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WHAT'S BEHIND **VEGETARIAN** SOFT CAPSULES?

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AB-STRACT

The present is an overview of the state-of-the-art for vegetarian soft capsules in terms of materials (sourcing and demand), applications, processing, products and a general insight of the current state of materials and technology of these gelatin alternatives.

FROM THE BEGINNING...

Soft capsules are one of the widely used dosage forms especially in the nutraceutical market, the segment where the interest for soft vegetarian capsules started. There is a history of material science and technology behind the products that are available. Since the launch of the first vegetarian capsule around 2001, continuous progress has been done in materials, equipment and processing to offer a platform in the same way as it is known for soft gelatin capsules (SGC).

Raw material and equipment manufacturers have built new knowledge coming from a new material with quite different properties from gelatin. On this track, some physical, chemical and functional features of the capsules due to the properties of the materials arose such as low hardness, leakers, low dissolution of the polymer shell and increase of dissolution times at accelerated stability conditions. Processing the polymer masses for encapsulation was challenging for mixing, deareation and transfer because of the high viscosity and the high processing temperatures. At its first stage, materials, equipments and processes were developed for encapsulating oils and suspensions for dietary and cosmetic products.

Sealing process of vegetarian gelatin substitutes does not proceed by sol-gel transition as it does in gelatin but through a gelatinization in the cases of starches

promoted by a decrease in temperature. First encapsulation equipments for manufacturing VSC using carrageenan-modified starch (C-MS) submitted the capsules to a curing step where the capsules pass through a band with hot air. Later on, multistep die rolls were designed for the technology aiming to increase the thickness of the seal up to 90% and to prevent leaking of the fill content.

A second generation of materials with improved properties mainly based on carrageenan-modified starch was developed. The hardness of the capsules was increased enough and the shell dissolution met the criteria. In the same way, improvements were done in order to offer a process as similar as possible to gelatin encapsulation. In the case of modified starches (MS), materials were modified to work using the mixing system and the encapsulation equipment of the SGC manufacturing and to reach higher encapsulation speeds.

Beyond technical issues in product development and manufacturing, the technology has evolved during the last 20 years. As an alternative to soft gelatin capsules, nowadays the soft vegetarian (veg) capsules have gained a position in the nutraceutical market and constitute ~10-15% in total soft capsule market (including gelatin and non-gelatin) in terms of revenue. Furthermore, there is a big expectation regarding a more competitive offer of the materials, the optimization of processing technology as well as its expansion to the pharmaceutical market. Besides the higher costs of materials and technology compared to SGC manufacturing, concerns about clean label of soft veg capsules continue to arise since in the case of starches, these are chemically modified materials and in the case of carrageenan it is currently listed as generally recognized as safe (GRAS) after a long time of safety concerns for it use in foods.

Nowadays, the soft veg capsules are available in the segment of nutraceutical, cosmetics, food and in few cases for pharmaceutical products.

FOR WHO/WHAT VEG SOFTGELS ARE MADE FOR?

Besides the potential market for vegetarian capsules including ethnic, religious, and dietary groups, the vegetarian capsules were expected to cover the gap of most of the limitations of gelatin as polymer for soft capsules manufacturing such as high temperature encapsulation or high pH fill content. However, currently few pharmaceutical vegetarian soft capsules have reached the market

In one hand, the material is more resistant to high temperatures and do not proceed to crosslinking under high temperatures or humidity as in the case of gelatin, however it has been found that some VSC products do not meet the rupture time criteria when they are submitted to accelerated stability.

In sourcing terms, buyers are looking for potential alternatives to substitute gelatin because it is animal derived, prone to price fluctuations and aiming the reduction of the carbon footprint. This leads to an increased demand of veg alternatives with C-MS being currently dominating the market.

WHAT ARE THE VEG SUBSTITUTES OF SGC?

Carrageenan, modified starch and alginates have been considered as alternatives to SGC. Sourcing and challenges in demand are briefly were reviewed and summarized for all of them (see Table 1)

A) Carrageenan:
The global market is ~60-70 Kilo tonnes with demand CAGR of 4-5%, however its usage in pharmaceutical industry is less which is >10%. It is mostly used in food industry (70-80%) for its gelling, thickening, and stabilizing properties.

For pharmaceutical applications, particular to soft capsules this market is still considered a niche segment.

In 2001, the first commercially feasible gelatin alternative entered the market, a soft gel shell alternative made of a blend of modified starch (hydroxypropyl starch) and carrageenan. Two decades later, most of the nutraceutical VSC contains carrageenan based formulations.

Few of the suppliers who manufacture carrageenan based soft capsules are Ayanda, Captek, Catalent, Dupont, Eurocaps etc.

