WHITE PAPER

CHOOSING THE RIGHT SHELL EXCIPIENT TO MEET FUTURE CAPSULE CHALLENGES

LET'S SHARE CLEAR IDEAS ABOUT GELATIN

This white paper outlines the key challenges facing capsule formulation and focuses on the importance of choosing the right excipient to optimize the delivery of active pharmaceutical ingredients (APIs) in soft and hard capsules. It also explains why gelatin is the excipient of choice for pharmaceutical manufacturers, and highlights the advantages and disadvantages of the latest alternatives that have been developed. The primary shell excipients for the manufacture of hard capsules under review here are gelatin, hydroxypropyl methylcellulose (HPMC), and pullulan, while for the manufacture of soft gels, gelatin and modified starch will be discussed.

By Dr. Vergauwen, Principal Scientist, Rousselot, July 2017

Reaching Further Together

Rousselot

DARLING INGREDIENTS

INTRODUCTION

The primary goal of the pharmaceutical industry is to satisfy the therapeutic needs of patients. Active ingredients are, of course, essential to realizing this. However, excipients also play a major role, particularly in formulation development and in the way in which active drugs are delivered. As a pharmacist, this means you have to make sure your knowledge and expertise extend beyond active ingredients to include all components of a pharmaceutical product. In order to clarify the role and behavior of ingredients routinely used in pharma capsules, we examine various shell excipients used to manufacture hard and soft capsules, and critically discuss their advantages and disadvantages.

The global empty hard capsules market including pharmaceutical and nutraceutical sales channels is anticipated to increase at a CAGR of 7.2% and to reach US$ 2,13 billion in revenues by 2022.[1] Over the past five years, about 12% of all prescription based (Rx) and over-the-counter (OTC) pharmaceutical products are dosed with hard capsules (Figure 1). While soft capsules on the other hand have been somewhat overlooked to formulate prescription drugs, the market of soft gels will grow to 755 million USD in 2022[2] with a CAGR of 5.5% to 2022. This is mainly due to its popularity in the nutraceutical market[2] and to its added value for difficult Rx formulations, such as those dealing with very low dose APIs (< 3 mg), potent compounds, hormones, and cytotoxic compounds (safe handling), oxygen-labile APIs, and especially poorly soluble or poorly permeable APIs.

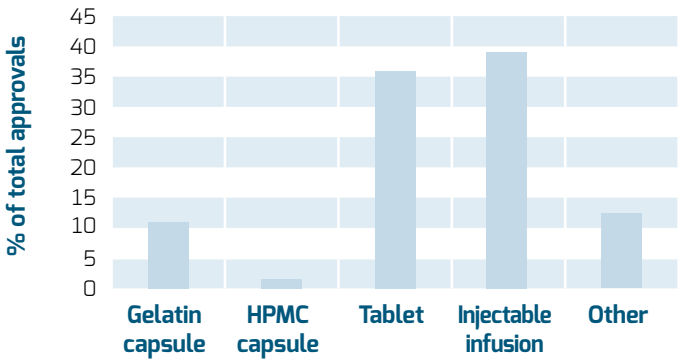

Figure 1: Dosage form breakdown of FDA approved drugs from 2011 to 2017.

In the chapters that follow, the performance of different key capsule shell excipients will be reviewed: the market leader gelatin, the alternatives for hard capsule manufacturing, HPMC and pullulan, and the alternative for soft gel manufacturing, modified starch.

Key considerations

The main factors influencing excipient choice are clean label, optimal technical performance, operational effectiveness and safety.

[1] Empty capsule market, Marketsandmarkets, May 2016
[2] Global soft gel capsules industry, HJ research, June 2017

Growing popularity of capsules

The growing popularity of capsule dosage forms has strong roots in their functional properties. Advantages over other delivery forms – mainly tablets – include: a simpler manufacturing process with fewer production steps, the possibility to encapsulate most types of solid, semisolid, and liquid fill formulations, and the offering of unique color and shape configurations to enhance product identity. On top of that, compared to tablets, capsules improve patient compliance as they are easier to swallow and conceal API-derived unpleasant taste or odor.

Favored for its high functional capabilities, gelatin has been used in both hard and soft capsules in the pharmaceutical and nutraceutical industry for over 100 years. Capsule manufacturing started in 1834 but would not have been possible without gelatin, which for decades has been the safe and only choice to manufacture hard and soft capsules.

