Softgels’ Clear Advantages

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Deep Dive: Softgels 2019

Deep Dive Report

Softgels’ Clear Advantages

by Lisa Schofield

Of all the dietary supplement forms, hands down, softgels are the most beautiful.

Hold a bottle filled with gold or blue softgels up to the light, and it’s difficult not to revel for a moment in their gemlike splendor.

Sure, gummies are having a moment. But some people don’t like to chew their supplements, and some don’t like the taste, sweetener content or texture. Softgels, unlike many capsules and tablets, go down smooth, just like aged whiskey.

Without softgels, it’s also a sure bet that millions of individuals worldwide would be lacking the health benefits of omega-3 essential fatty acids (EFAs), vitamin E and other nutraceuticals shown to bolster human health in myriad ways.

Market snapshot

According to the October 2016 market research report, “Softgel Capsules Market Analysis & Trends—Application (Health supplement, Vitamins & Dietary Supplements, Cardiovascular Drugs, Anti-Inflammatory Drugs and Antibiotic & Antibacterial Drugs), End-User—Forecast to 2025” from Research and Markets, the global softgel market was estimated to increase at a 5.4 percent compound annual growth rate (CAGR) to reach approximately US$316.6 billion by 2025, a figure that encompasses both pharmaceuticals and dietary supplements.

Meanwhile, a more recent Allied Market Research paper, “Enteric Softgel Capsules Market by Application (Health Supplements and Pharmaceuticals), and Sales Channel (Supermarket & Hypermarket, Pharmacy & Drug Store, and Online Provider): Global Opportunity Analysis and Industry Forecast, 2018 – 2025,” enteric softgels are expected to enjoy robust growth stemming from a “surge in demand for omega-3 supplements, growth in promotional activities by manufacturers, and rise in consumer awareness for preventative health care.”
Further, the report noted that the global enteric softgel capsules market was dominated by the pharmacy/drug store segment in 2017, and the online provider segment will likely experience rapid growth during the forecast period, as more consumers become digitally literate.

*Nutrition Business Journal (NBJ)* 2017 data estimated softgels captured 19 percent of U.S. supplement sales, bested only by pills at a 31 percent market share. Powders (16 percent), gummies (11 percent) and liquids (10 percent) followed softgels most closely.

Regionally, according to Allied Market Research, Asia-Pacific is poised for outstanding opportunities to companies in the enteric softgel capsules market, "owing to high population base, growth in awareness about health supplements, development in health care infrastructure, and increase in demand for enteric softgel capsules. The rise in the geriatric population is one of the key reasons that boost the consumption of the enteric softgel health supplements in the Asia-Pacific market.

In the EU, according to a May 2018 Grandview Research report, “Europe Nutrition and Supplements Market Size, Share & Trend Analysis Report, By Function, By Formulation, By Consumer, By Distribution Channel, By Region and Segment Forecasts, 2018 – 2025,” softgels are among the most preferred delivery system for lipid-soluble nutraceuticals like vitamin E and conjugated linoleic acid (CLA). Echoing the aforementioned Allied Market Research report, the growing popularity of omega-3 supplements (fish oils) and vitamin E is expected to spur the growth of softgel use.

**Consumer appeal**

In a recent consumer study conducted by Catalent, participants rated Catalent RP Scherer softgels as highly desirable, with 82 percent of participants citing softgels as “fast-acting and effective,” and 89 percent reporting they were easy to digest.
According to IRI, softgels make up 25 percent of the total market for nutritional supplements and are the second most-prevalent dosage form behind tablets. “When compared to gummies, softgels remain a leading dose form for many nutritional supplement brands,” commented Jessica Cao, vice president, global nutritional marketing and business development, Catalent.

Softgels have captivated consumers for years. Andrew Goldman, vice president of digital marketing for NutraScience Labs, points to two key market research studies showing softgels’ appeal to consumers in the United States and Europe.

In 1999, the Mattson Jack Group polled approximately 300 consumers in six states comparing preference of softgels versus other delivery forms. Nearly 90 percent said clear softgels were easier to swallow than two-piece hard capsules, tablets and gelatin-coated tablets. Most of those polled also said they believed softgel products acted more quickly in the body compared to the other forms, and most stated they would not have objections to paying a little more for products in softgel versus other forms.

Goldman noted a 2009 poll of 607 consumers in the U.K., France and Italy, conducted by Expressions Planning Limited, likewise found consumers preferred softgels to other conventional and newer delivery forms, such as coated tablets, fast-melt tablets, soft-shell capsules, hard-shell capsules and sachets/powders.