Raw material (Red Seaweeds): The cultured red seaweeds that produce carrageenan are Kappaphycus alvarezii and Eucheuma species that is estimated to be 8.3 million tons in 2012. Indonesia and Philippines are the two major producing regions of these two raw materials. The price of the raw material is approximately USD 1800/MT.

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B) Modified starch:
Global market overview: The production of modified starch was 9-10 million tons in 2017. The import price in the EU was USD 922/t in 2017 which rose by 3.9% against the previous year. Starch based soft capsules are a low price alternative to soft gelatin capsules or other veg capsules.

Along with the price advantage, it has good film forming properties and good availability in terms of raw material also which makes it a good choice of gelatin substitute.

Plantgels™, the world's first carrageenan-free vegan softgel, made from modified tapioca starch, glycerin, purified water and caramel only. In Jan2018, SIBU LLC. introduced StarchGelTM which replaces the carrageenan in the SIBU soft gel. Tapioca Starch is naturally derived from the Cassava Root. Er-Kang Pharmaceuticals is one of the suppliers of modified tapioca starch for application in soft capsules.

C) Alginate:
Global Market overview: From the global market, Europe and North America account >50% of demand share together, growing at a CAGR of 1-3%. Market in Asia-Pacific region is growing at a higher rate due to increased demand from processed food and pharmaceutical industries.

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Currently supply is sufficient to meet the demand and in case of sudden increased demand, supplier whose focus is on food grade can switch to production of alginates for pharmaceutical applications, considering all regulatory approval are obtained.

Raw material: Brown seaweed is the sole raw material for alginate production at commercial scale. Cultivation of brown seaweeds is time consuming and labor-intensive process for alginate production. Currently, supply is enough to produce alginate. Hence, there are no capacity issues with the feedstock.

Sourcing challenges: Limited number of qualified suppliers and high entry cost for a new supplier provides less negotiation power to buyers of alginates.

WHAT IS NEEDED FOR VSC PRODUCTION?

The first approach to VSC manufacturing is to understand that the properties of the materials differ from gelatin. Meanwhile the film formation in gelatin is due to the tertiary structure of the gelatin induced at the gelation temperature (30-40 C), in the case of starch formulations the film formation proceeds mainly by the swelling and irreversible gelatinization of starch (90-95 C).

Gelatin films cast easily and quick, they are highly elastic and highly resistant to strain and dry fast. In contrast, starch carrageenan films cast slowly and controlled, films are elastic, resistant to strain and dry slow. Starch films cast slowly, the the film is highly liable to relative moisture and elasticity and resistance is low and dry slowly.

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

In the last years, modified starch suppliers have offered materials that can be handled in SGC equipments around viscosities about 40000 to 50000 cP. In contrast, the viscosity of MS-carrageenan formulations can be as high as 90000 cP. As shown in the table, such polymer masses require mixing, heated, transfer and spreading systems designed to handle high viscosities.

In general, for starch formulations, moisture control is required since the film is sensitive to HR higher than 30%. The sealing process is the result of the film quality, the design of the die roll, the pressure force as well as the curing process at low temperature after encapsulation in some cases. During encapsulation, the heating of the wedge is not required since the sealing is not dependent on temperature. Because of the weak seal, capsules are not submitted to predrying.

Moisture content in the shell of fresh capsules could be about 30% depending on formulation and drying time can be as long as 7-9 days. In addition, the filling volume should be considered to define the proper die roll size since the overfilling affects the seal strength and the contraction of the shell during drying, that in some cases could be as high as 30%.

In spite of some particular processing requirements, formulations containing carrageenans are straightforward to encapsulate compared to MS because of the consistency batch to batch, the robustness of the film formation, the elasticity of the films, the strength of the seal and the stability at moisture and temperature conditions. In contrast

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 thickness and % seal.

HOW IS THE STABILITY OF THE PRODUCTS?

Testing made at Procaps on some VSC marketed products was aimed to characterize them at stability conditions by means of hardness, burst test, % seal and disintegration time. Figure 1 shows the comparison of the physical characterization for two VSC made at Procaps (S1 and S2) and four comercial VSC products made from C-MS at initial time (M0) and 40C, 75%RH at 1 (M1) and 3 months (M3).

In general, hardness of VSC has been reported to be as low a 2.0 N and not to be comparable to SGC. Most of them are nutritional products containing oils and supensions using glycerol as plasticiser. Hardness is a standard control parameter for the final drying time and low hardness values should be considered for bulk storage and transport. Burst test and % trailing seal were considered a measure of the quality of the seal, ranging roughly form 100 to 300N and from 50-87%, respectively at the initial time (Fiugre 1). % seal values in VSC could be as high as 80% because of the design of the die rolls. Disintegration times were determined in the USP conditions for rupture time of soft capsules as an easy final point for visual detection. At stability conditions, physical properties tended to decrease but not to an unacceptable level with the exception of disintegration times that in some cases did not meet the criteria at 2h. In spite that VSC show a lag time in dissolution due to the slow hydration of the shells, they are not prone to crosslinking as gelatin

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does and the cause of the increase in disintegration times at stability conditions still remains uncleared.