The first commercially feasible gelatin alternative entered the market in 2001, a soft gel shell alternative made of a blend of modified starches (hydroxypropyl starch) and carrageenans. The following year a hard gelatin capsule alternative was commercialized that made use of HPMC as the main shell ingredient and carrageenans or gellan gum as gelling aids. Referred to as first generation HPMC capsules, these are different in terms of manufacturing and attributes compared to the more recently commercialized HPMC capsules that do not require a gelling aid. The latter are produced with adjusted proprietary machinery and are referred to as second generation HPMC capsules.

INTRODUCING DR. BJORN VERGAUWEN

Dr. Bjorn Vergauwen is Principal Scientist at Rousselot. He currently coordinates R&D projects aiming at unlocking the unmet potential of gelatin. His main expertise relates to the biophysical and biochemical principles underpinning gelatin's behavior in food and pharma applications and to its use in pharmaceutical dosage forms.

Dr. Vergauwen has a PhD in biochemistry from Ghent University, Belgium. Before joining Rousselot in 2014, he had several missions as Post-Doctoral Researcher at Ghent University where he conducted research in enzymology and structural biology for 17 years.

THE CLEAN LABEL AND NATURAL TREND

Natural continues to be a desirable attribute for consumers, and has a direct impact on product shelf appeal. A study on health and wellness found that 'all-natural' is one of the highest rated food claims, with more than 50% of respondents identifying it as very or moderately important.[3]

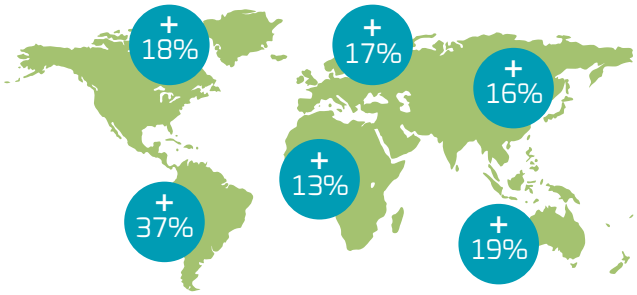

Figure 2 : Global double digital growth in clean label-related NPD.
Top Ten Trends for 2017, by Innova Market Insights, Nov 2016.

Following the natural trend, consumers are becoming less interested in 'processed' products and are now looking to clean label, progressing to clear label. This is reflected in the number of new food and beverage product launches that are clean label (see figure 2). Clean label is a non-regulated term, but is known for containing recognizable ingredients, the absence of artificial or chemical ingredients, and the addition of sustainable and naturally sourced ingredients.[4] Surprisingly, people often mistakenly associate vegetal origin with clean label although products of vegetal origin that are considered as suitable for vegetarians can be strongly processed and not clean label entitled. In Europe, E-numbers (additives) should also be absent to be considered clean label. Firstly developed in food, this trend has expanded to capsule manufacturing, with the nutraceutical market leading the way.

Not all excipients reviewed in this paper follow the natural trend. Gelatin is clean label as defined above; it is a recognizable and sustainable ingredient and can therefore provide additional benefits for manufacturers looking for healthy nutraceutical and pharmaceutical products, without additives. Also pullulan (and carrageenan used as gelling aid), although E-number labelled in Europe, are brought to the market essentially undistinguishable from the natural design. The relatively new capsule excipients HPMC and modified starch on the other hand are not at all found in nature as they are the result of a chemical synthesis process. These excipients are classified as additives and are of course E-number labelled in Europe. Traditionally used for its adhesive properties in the construction industry (HPMC) or for fluid-loss control in drilling muds of oil fields (modified starch), these designer polymers are now increasingly being used to formulate hard capsules and soft capsules for nutraceuticals, in response to the trend for veganism. Obtained from felled and shredded trees (HPMC), or corn crops (modified starch) and partially etherified with methyl and/or propyl groups, these ingredients undergo a heavy chemical process to provide capsules with a synthetic base.

Pullulan is a polymer produced by the fungus *Aureobasidium pullulans* through a fermentation process, and has traditionally been used in the manufacture of edible films for oral hygiene products. Pullulan shells require a plasticizer or dissolution enhancer (such as polydextrose, mannitol or sorbitol) to avoid brittleness and a gelator (such as kappa-carrageenan or gellan) for adaptation to the production process of hard gelatin capsules (conventional dip molding machines).

Containing relatively few and recognizable ingredients, naturally sourced with no chemical modification and no E-numbers, gelatin is the only shell excipient reviewed that adheres to the clean label trend.