The following preferences were also revealed:
- Consumers found softgels are easiest to swallow
- Consumers liked oval-shaped softgels
- Consumers preferred plant-based over animal-based softgels
- And, like the 1999 study, more than 25 percent of respondents were willing to pay higher prices for softgel products

Nearly 90 percent of consumers said clear softgels were easier to swallow than two-piece hard capsules, tablets and gelatin-coated tablets.

Source: Mattson Jack Group

“Consumers prefer soft gelatin capsules over other dosage forms in terms of ease of swallowing, speed of delivery, masking of unpleasant odors and tastes, and product differentiation and appearance,” said Steve Holtby, president and CEO of Soft Gel Technologies Inc. (SGTI). “Soft gelatin capsules are also favorable to health-conscious consumers who try to avoid artificial excipients used in the tableting process.”
Lara Niemann, marketing director at GELITA, agreed, observing, “Consumers appreciate the smooth surface of the softgels making them easy to swallow, which is an important aspect of patient compliance.” Further, as the main component, gelatin is not only a clean label ingredient, it is highly compatible with other ingredients, nonallergenic and comprises proteins that are easily digested in the gastrointestinal (GI) tract, which facilitates the release and absorption of active ingredients. “Consumers recognize the safety, efficacy and convenience of gelatin delivery systems, which helps to promote compliant behavior,” she said.

According to Cao, the European Food Safety Authority (EFSA) recommended adults take 250 mg of docosahexaenoic acid (DHA) per day to help support brain and vision health (EFSA Journal. 2014;12[10]:3840). “By choosing the correct fish oil concentration, one softgel could easily deliver this recommended daily dose, whereas a typical gummy only delivers 30 mg of DHA and would therefore require a daily dose of eight to nine gummies to deliver the same dose,” she explained. “Many gummies also have high sugar content which might not be attractive to health-conscious consumers.”

Softgels somehow have the appeal of a newer technology—it’s their sleekly simple elegance that silently conveys 20th century state-of-the-art engineering. But the origins of the modern softgel are much older.

**Softgel history**

The original soft gelatin capsule was created by “a manual, discontinuous process in laboratories and pharmacies,” described Claudia Valla, product development advisor for Catalent. In 1833, French pharmacists applied to patent a process of softgel production that entailed immersion of skin bags filled with mercury into a bath of gelatin solution. When a film solidified around the bag, it was removed and the gelatin case was filled before being sealed with a drop more gelatin; the patent was awarded in 1834.

The Fournier method was developed in the mid-1880s. In this method, Valla elaborated, gelatin was first layered over a hot plate featuring a series of cavities, filled and then covered with a second layer of gelatin on top before a second hot plate sandwiched the gelatin films together, forming hemispherical gel capsules. Around 1900, attempts were made to automate the process.

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— Jessica Cao, vice president, global nutritional marketing and business development, Catalent
In 1930, Robert Pauli Scherer of Detroit invented the rotary die process for softgel encapsulation in his home’s basement. Scherer’s invention was considered a revolutionary breakthrough, as it transformed softgel production from a manual method to a commercial, high-volume process. His invention was granted a patent in 1933 (he was awarded 52 more patents in his lifetime—and in 1955, his experimental machine was placed in the Smithsonian Institution in Washington). Scherer’s production process for softgels is still widely used today; and his company, the R P Scherer Corp., is now a part of Catalent.

Humera Ahmad, director of product development at Catalent, observed that compared to pharmaceuticals, nutraceutical markets “have experienced more innovation regarding development in softgel capsules, especially in the size, shape, taste and color of capsules to suit individual brand needs. Use of natural colors and flavors also makes the capsules more palatable and appealing to consumers seeking products of natural origins, and there has been an increased focus on the quality and safety of capsules.”

Nutraceutical innovation has been energized by some of the advantages of selecting softgels as a delivery system.

**Advantages of softgels**

Widespread consumer preference for and belief in the superiority of softgels as a pill form attract many users. However, softgels offer several tangible advantages as well. For instance, they can be used to deliver oils and oil-soluble materials, which cannot be done with most other delivery systems. Because the body more readily and effectively absorbs fat-soluble nutrients enrobed in an oil-based matrix, softgels are ideal for delivery of these nutrients and to hold their integrity.