FINAL REMARKS

Growing demand for veg capsule shells (either plant derived or synthetic polymers) for cultural and religious reasons makes all these alternatives a popular choice. However, supply of soft capsule free of gelatin is still at nascent stage but they have potential to reach a considerable market share in future. The above substitutes could be considered keeping technical and sourcing challenges in check. Cost reduction of materials and process optimization offer an opportunity for growing the VSC share in the nutraceutical market.

Existing products have demostrated that the materials as well as the manufacturing process are feasible and consistent. Some considerations about the process stages were mentioned. and products were shown to be physically stable at accelerated conditions. Disintegration times were longer compared to gelatin and increasing times at stability should be evaluated since it is a critical quality attribute of the products.

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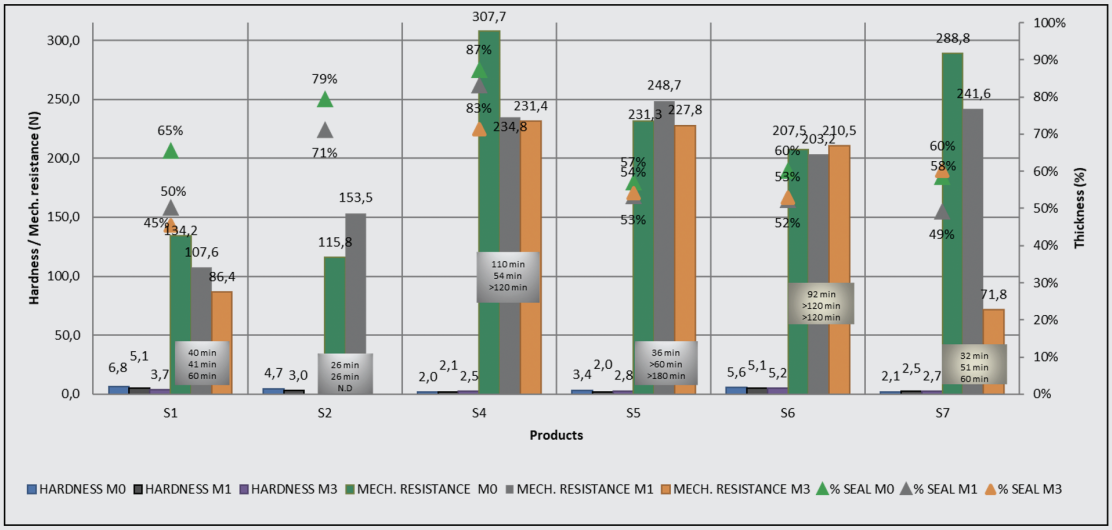
TABLE 1: Market and supply for gelatin substitutes in soft gelatin capsules

Substitutes of Gelatin in Soft Capsule Shell	Global Market (2018)	% Usage in Pharmaceutical	No. of Major Suppliers – Pharma*	Average Price ($/Kg)	Raw Materials	Sourcing Challenges (If any)
Carrageenan	60-70 Kilo tonnes	7%; VSC: 500 tonnes	~10-12	11-12	Red seaweeds	Limited supply base and concerns with feedstock availability might occur due to climate change (*currently there is no supply issue with feedstock in major producing regions)
Alginates	40 Kilo tonnes	8-10%; SGC: Not known	~2-4	12-14	Brown seaweed	Highly consolidated supply base and high entry cost for a new supplier
Modified starch	9-10 Million tonnes	10-15% (as an excipient)	~5	4-5	Many like potato, corn, cassava starch etc.	Keeping track on price movement is important

Source: Beroe Analysis
(*Indicates suppliers who cater to pharmaceutical applications but not necessarily soft capsule shell)£

FIGURE 1: Characterization of vegetarian soft capsules at accelerated stability conditions (40 C, 75%RH)



Source: Procaps SA

	GELATIN	MODIFIED STARCH (MS)	CARRAGEENAN-MS
Film casting, film feeding	Fast, easy	Slow, difficult, sensitive to RH	Slow, easy (equipment adaptations)
Polymer mass preparation	No	No	YES Specific mixing systems can be required
High temperature heated-transfer system	No	Yes	YES Extrusion systems can be required
Conventional die rolls	No	NO	NO
Encapsulation	No	NO	YES
Water-cooled casting			
Spreader boxes design	No	NO	YES (SOME CASES)
Curing step	No	NO	YES
Tray- drying (days)	2-5	5-7	2-3
Batch to bach variability	NO	YES	NO
Cost (Process)	$	$	$$

Source: Procaps SA