Safe choice

Particularly in a highly regulated industry, such as pharmaceuticals, the fact that gelatin is an excipient produced using a globally standardized process remains appealing to capsule manufacturers and offers a guarantee for high quality. Moreover, the gelatin production process does not fall under the European Commission Seveso Directive for the prevention and control of chemical plant accidents, unlike the manufacturing process of many other pharmaceutical ingredients, such as HPMC or modified starch. In addition, gelatin adheres to the circular economy model, as it maximizes output in the meat industry and avoids any additional waste.

[3] Nielsen, 2015. We are what we eat: healthy eating trends around the world.
[4] Euromonitor, 2016. Passport: clean label revolution: response of the ingredients industry.

OPTIMAL TECHNICAL PERFORMANCE

There are several criteria to evaluate objectively the overall performance of capsules. Their mechanical resistance, brittleness, oxygen permeability and crosslinking ability are all key for assessing formulation suitability. The most important attributes for optimal capsule performance however are the level of API release and the rate of dissolution.

API release/dissolution

Gelatin is widely used in hard and soft gel applications because of its functional properties and suitability for immediate release dosing. The sooner the capsule opens in the stomach, the sooner the API becomes available for absorption by the body. Therefore, capsule opening time represents the most important parameter for capsule-dosed medicines formulated for immediate release. Considering this key attribute, with respect to hard shells, gelatin and pullulan capsules represent the best options, followed by second generation HPMC capsules[5] (figure 3). The opening of first generation HPMC capsules is very unpredictable, with 50 % release ranging from 24 minutes[5] to more than two hours.[6] Unlike the case for hard gelatin shells, the first generation HPMC capsules from different manufacturers are not interchangeable for every purpose, and these capsules should therefore be avoided to formulate pharmaceutical grade medicines (except if gastro-resistance is aimed for).

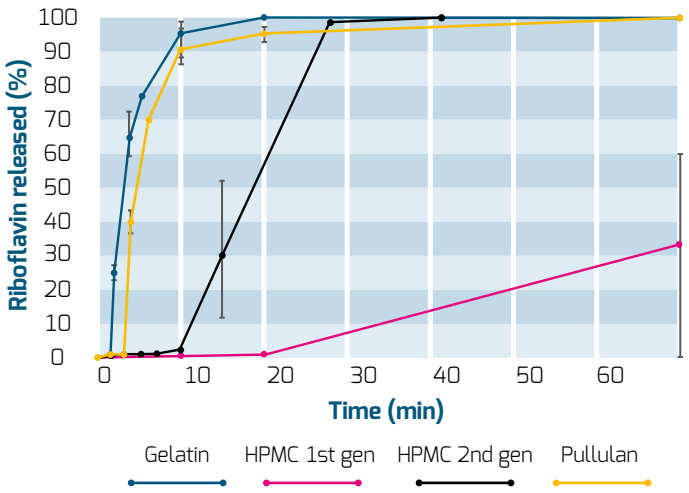

Figure 3: Rousselot internal study, R&D Expertise Center Ghent, May 2017. Dissolution profiles showing the mean percentage of riboflavin released from gelatin, HPMC/gelling aid (HPMC 1st generation), HMPC (HPMC 2nd generation), and pullulan/gelling aid capsules in 0.1 M HCl buffer at pH 1.2, 37 °C, 75 rpm, 1 h. Bars represent SD, n = 3.

The USP chapter ‹2040› on Disintegration and Dissolution of Dietary Supplements discloses a rupture test for soft shell capsules for which the requirements are met if all of the capsules tested rupture in not more than 15 minutes. In the Rousselot laboratories, purchased Vitamin E (400 IU) filled gelatin- and modified starch-based soft shell capsules branded and brought to the market by the same supplier were put to the test (0.1 N HCl, pH 1.5; n = 2). The gelatin capsules opened at 9.0 and 9.5 min (average 9.25 ± 0,35 min), while the modified starch-based dietary capsules did not pass the USP suitability test as they opened at 18.5 and 36 min (average 27.25 ± 12.37 min).

Crosslinking

In a crosslinking reaction, two or more molecules are joined by a covalent bond. Due to the concomitant increase in molecular weight, the crosslinked polymer's solubility might decrease affecting the capsule opening time, and ultimately bioavailability. Proteins in general crosslink in the presence of certain aldehydes. Being a protein, gelatin is also susceptible to this phenomenon whereas the polysaccharides HPMC, pullulan, and modified starches are not.