For example, according to Euromonitor International, sales of fish oils/omega-3 EFAs grew from nearly $1.1 billion to $1.27 billion between 2013 and 2018, while sales of vitamin E grew from $276 million to $285 million in the same time period. As these two nutraceuticals are manufactured primarily in softgel form, the steady, robust growth suggests opportunities for softgel products.
Carotenoids are also big for softgel delivery. Golan Raz is head of global health at Lycored, the originator of Lycomato™ standardized natural tomato extract. “As all carotenoids are oil-soluble, encapsulating the natural extract in a softgel is, to date, the most effective and bioavailable way to consume these important nutrients,” he commented. Others, such as astaxanthin, beta-carotene, lutein and vitamin A are being encapsulated in softgels in many brands across the globe. “Softgels are simply a perfect match for carotenoids,” he asserted.

According to Rosa Bertolami, senior scientist advisor, physical science, Catalent, additional advantages of formulating with a softgel delivery system include:

- High tolerability: the 100 percent biodegradable shell and the oil-based medium of the fill make softgels gentle on the gastric mucosae, a benefit for the elderly and those with sensitive digestive systems
- Softgels dissolve more quickly in the gastric juices of the digestive tract and, depending on the formulation, may enhance the bioavailability of the active ingredient(s)
- High-dose potency, especially for oil-based active ingredients like omega-3 EFAs
- Uniformity: “Because the fill is in a liquid state and can be thoroughly mixed before encapsulation, softgels allow excellent reproduction of the dosage volumes. The raw material mix is echoed very accurately in each dose using a precise volumetric pump in softgel production,” she explained. “This is particularly important for micro-dosed active ingredients.”

Niemann noted softgels protect sensitive ingredients such as fish oil from oxygen, light, contamination and/or microbial growth. Although hard capsules are primarily used for powder applications, soft capsules are the preferred dosage form for liquid, paste-like or oil-based fills. Unlike any other type of capsules, softgel versions are hermetically sealed and airtight, thus masking any potentially existing unpleasant taste or odor of the fills (i.e., “fishy taste”). This also makes the softgel format tamper-evident while providing high dose accuracy.

Besides offering quick assimilation and bioavailability of the actives, Holtby said softgel capsules can be adapted for many specialized uses. “Consumers can see that softgels are hermetically sealed, which not only protects the active ingredients in the fill material from oxidation, moisture and microbial contamination,” but he noted it also provides safeguards against tampering. “Problems with the one-piece softgels would be indicated through leakage or discoloration. This dosage form is precise and uniform, providing greater stability, purity and consistency of the nutrients encapsulated.”

Another key strength of softgels is their visual versatility, allowing brand marketers to take advantage of product differentiation. Wide varieties of shell colors, shapes and sizes are available from softgel manufacturers to provide brands with options for precise dosage and added consumer appeal. Although aesthetically pleasing supplements can catch the eye of consumers, the inner fill of the capsule, Holtby emphasized, is even more important.
A variety of emulsions and microencapsulated materials are being put into softgel capsules, creating high functionality and myriad choices in availability and dosing. Manufacturers can use micronized materials in inner fills of softgel capsules, whereas tablets and hard-shell capsules require larger particle sizes, so that the powder will flow in the tableting or encapsulating machines. “Softgel capsules can also be used to improve bioavailability by delivering the nutrient in solution or other absorption-enhancing media,” he explained. “The advantage to small particle or crystal size is that the smaller the particle, the better and quicker it is absorbed in the digestive tract. By providing enhanced absorption and bioavailability, consumers can expect fast disintegration and immediate nutrient delivery to produce a quicker onset of action. Better bioavailability also translates to a possible reduction in the required dose of the active compound.”

**How softgels are made**

Ahmad provided a general overview of the softgel matrix. The shell is composed of a one-piece, hermetically sealed soft gelatin or plant-based material. It can contain a liquid (primarily an oil), a suspension or a semisolid, generally referred to as a fill. The shell is comprised of a film-forming material (gelatin or animal-free alternative material blends), water and plasticizers (such as glycerin and/or sorbitol) that influence its flexibility. It can also include minor additives such as opacifiers, coloring agents, flavors and sweeteners.

“While an animal gelatin-based shell remains the most common form used for softgels, animal-free vegetarian shells, based on different materials such as carrageenan—which is extracted from seaweed—have been developed as alternatives,” she noted, adding that softgel capsules can also have an enteric coating, a polymer barrier applied to prevent or delay dissolution or disintegration in the gastric environment, for certain applications.

The article, “The significance of the perfect gelatin in softgel production,” from the September 2018 issue of *Manufacturing Chemist*, pointed out that selecting “the right gelatin with the desired characteristics is a vital part of creating the perfect softgel capsule, and plays a critical role in promoting an efficient and smooth manufacturing process. Typically, any gelatin offers solubility, ease of use and has good mechanical strength. It also meets growing consumer demands for clean label, natural products and stringent regulatory compliance.”

