modified starch</td>
<td>9,000-10,000</td>
<td>10-15% (as an excipient)</td>
<td>~5</td>
<td>4-5</td>
<td>Many, including: potato, corn, cassava, etc.</td>
<td>Important to track price movement.</td>
</tr>
</tbody>
</table>

Source: Beroe analysis

* Indicates the number of suppliers who cater to pharmaceutical applications but not necessarily soft capsule shells.
Manufacturers offering carrageenan-based soft capsules include Procaps, Ayanda, Captek, Catalent, and Eurocaps, among others.

Carrageenan is produced by two species of cultured red seaweeds, kappaphycus alvarezii and eucheuma spp. Production of these seaweeds was estimated at 8.3 million tonnes in 2012 [3]. Indonesia and the Philippines are the two major producers of this raw material, which sells for approximately $1,800 per tonne [4, 5].

Climate change has the potential to affect the red seaweed supply, but suppliers are taking actions to avoid shortages. For example, the carrageenan manufacturer Cargill has committed to sourcing 60 percent of its red seaweed sustainably by 2025 [6].

The number of suppliers manufacturing pharmaceutical-grade carrageenan suitable for soft capsule production is limited, but it is expected that suppliers will expand and improve their product portfolios due to increased demand from end-user industries.

Modified starch. Global production of modified starch was between 9 and 10 million tonnes in 2017 [7], and the import price in the European Union was $922 per tonne, which represented a 3.9 percent increase over the previous year [8]. Starch has good film-forming properties and good raw material availability, which, along with its price advantage, makes starch-based soft capsules a good low-price alternative to GSCs or other vegetarian capsules.

The world’s first carrageenan-free vegan softgel, Plantgels, replaces carrageenan with modified tapioca starch, which is derived from the cassava root [9]. Some other modified starches such as corn or pea are used in combination with carrageenan for softgel applications.

Alginate. Europe and North America combined account for more than 50 percent of the global alginate market, which is growing at a CAGR of 1 to 3 percent. Growth in the Asia-Pacific market is higher due to increased demand from the processed food and pharmaceutical industries. The pharmaceutical market for alginate is consolidated, with two major suppliers that account for more than 90 percent of global market share [10].

Currently, the pharmaceutical alginate supply is sufficient to meet demand, and if demand should increase suddenly, suppliers focused on food-grade alginate could switch production to pharmaceutical applications, since all regulatory approvals are in place.

The sole raw material for commercial-scale alginate production is brown seaweed, which is time consuming and labor intensive to cultivate. Currently, the brown seaweed supply is sufficient to meet the needs of the alginate market, and there are no issues with feedstock capacity. However, because there is a limited number of qualified suppliers and a high entry cost for new suppliers, alginate buyers do not have much negotiating power with suppliers.

### Table 2

Comparison of processing steps for GSCs versus VSCs

<table>
<thead>
<tr>
<th></th>
<th>Gelatin</th>
<th>Modified starch</th>
<th>Carrageenan-modified starch</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Film casting</strong></td>
<td>Fast, easy</td>
<td>Slow, difficult, sensitive to RH</td>
<td>Slow, easy (equipment adaptations)</td>
</tr>
<tr>
<td><strong>Polymer mass preparation</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>specific mixing system</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High temperature heated-transfer system</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes (extrusion systems can be required)</td>
</tr>
<tr>
<td><strong>Conventional die rolls</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Encapsulation</strong></td>
<td>No</td>
<td>No</td>
<td>Yes (some cases)</td>
</tr>
<tr>
<td><strong>spreader boxes design</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Required curing step</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Tray-drying (days)</strong></td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td><strong>(oil-based capsules)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Batch-to-batch variability</strong></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Process cost</strong></td>
<td>$</td>
<td>$$</td>
<td>$$$</td>
</tr>
</tbody>
</table>

Source: Procaps
VSC manufacturing

As previously mentioned, the properties of the materials used to make VSCs differ from gelatin. Raw material and equipment suppliers have had to learn how to work with these new materials to overcome challenges related to the resulting capsules’ physical, chemical, and functional properties, such as softness, leaking, poor dissolution, and increased dissolution times at stability conditions. Also, VSC polymers have higher viscosities and require higher processing temperatures than gelatin, which makes mixing, deaeration, and transfer processes challenging.