[5] MM Al-Tabakha, et al., 2015. Drug development and industrial pharmacy, 41, 10.
[6] N Glube, et al., 2013. Capsule shell material impacts the in vitro disintegration and dissolution behaviour of a green tea extract. Results in pharma sciences, 3,1-6.

However, high quality pharmaceutical excipients and active ingredients are free of aldehyde contaminations, which is why crosslinking is usually not an issue for OTC and Rx commercial products. On the other hand, the freshly extracted, unpurified, or complex fillings that are sometimes formulated into nutraceutical products might leak crosslinking agents into capsule shells.[7] In order to minimize the associated crosslinking risk with such nutraceutical products, innovative gelatins have been developed that overcome this problem.[8]

Oxygen and water vapor permeability

Certain APIs display complex stability profiles and are sensitive to light, temperature, moisture, pH, and/or oxidation. In general, capsules represent the safest choice for formulating with such APIs, even though oxygen permeability differs significantly amongst the commercially used capsule shell ingredients. For instance, gelatin and pullulan hard shells display equivalent, low oxygen permeability, while first and second generation HPMC capsule shells permit oxygen transfer up to 50 times faster.[9] When oxygen-sensitive compounds are encapsulated into HPMC capsules, it is recommended to include an antioxidant in the fill formulation or to package the capsule product into an oxygen-resistant configuration, such as a blister package with aluminium foil.[10] Soft gels offer the safest choice for formulating oxygen sensitive APIs because of the absence of a headspace. Moreover, although glycerin weakens the oxygen barrier of gelatin[11], soft gels, owing to their five-fold thicker shell, allow oxygen to pass at a two- to -four-fold lower rate than hard gelatin capsules. Information on oxygen permeability of modified starch soft gels is currently not publicly available.

Water vapor interplays differently with the capsule types examined. Pullulan is the most hygroscopic translating in an unwanted perceived tackiness when holding pullulan capsules in the hand for 30 seconds or more. HPMC capsule shells have a three-fold lower average moisture content than hard pullulan

and gelatin capsule shells, and are therefore thought to be the logical choice to formulate moisture sensitive APIs. However, studies have been unsuccessful to demonstrate this suspected benefit.[12] In fact, gelatin and HPMC films allow water to pass equally fast and thus display similar water vapor permeabilities (~2.5 ng m/m2 s P).[13]

Brittleness and mechanical resistance

Forming harder and stronger shells, gelatin capsules display a higher resistance to mechanical stress than HPMC and pullulan hard capsule alternatives.[13] This attribute translates into lesser defects and lower rejection rates during capsule filling. Pullulan capsules display the lowest tensile strength at low ambient humidity, hence a higher risk of shell brittleness, followed by gelatin and both generation HPMC capsules.

No differences of note are to be reported for the mechanical resistance of gelatin- and modified starch-based soft shell capsules as both types are very strong.

[7] Donald K. Lightfoot. Capsule filling: answers to 10 common questions. Tablets & Capsules.

[8] Rousselot, 2017 - White paper: Producing the perfect soft gel.

[9] R Gullapalli and C Mazzitelli, 2017. Gelatin and non-gelatin capsule dosage forms, Journal of Pharmaceutical Sciences, 106(6), 1453-1465.

[10] S. Nagata, 2002. Advantages to HPMC capsules: a new generation's hard capsules. Drug Deliv. Technol., 2(2), 35-39.

[11] Soft gelatin capsules II: oxygen permeability study of capsule shells original research article Journal of Pharmaceutical Sciences, Volume 64, Issue 5, May 1975, Pages 851-857 F.S. Hom, S.A. Veresh, W.R. Eber.

[12] Ahmad S.Barhama, Frederic Tewes, Anne MarieHealy International Journal of Pharmaceutics Volume 478, Issue 2, 30 January 2015, Pages 796-803 Moisture diffusion and permeability characteristics of ydroxypropylmethylcellulose and hard gelatin capsules.

[13] S.Missaghi, R.Fassihi, 2006. Evaluation and comparison of physicomechanical characteristics of gelatin and hypromellose capsules. Drug Development and Industrial Pharmacy, 32(7), 829-838.

OPERATIONAL EFFECTIVENESS

While capsules offer manufacturing advantages over other dosage forms, there are still several factors to consider when determining operational effectiveness. Machinability, weight variations and cost-efficiency have to be well thought out before deciding on the right excipient.