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**There are two main types of gelatin:**

- **type A** is derived from collagen with acid pretreatment
- **type B** is the result of an alkaline pretreatment of the collagen.

*Gelatin used in softgels can be a blend of both types or used individually.*

— Steve Holtby, president and CEO of Soft Gel Technologies Inc. (SGTI)

Holtby explained, “Before softgel manufacturing can even take place, gelatin preparation is required to create its liquid state.” Gelatin, which is obtained by the thermal denaturation of collagen (typically animal sourced), is provided in granular powder form. Although gelatin is
often considered a commodity like sugar, it has the potential for being a variable component and, cautioned Holtby, “encapsulators should ensure that they are using the best product for their specific application of making soft gelatin capsules. In addition, gelatin is an excellent growth medium for most bacteria; hence considerable care needs to be taken during manufacture to avoid contamination. There are two main types of gelatin: type A is derived from collagen with acid pretreatment; and type B is the result of an alkaline pretreatment of the collagen. Gelatin used in softgels can be a blend of both types or used individually.”

At the initial stage of the manufacturing process, raw granular gelatin is blended with a plasticizer (e.g., glycerin) and water. Dry gelatin swells or hydrates when stirred into water. A colorant is also added at this stage, if it is specified in the formula. Other plasticizers can be used either alone or in combination with glycerin. “Like any recipe, careful consideration of each ingredient’s proportions found in the mixture is required and is dependent upon the formulation and/or environmental conditions,” Holtby said. For instance, the gelatin recipe may need to be adjusted to account for water content of the fill material, so that the integrity of the outer shell remains intact.

After the ingredients are blended and a uniform consistency is achieved, the resulting mixture is poured into a reactor called a gelatin melter. Surrounded by a thermal jacket, the gelatin melter heats the mixture while stirring it. This process turns the gelatin into a molten liquid mass. As soon as the liquid gelatin mixture is complete, it is transferred to heated receivers, in which the gel mass passes through an aging period for approximately four to eight hours before going on to the encapsulation machine. Holtby noted it is critical to keep the liquid gelatin warm before and during the encapsulation process; otherwise, it will solidify.

Other concerns and steps in the process need critical monitoring and quality control (QC).

“Blend time is of interest, as a measure of process and raw material performance. An important specification for gelatin is bloom strength—a quality of the raw material that determines whether or not a capsule can be formed and sealed,” he elaborated. “Additionally, the sensitivity of gelatin demands the strictest of controls over temperature settings. Ribbon condition is highly influenced by the temperature of the gelatin mass. The temperature of the molten gelatin just prior to formation into a ribbon is critical; too high a temperature causes the gelatin to deteriorate, and a low temperature affects flow rate. Both conditions are to be avoided for their deleterious effect on capsule formation.”

Controlling the thickness of the gelatin ribbon being formed is also critical during encapsulation. Gelatin ribbon thickness determines capsule wall and seam thickness. Insufficient thickness will contribute to poorly formed capsules and create leakers. An overly thick ribbon results in shell-sealing problems.

Gelatin ribbon thickness determines capsule wall and seam thickness. Insufficient thickness will contribute to poorly formed capsules and create leakers.
Poorly developed seams also affect softgel quality, which is highly dependent upon the rotation speed of the dies that control dwell time. If there is inadequate contact time, the capsule halves will not properly seal.

Next is the process of making the pill. Holtby explained the encapsulation process begins when molten gel is pumped to the machine and two thin ribbons of gelatin are formed. These ribbons then pass over a series of rollers and are continuously fed between two rotating die cylinders that determine the size and shape of the capsules, which form the two halves of a capsule. The ribbons converge next to a fill injector, where the appropriate volume of fill material to be encapsulated is measured and dispensed by a pump. As the die assembly rotates, the filled capsule halves are then sealed together through the application of heat and pressure, and are then ejected. Since softgel manufacturing involves high precision, this process permits accurate and reproducible fill uniformity. During the rotary die process, the gelatin temperature, ribbon thickness, seam width and fill quantity all need to be monitored and controlled.

Following encapsulation, Holtby continued, the capsules are first dried in tumblers containing lint-free towels and large volumes of forced air. The capsules are then transferred from the tumblers onto trays and placed into low-humidity drying rooms, where the softgels are dried again at room temperature to remove any excess moisture. Gelatin hardness needs to be monitored during this phase of the process, he said. The water content of the gelatin shell starts out around 30 percent, and as it evaporates, will reach as low as 8 or 9 percent, which is the desirable moisture content for bottling and shipping.

**Softgel challenges and solutions**

Despite the array of challenges that can occur when working with softgels as a delivery system, through the years, manufacturers have been able to find solutions. Premature oxidation and masking off-flavors are two examples.

