



# Liquid encapsulation In hard capsules:

Giving the edge over softgel capsules

# Abstract

Although the technology for filling hard capsules with liquids has been around for a long time, with rapidly changing trends, the nutraceutical industry has undergone a major change in the recent past. Formulators are now rediscovering the myriad benefits of using this technology, such as the ability to formulate products that combine incompatible ingredients, increased bioavailability, ease of producing small-scale batches, reduced production and market lead time, distinct brand differentiation, and many others, to meet emerging and eclectic market needs.

# Introduction

The global nutraceutical industry is expanding at a compound annual growth rate (CAGR) of 8.8% and is expected to reach USD 578.23 billion by 2025.<sup>1</sup> This figure itself explains the enormous potential of the nutra market, and the increasing preference for nutraceutical products across the globe. Consumption of fast foods, packaged foods, and adoption of a sedentary lifestyle have led to an increase in the incidences of lifestyle diseases such as diabetes, cardiovascular diseases, and obesity. As a result, consumers are perceiving nutraceuticals as alternatives to prescription drugs. The use of dietary supplements is not limited to the fulfillment of daily requirements of particular required nutrients, as consumers are also considering the functional health benefits of these supplements for the prevention of diseases. Furthermore, consumers have shown a keen interest in products that boost energy and improve physical endurance and mental alertness.





Currently, consumers' preference has undergone a paradigm shift from choosing synthetic ingredients (medicines and supplements) to natural and organic foods, beverages, and dietary supplements. A recent survey found that approximately 70% of consumers are happy to pay a higher retail price for a product made with ingredients they recognise and trust. Essentially, consumers want to know what they are putting into their bodies.

The production and consumption of 'clean label' nutraceuticals, containing natural ingredients that consumers recognise, is the latest trend in the nutraceutical industry. In contrast to the well-defined chemical entities used in pharmaceuticals, the ingredients used in nutraceuticals are diverse,

containing multiple components (often several classes of compounds) in a single product. Many of these natural ingredients have physicochemical properties that pose a challenge for formulation scientists. Such properties (particularly low solubility) often jeopardise the efficacy and effectiveness of the product. Therefore, the successful development of nutraceuticals requires knowledge of the fundamental aspects of the physical and chemical properties of the ingredients and selection of the right delivery system.

Liquid encapsulation in hard capsules is one of the most promising and cost-effective strategies to address the multiple physicochemical challenges associated with the use of nutraceutical ingredients, especially those with poor solubility. Liquid encapsulation is a

highly appealing option as poor solubility of active ingredients is one of the major hurdles for formulation scientists. Additionally, liquid encapsulation can help shorten the time to market by providing flexibility to rapidly develop and test formulations in-house on a large scale.

Besides alleviating formulation issues, liquid-filled hard capsule technology is a promising tool for brand recognition. Liquid-filled capsules can create a distinct brand differentiation in line with the latest trends in health and wellness. This novel dosage form can also be utilised to reintroduce existing formulations in a new attractive format that revitalises the brand and extends the brand life.

# Why liquid-filled hard capsules are a wise choice than softgel capsules

Soft gelatin capsules have remained the most popular dosage form for liquid and poorly water-soluble compound formulations in liquid vehicles.<sup>3</sup> While many nutraceutical companies continue to use softgels for liquid encapsulation, this technology has its own set of limitations, such as high moisture content, use of plasticisers and preservatives, inability to use high melting point excipients, difficulty in coating, higher rate of oxygen and gas permeability, as well as cumbersome processing. To overcome many of these challenges, liquid-filled hard capsule technology was established in the early 1980s. For nutraceuticals such as vitamins (e.g., vitamins E and A) and pure oils or oil-based products (e.g., safflower oil, flaxseed oil, garlic oil, evening primrose oil, Habbatus sauda oil, and fish oil), liquid-filled hard capsules offer the important advantage of easy filling and sealing.

## Easy processing

The basic and most vital difference between the hard and soft gelatin capsule technologies is the encapsulation process. Softgels are manufactured via a unified process of capsule formation that includes filling and sealing in a single step. On the other hand, hard capsules are manufactured using a different operation. These pre-fabricated, two-piece, empty, hard gelatin/hydroxypropyl methylcellulose (HPMC) capsules are supplied to pharmaceutical or nutraceutical companies for in-house manufacturing. Capsules are then filled with liquid or semi-solid formulations and sealed sequentially.



## Low waste

Because of the unified manufacturing process, the quantitative and economic impact of waste is higher in the production of softgel capsules. There is significant waste in the form of excess gelatin that is cut-off during the formation of softgels. Furthermore, embossing or printing, if any, takes place after encapsulation. Therefore, if there is any error or quality problem after printing, the losses incurred would include costs associated with the waste of the active ingredient. However, hard capsules can be easily sourced as empty, pre-printed shells from the capsule manufacturer. As these empty capsules

undergo rigorous quality checks, the end-product manufacturer can be sure of the quality of the capsules that are used in the encapsulation process.