Machinability

Gelatin's thermo-reversible properties allow a high level of machinability, as only a single shell ingredient is required for use with dipping pin machines (hard capsules) or rotary die encapsulation machines (soft gels) that have been finely tailored over decades to fit expedited and reliable production. The manufacture of first generation HPMC capsules and pullulan capsules instead requires secondary gelling agents to meet the viscosity requirements of the dipping pin molding production process. Second generation HPMC hard capsule production does not employ the standard dipping pins equipment to manufacture hard gelatin capsules, but requires adapted machines featuring thermoregulated pins. Nonetheless, the manufacture of thin HPMC and pullulan films is not as simple as with gelatin, increasing manufacturing times slightly, and resulting in higher weights and increased weight variation of the finished products.

Likewise, machine modifications (e.g. melt-extrusion devices as alternative to the spreader boxes) are generally required to tailor the rotary die process to the use of soft shell alternative ingredients (modified starch/carrageenans). Commercial soft shell capsule shapes and sizes have been worked out with a gelatin-based process, and are therefore all commercially available, whereas 12 oval represents the size limit of modified starch-based soft shell capsule alternatives.

Weight variations

Pullulan capsules are somewhat more weight-stable than HPMC capsules, which vary substantially (see figure 4). Gelatin capsules offer the most reliable weight stability profile of all tested types of hard capsules. While weighing alike, nutraceutical vitamin E filled commercial soft shell capsules made from modified starch/carrageenan are somewhat more weight stable than the gelatin-based counterparts.

Cost efficiency

Considering the overall cost of manufacture, raw materials for first generation HPMC capsules cost approximately four times more than gelatin, while manufacturing costs are three times as much.[14] In addition, supplying the raw materials for HPMC accounts for 50-60% of the total production costs, while this is only 45-50% in case of gelatin hard capsule productions. At least 40% less raw material is required to manufacture a batch of hard gelatin capsules as compared to alternative productions with HPMC.

Figure 4 : Rousselot internal study, R&D Expertise Center Ghent, May 2017.
Average weight and variation measured on a single purchase of various hard capsule types and two commercially available nutritional soft gel types; n = 50.

	Gelatin HC (size 1)	HPMC HC 1st gen. (size 1)	HPMC HC 2nd gen. (size 0)	Pullulan HC (size 1)	Gelatin vitamin E filled soft gel	Modified starch vitamin E filled soft gel
Average (mg)	71,3	79,0	95,9	79,1	1055	1085
Stdev (mg)	1,2	2,4	3,1	1,7	22	5.1
RSD(%)	1,7	3,0	3,2	2,2	2.12	0.47

[14] Business Standard, 2016. Gelatin capsules have technical advantage over HPMC capsules: PHD Chamber to DCGI.

CONCLUSION

Diverse challenges in the capsule industry have allowed new shell ingredients to break into the market. All exhibit different characteristics. However, in the face of increasing demand for clean label products, rising costs and the high importance of operational effectiveness, sophisticated fill formulations and stringent regulatory pressures, gelatin offers a future-proof solution to meet these capsule challenges.

The following table summarizes the key points of this white paper.

Capsule type	Hard caps			Soft gels	
	Gelatin	HPMC	Pullulan	Gelatin	Modified starch
Consumer preferences					
Synthetic/ chemically modified	no	yes	no	no	yes
Fully digestable	yes	no	no	yes	no
Clean label/E-number free	yes	E464	E1204	yes	E1440
Halal/Kosher certified grades	yes	yes	yes	yes	yes
Vegan	no	yes	yes	no	yes
Technical aspects					
Fast API release	++	--(HPMC1) +(HPMC2)	++	++	--
Crosslinking sensitivity	-	++	++	-	++
Resistance to brittleness	+	++	-		
Limited oxygen permeability	++	--	++	++	No data available
Mechanical resistance	++	+	++	++	++
Operational effectiveness					
Machinability	++	+	-	++	-
Cost in use	++	--	--	++	-
Weight variation	++	--	+	+	++

From ++ great advantage to -- negative impact

Your Rousselot and Peptan sales contact information:

About Rousselot. Reaching Further Together.

Rousselot is a brand of Darling Ingredients Inc.
Rousselot is the global leader* of gelatin and collagen peptides.
Rousselot's wide range of collagen peptides are marketed under the Peptan brand. We work in partnership with our customers all over the world, delivering innovative and advanced ingredient solutions manufactured through state of the art operations. We help our customers achieve their goals, enabling them to create world class pharmaceutical, food and nutritional products to inspire and excite today's demanding consumers.

**Source: Global Industry Analysts, Inc, Gelatin a Global Strategic Business report, Nov 2016*

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