**Oxidation**

According to Valla, softgels can provide a closed system to address the needs of highly oxidative oils. Omega-3 oils are prone to degradation by exposure to heat and light, therefore careful handling throughout the manufacturing process is critical. Catalent’s process includes:

- Sampling and dispensing (warehouse management): closed system to transfer oil through an inert gas (keeping oxygen from contact with oils prone to oxidization)
- Fill preparation: occurs in closed equipment under inert atmosphere, which also limits the temperature increase during this step
- Fill storage: pressure-gauged drums store the preparation in a protected environment
- Encapsulation: a closed hopper (dispenser) encapsulates the product within an inert atmosphere
- Packaging: the highest-performing packaging materials are selected (depending on the characteristics of the finished product) to optimize the conditions during shelf life. Blister packaging takes place under inert atmosphere and blister cavities are tested for residual oxygen quantity
- Environment, health and safety/quality and compliance: inert gas sensors are used for sampling and dispensing area, and related standard operating procedures (SOPs)
Whereas process customization is important to keep oxidation under control, Catalent also conducts a thorough risk assessment for each product. Suitable countermeasures are calibrated on each product formulation (fill/shell). All countermeasures are not needed for all products, but a case-by-case evaluation is always necessary. Catalent works with its customers to identify the most suitable solution for their product.

**Consumer experience**

Another challenge is to deliver the benefits of formulation without any unpleasant experience for consumers. This is especially true in the case of odorous oils such as omega-3s, as many consumers can be put off by any sense of fishy odor or lingering aftertaste, Valla explained. Consumers are seeking softgel supplements that do not impose negative side effects and, if possible, are actually enjoyable to take. According to Valla, Catalent’s OmegaZero® microemulsion technology is a solution to deliver odorous oils such as omega-3 products. It ensures odorous oils are emulsified in the gut instead of forming a layer on the surface of the gastric fluid. This significantly reduces the contact surface of the oil with air, thereby reducing unpleasant fish-smelling reflux. Existing odor is further masked by formulating the fill of the softgel with flavored essential oils.

**Dietary considerations**

Supporting the needs of the growing vegan and vegetarian population was challenging initially, because the gelatin used for softgels was primarily only available as bovine or porcine skin or bone derivations. And beyond strict vegans and vegetarians, an increasing number of individuals—for cultural, religious or personal reasons—adhere to vegetarian, kosher or halal diets wherein consuming certain animal products is verboten or undesirable. In recent years, dramatic fears have also arisen related to certain diseases transmitted through livestock, notably, bovine spongiform encephalopathy (BSE or mad cow disease). Currently, softgel capsules can be made from a variety of materials, including fish, poultry and some nonanimal-derived gelatin.

**Softgel capsules can be made from a variety of materials, including fish, poultry and some nonanimal-derived gelatin.**

Traditionally, nonanimal-derived gelatin has been more expensive than animal-based gelatin, Holtby noted. Another limitation of conventional vegetable-derived gelatins is that the shell is not as durable as animal gelatin. “The physical characteristics of many vegetarian gelatin blends make it difficult to encapsulate all but the simplest oils. In addition, the unique advantage of standard softgels is rendered nil in vegetarian format: The softgel’s fill material is usually protected from oxygen exposure after encapsulation, but vegetarian gelatin is porous, causing rancidity in only a few months,” he explained.
However, in 2015, Captek Soft Gel International debuted a vegetarian softgel with coenzyme Q10 (CoQ10) suspended in a liquid emulsion. “A growing number of consumers only want vegetarian products,” said Tim Chiprich, vice president of product development. “This softgel meets their needs while protecting the CoQ10.”

Captek’s MarineGel material is free of food animal derivatives, genetically modified organisms (GMOs), sugar, gluten and preservatives. According to Chiprich, softgels made from it may be certified halal or kosher, improve the bioavailability of oil-soluble ingredients, exhibit better disintegration than other nonanimal materials, and maintain stability in hot climates with no stickiness or cross-linking disintegration problems.

Captek CEO David Wood believes nonanimal softgels are one of the most important market drivers in the natural segment. “There has been a dramatic increase in demand for products with a clean label,” he emphasized. “For non-GMO and organic products, our MarineGel nonanimal capsule technology offers the cleanest possible label for customers looking to avoid animal-based ingredients and other additives.”