With gelatin, film formation is due to the tertiary structure of the gelatin induced below the gelation temperature (30°C to 40°C). With starch formulations, film formation proceeds mainly by the swelling and gelatinization of the starch (at 90°C to 95°C). Gelatinization refers to irreversible gel formation due to the release of amylose in the starch granules when they are heated and cooled.

Gelatin films cast easily and quickly, are highly elastic and resistant to strain, and dry quickly. Carrageenan-starch films cast slowly under controlled conditions, are elastic and resistant to strain, and dry slowly. Starch films cast slowly, are highly susceptible to relative humidity (RH), have low elasticity and resistance to strain, and dry slowly.

Table 2 shows a summary of the technical requirements for VSC production and compares the pros and cons of VSCs and GSCs. Items in red show processing differences compared to GSCs due to new equipment, adaptations to existing equipment, or additional processing steps, such as heated transfer and curing.

In recent years, modified starch suppliers have offered materials with viscosities of about 40,000 to 50,000 centipoise that can be handled in GSC equipment. In contrast, C-MS formulations can have viscosities as high as 90,000 centipoise. As the table shows, such polymer masses require mixing, heating, transfer, and spreading systems designed to handle high-viscosity materials. In general, starch formulations require moisture control, because the film is sensitive to RH values higher than 20 to 30 percent.

For GSCs, the sealing process occurs by sol-gel transition (also called gelation), but for VSCs, sealing occurs through gelatinization of the starches. The sealing quality is determined by the film quality, the design of the die roll, the pressure force, and in some cases by processing steps after encapsulation. During encapsulation, heating the wedge is not required since sealing is not dependent on temperature.

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**Figure 1**

Characterization of VSCs at accelerated stability conditions (40°C, 75% RH)
The moisture content in fresh capsule shells may be about 20 percent, depending on the formulation, and drying time is comparable to GSCs. The filling volume should determine the proper die roll size, since overfilling affects the seal strength and the shells may contract during drying.

Despite some particular processing requirements, formulations containing carrageenan are straightforward to encapsulate compared to modified starch because of their consistency batch to batch, robust film formation, elasticity, seal strength, and stability at varying moisture and temperature conditions.

In-process controls include temperatures at different points in the encapsulation machine, film thickness, and weight variation. Physical testing of the capsules includes hardness, burst test, film and seal thickness, and shell moisture content.

**Stability of VSC products**

Figure 1 shows the results of a study comparing the hardness, burst test, seal percentage, shell moisture content, and disintegration time for several marketed VSC products at stability conditions. The study compared the properties of two Procaps VSC products (S1 and S2) and four commercial VSC products made from C-MS at 40°C, 75 percent RH at initial time (M0), 1 month (M1) and 3 months (M3).

In general, VSC hardness has been reported to be as low as 2.0 newtons and not comparable to GSCs. Most VSCs are nutritional products containing either single oils or oily suspensions using only glycerol as a plasticizer. Hardness can be a reference for the final drying time, and low hardness values could compromise the products during bulk storage and transport. Burst test and percentage of the trailing seal are a measure of the seal quality, ranging roughly from 100 to 300 newtons and 50 to 87 percent, respectively, at the initial time, as shown in the figure.

Percent seal values in VSCs can be as high as 80 percent depending on the die roll design. Disintegration times were determined under USP conditions for rupture time of soft capsules (USP apparatus 2), considering the total disintegration of the shell as final point for visual detection. At stability conditions, physical properties tended to decrease but not to an unacceptable level, with the exception of the disintegration times, which in some cases, were observed to be longer than 30 minutes. While VSCs show a lag time in dissolution due to the slow hydration of the shells, they are not prone to crosslinking, as gelatin is, so the cause of the increased disintegration times at stability conditions is unclear.

**VSC outlook**

While the supply of gelatin-free soft capsules is still in its nascent stage, demand for vegetarian capsule shells, whether plant derived or synthetic, is growing. VSCs have the potential to reach a considerable market share in the future using the gelatin substitutes discussed in this article. Decreasing material costs and increasingly optimized processes also provide opportunity for growth in the number of VSC products on the market.

Existing products have demonstrated the feasibility and consistency of VSC materials and manufacturing processes. While there are some challenges associated with VSC manufacturing, the products demonstrated physical stability at accelerated conditions. However, disintegration times were longer for VSCs at stability conditions compared to GSCs, which should be evaluated, as disintegration time is a critical quality attribute.

**References**

2. FAO report.
3. Beroe analysis.
5. Beroe interaction with supplier.
7. Beroe analysis based in secondary research.