And in 2016, Robinson Pharma Inc. (RPI) launched a vegan softgel multivitamin consisting of more than 20 vitamins, minerals and other nutraceuticals. It features a thinner, more compact design than traditional multivitamins, delivering nutrients derived from nonanimal sources for compliance with a vegan diet. The softgel shell is made of SeaGel®, a starch and carrageenan/oil, in place of soy, so it can also carry an allergy-free claim. Further, according to the company, the vegetarian gelatin is compliant for numerous claims, including non-GMO, halal, kosher and gluten-free. Other competitive advantages, the company claims, “are in the multivitamin’s enhanced presentation, with clearer colors, a sleeker design and minimal to no deformations in shape.”

RPI’s line of vegetarian and vegan softgel supplements include prenatal vitamins, memory support, eye health, weight management and beauty/skin support. RPI has produced vegan softgels of biotin, sunflower vitamin E, CLA, CoQ10, flaxseed oil and DHA. Vegetarian softgels RPI has manufactured include vitamin D3, and men’s and women’s daily multiples.

RPI uses a starch and carrageenan-based gel matrix in its vegetarian softgels, which, the company noted, provides “superior thermal stability which exceeds that of animal gelatin, and satisfies the vegetarian and vegan requirements” of those consumers. Carrageenan, from red seaweed, is a common ingredient used as an emulsifier and stabilizing agent in a diversity of food products (including baby food). Due to the thicker viscosity of the vegetarian gel, these softgels must be processed in specialized machinery to provide the highest quality production. The company implemented proprietary equipment that manufactures vegetarian softgels more efficiently, and in turn, it claims, is more cost-effective.
Shelf stability

In Niemann’s viewpoint, one of the biggest issues plaguing the softgel manufacturing industry has been related to shelf stability. Although most softgels are highly stable, certain environments with high humidity and/or high temperatures can impact stability by creating pellicles between the active fill and the capsule shell, resulting in less than desirable dissolution.

Her company’s patented gelatin solution is GELITA® RXL (reduced cross-linking). The company maintains reducing the amount of cross-linking enhances the dissolution properties of the capsules, as well as improving their shelf life at high temperature and humidity. “The new technology even allows the pharmaceutical industry to explore new capsule fillings and expand their distribution into regions that are exceptionally hot and humid,” Niemann commented.

For its innovation, GELITA determined that, under suitable conditions, small, highly mobile gelatin molecules are able to block the effects of the larger molecules, “similar to interfering with the interaction between a key and its lock,” Niemann explained. She said the company’s solution can be described as “a sort of ‘self-defense mechanism,’ brought about by a controlled molecular weight distribution. The smaller molecules react with the larger ones and block them, making them no longer available for self-cross-linking reactions and/or reactions with other reactive groups, such as traces of aldehydes or chromium, alumina and copper, within the capsule.”

Ahmad observed formulations have been stabilized further due to the availability of suitable excipients and active pharmaceutical ingredient (API) combinations that are compatible with one another. “A stable fill formulation can provide a robust soft gelatin capsule, which can help meet compliance and regulatory needs,” she said.

Multiple techniques are being utilized to achieve stability in softgel formulations. For example, Cao said, “The oxidation of omega-3 oils is irreversible, so one of the techniques used to overcome this challenge is to incorporate an antioxidant molecule alongside the oil to ‘scavenge’ the free radical species that are produced during the oxidation process. Commonly used antioxidants include tocopherols, citric and ascorbic acids, and a range of spice extracts. Sometimes, a blend of antioxidants is used to create a synergistic effect against oxidation.”

Bioavailability

Yet another challenge is that of assuring bioavailability of softgels. Bioavailability indicates the rate and extent to which a bioactive ingredient is absorbed from the GI tract, reaches the bloodstream intact and thus becomes available for use or storage in the body—an important part of delivery is absorption into the circulation. “The bioavailability of each dosage form depends on how rapidly the particular form releases the nutrient into the biological fluids or how rapidly the nutrient may enter a cell,” Holtby explained. “Low bioavailability is most
common with oral dosage forms of poorly water-soluble, slowly absorbed nutrients. Not surprisingly, absorption is most rapid from solutions and decreases in the order: solutions, suspensions, capsules, compressed tablets and coated tablets."

Holtby shared four main factors that can affect bioavailability:

**Disintegration time.** The U.S. Pharmacopeial Convention (USP) has time limit standards for disintegration (the supplement’s ability to break apart and fragment into small particles). Most products should disintegrate within 30 minutes to one hour, except for time-release products. Disintegration time can be affected by variables such as particle size, crystalline form, disintegrants and/or lubricants used, the compression force used to press tablets, etc. Reputable manufacturing companies will comply with USP standards for disintegration and/or dissolution.

**Dissolution percentage.** Dissolution is the ability of a supplement to dissolve in solution, usually expressed as a percentage or rate. A prerequisite to absorption is dissolution, which determines the availability of the nutrient for absorption. Nutrients are absorbed in a specific region of the intestinal tract once in solution. Overall absorption can be controlled by manipulating the formulation. For example, reducing the particle size increases the nutrient’s surface area, thus increasing the rate and extent of absorption.

**Nutrient forms and characteristics.** Bioavailability can be affected by nutrient form, i.e., the biochemical makeup of the compound. Minerals, in particular, come in different chemical forms (chelated, etc.). Certain forms are better absorbed than others. In addition, nutrients are more bioavailable when necessary cofactors are present in the formula. Various ingredients have differing characteristics such as solubility in lipids or water, small or large particle size, and granular or crystalline form. Different delivery systems such as tablets, two-piece hard-shell capsules, and softgel capsules have characteristics that lend themselves to optimizing the delivery and absorption of various ingredients.
Individual composition. Supplement bioavailability will vary from person to person because each individual has a unique biochemical makeup that will affect how nutrients get absorbed. It can depend on the individual’s nutritional needs, the time a supplement is ingested, the presence or absence of drugs that could have potential interactions, if disintegration occurs in the body, the amount of time in the GI tract, how well absorption takes place in the GI tract and cellular uptake. “These factors are outside of the control of a supplement manufacturer or marketer, although education about proper ways to take supplements is crucial,” Holtby opined.

Innovative developments
The dietary supplements industry has witnessed several advancements in softgel technology. Most have been driven by the need to improve consumer experience and enhance product performance. According to Cao, various formulation strategies can be used to improve the performance of a softgel supplement. “One of them is by improving the absorption profile. Enhanced dispersion technologies have been shown to improve the dissolution profile of calcium-based softgels and can be applied to other products.” Cao explained a softgel supplement’s efficacy can be improved by utilizing the following techniques:

Enhanced bioavailability: Self-emulsifying and self-microemulsifying drug delivery systems (SEDDS, SMEDDS) have been developed to improve bioavailability of complex ingredients such as CoQ10. SEDDS that contains suitable surfactants convert an API into a uniform microemulsion before encapsulation, which often leads to better bioavailability and higher levels of API reaching the bloodstream.

Improved stability of polyunsaturated fatty acids (PUFAs): Stability of omega-3s has been a significant challenge in the industry due to oxidation and other chemical changes that occur when they are exposed to light, air and heat, or if they are stored inadequately during processing. Oxidation of omega-3 can lead quickly to rancidity and degradation of oil, as well as conferring an undesirable flavor. “The major challenge during manufacture is to prevent or limit this oxidation to permitted levels, but this can now be overcome by minimizing the contact of PUFAs with oxygen throughout the production process and shelf life, using antioxidants in the product and nitrogen blanketing of oil during processing and encapsulation,” she noted.

GELITA also has addressed this issue with innovation by launching GELITA EC—a gelatin product for enteric soft capsules. It allows production of clear enteric capsules that open in the intestine (instead of the stomach, as with traditional gelatin capsules) and adhere to USP dissolution parameters. “Most enteric delivery systems are produced by applying an acid-insoluble coating to fresh soft capsules,” Niemann explained. “This intensive two-step process adds time and money to the cost of each enteric capsule. Additionally, this coating produces an opaque shell, which is less desired by consumers.”
GELITA’s pharmaceutical competence team also recently advanced its patented reduced cross-linking gelatin and technological proficiency for improved capsule stability and shelf life. It now offers a line extension to its RXL line, GELITA RXL R², to include gelatin with specifically controlled and fast-releasing properties.

Captek, which manufactures more than 13 billion softgel capsules each year, launched several innovations in 2015, which Chiprich identified as significant advancements. “The three concepts we developed showcase what the next generation of softgels can do,” he stated.

One was the aforementioned vegetarian CoQ10 softgel. The second was a two-tone prenatal vitamin with DHA and folic acid. “We found a way to reduce the size of the softgel, making it more comfortable to take,” Chiprich stated. “The differently colored top and bottom demonstrate what we can do from a manufacturing standpoint.”

The third concept was a probiotic softgel. “Probiotics are sensitive to light, heat and moisture, and must be handled carefully throughout all phases of production,” Chiprich explained. “We found a technique to add them into a softgel so that they are protected from degradation.”

Catalent’s advancements in softgel production technologies include plant-based and chewable formats to meet consumer demands for healthy and convenient dose forms. Its EasyBurst® chewable softgel delivers a potent burst of flavor, alongside the benefits of the nutrients, Cao shared. “More importantly, it is convenient as it does not require water and is easy to chew and swallow.”

As with offerings from Robinson Pharma and Captek, Catalent’s Vegicaps® capsules meet the needs of consumers looking to avoid animal-derived gelatin. The plant-based capsules are free from gluten and GMOs, widening potential consumer appeal. “They look very similar to gelatin-based capsules and retain their easy-to-swallow properties,” Cao commented.

Additionally, Catalent has created—to proof-of-concept stages—novel softgel formulations using innovative ingredients. For example, Cao offered, eye health is a growing concern for both the aging and the younger generation, especially as consumers spending more hours in front of luminescent screens. “Catalent has developed a new blue light formula (containing antioxidants such as bilberry extract, lutein and zeaxanthin) that takes into consideration the existing research on nutrition and eye health and expands it to include the risk represented by blue light from electronic devices,” she said.

Softgels are also used in the beauty industry, Cao added, which has adopted initiatives based around a “beauty inside and out” concept, “where nutritional supplements are taken in conjunction with topically applied lotions, also contained within frangible softgel ‘unit measures,’ for example, to improve the appearance of the skin.”

Major advances have also been made in processing and operations, Holtby shared. For example, SGTI’s operations are becoming paperless, and it is relying on integrated software programs like Deacom and Redzone for storing critical documentation that, historically, has been recorded as hard copies.
Improvements in manufacturing technology have made the machinery faster and easier to operate, he said. For example, optical inspection systems, which have almost entirely removed human operation, inspect up to 300,000 capsules per hour. This equipment, Holtby said, also provides increased productivity; reduces the risk of cross contamination; inspects every softgel capsule for color, area, width, length and symmetry (shape); and provides consistent quality 24/7. Several years ago, he reported, SGTI automated its inspection process by implementing a SYMETIX automated optical inspection system.

“Traditional softgel inspection SOPs involve human operators visually inspecting hundreds of trays containing thousands of softgels each day, which may lead to operator fatigue based on the repetitive nature of the work,” he commented. But the automated system digitally photographs each softgel with up to four cameras and compares the images to an approved reference standard. The continuous system can process up to 1 million doses per hour. The machine can check for irregularities (in everything from size to surface quality) and detect foreign objects or flaws by rejecting unacceptable individual doses with a jet of air as the product moves through the conveyor belt. “This world-class continuous processing system is designed to FDA Title 21 Code of Federal Regulations (CFR), Part 111 requirements and helps increase throughput and reduce labor costs,” he stated.

Advancements in how product is delivered were also recently incorporated in SGTI’s business model. To prevent the bulk softgels from being exposed to unfavorable temperatures that would create clumping during the warm summer months, SGTI would ship smaller orders in foam-lined coolers and other nonbiodegradable shipping containers. Now, Holtby related, the supplier uses an alternative biodegradable, waterproof box liner called ThermoKeeper and ThermoPod. The inner surface is a biodegradable perforated poly film. A proprietary padding, which is also biodegradable, is sandwiched between the outer and inner films. The insulation is made from a blend of cotton and wool recycled textile fibers that are purified, flocked and bonded together, producing a soft, natural ultra-insulating material. When ready for use, ThermoKeeper easily assembles into an airtight, stand-up container with a full flap-over lid custom-sized to fit snugly inside customer shipping boxes. After use, the container is easy to collapse for reuse or for eco-friendly disposal.

“Softgel production has evolved significantly over time due to availability of more compatible excipients including colors and flavors,” Ahmad stated. Colors are now readily available as “nature identical” or “natural.” Nature-identical colors are like natural colors but not from a natural source, whereas natural colors are from natural plant or fruit sources.

This wider availability expands opportunities for differentiation in the market, allowing for more precise appeal to the target audience. “Softgel color provides a unique marketing tool for companies and can help consumers differentiate between products,” she emphasized. “Making capsules attractive using color makes the final product very attractive to consumers and can improve brand recognition and sales.”

As the dietary supplement industry continues to formulate and reformulate for an ever-widen ing and simultaneously fractionating user base comprised of multiple lifestyle demands (e.g., vegan, non-GMO, gluten free) softgels are keeping up. Therefore, when deciding upon a delivery system, softgels are not a hard choice.
What do you like most about the softgel supplement delivery format?

I am so much better about consistently taking my vitamin D and fish oil supplements when they’re in a softgel form because they are easy for me to swallow, and I don’t have digestive issues.

Softgels are much easier to swallow than a tablet and seem to be just as effective on delivery. I take four supplements in a softgel delivery format—vitamin D, coenzyme Q10 (coQ10) and two omega-3s.

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