## Maintaining product efficacy

During manufacturing of softgel gelatin capsules, the moisture content of the gelatin ribbon is approximately 30% to 50%, and equilibrium moisture content is achieved only after several hours of drying or can even take up to several days based on the formulation. During this period, migration and

degradation can occur in moisture-sensitive molecules either because of the presence of plasticiser in the shell or because of the higher moisture content in the shell before reaching equilibrium moisture content. Plasticiser (usually, glycerol, used at a concentration of approximately 15%-30%) is added to gelatin and water. As a result, the moisture uptake of soft gelatin capsules is considerably higher than that of hard capsules because of the hygroscopic nature of glycerol. Hard capsules do not contain plasticiser and have relatively low moisture content, and therefore, do not pose this problem for moisture-sensitive products.

## Lower oxygen transmission/ permeability rate

The oxygen transmission/permeability rate of a soft gelatin capsule is proportional to the level of glycerol in the film and the moisture content. Since a hard capsule contains no plasticiser, the permeability of the capsule shell is lower than that of a soft gelatin capsule shell. As a result, hard capsules containing even highly odorous products like fish oil, valerian oil, and garlic oil can be rendered odourless.

## No dark spots

The formation of dark spots on soft gel capsules is an inherent problem that occurs because of the basic nature of the encapsulation process. The poor aesthetic appeal of the finished product is an issue for most brand owners. This problem is completely eliminated when a liquid formulation is encapsulated in hard capsules and band-sealed. Moreover, this process adds to the aesthetics of the product, offering the flexibility of colour and type of pre-printed capsule.

## Convenient processing for low melting point compounds

Materials that have low melting points or are liquid at room temperature present difficulties when formulating as dry powders or tablet form, and often require high concentrations of excipients to avoid processing problems. The manufacturing process can be considerably simplified (a five-step process required to manufacture a tablet can be reduced to a simple mixing and filling operation) by filling. Consumer acceptance is also enhanced because of the smaller size of the final dosage form.

## Easy filling of hot liquids

The sealing temperature for softgels is 37°C. Therefore, formulations must be in a liquid state below 35°C to ensure appropriate encapsulation. Hard capsules can be filled with hot liquids (up to 75°C). An example is medicated cow butter melt (ghee).

## Flexibility of combination filling

Unlike softgels, hard capsules enable encapsulation of ingredients in the form of beads, microtablets, and pellets in combination with the liquid formulation.



## Choice of vegetarian dosage form

Unlike softgel capsules, hard capsules are available in vegetarian form, and can be made from HPMC, which is a 100% plant-sourced cellulose.

## Easy scale-up process

Liquid filling in hard capsules can make a significant contribution to the overall development of efficacious nutraceutical products. This technology provides flexibility to rapidly develop and test in-house formulations when only small quantities of the active substance are available in the initial pre-formulation and lab-scale development stage. The process can be scaled up while still kept in-house, similar to the process of tableting or powder/pellet filling of hard gelatin capsules.

The added advantage of this technology is that it maybe used at the very beginning of the development stage. New concepts can be evaluated for feasibility studies in an R&D lab without the involvement of any machinery. This is especially useful when the availability of the active substance is restricted or limited, or its cost is exorbitant.

## Reduced product development cost

Conventionally, hard gelatin capsules have been used as a solid dosage form for powder fill or pellets. However, the nutraceutical market demands novel formulations, which must be developed and launched as quickly as possible. Liquid-filled hard capsules can fulfil some of these demands. This is especially true for active compounds that are inherently liquid or semi-solid. This new concept can bring down the overall development time and thereby reduce time to market.

# Enhanced bioavailability

The bioavailability of poorly water-soluble active ingredients could be significantly enhanced when formulated as a liquid in a hard capsule. This increases the effectiveness of the active ingredient.

# Improved stability

The moisture sensitivity of an active ingredient and the formulation can be minimised by incorporating the ingredient into either a hydrophilic or lipophilic matrix.

**Table 1. Technical comparison between softgel capsules and liquid-filled hard capsules**

Aspect	Softgel capsules	Hard capsules
Small batch production	Cumbersome	Possible
Scale-up	<ul style="list-style-type: none"><li>• Requires large quantities of active substance</li><li>• Must be outsourced</li></ul>	Simple
Combination filling: liquid and pellets	Not possible	Possible
Partial filling	Not possible	Possible
Permeability of shell to oxygen	High because of plasticiser and moisture content	<ul style="list-style-type: none"><li>• Low permeability</li><li>• No plasticiser required</li></ul>
Filling temperature	Maximum 35°C	Maximum 70°C
Limitation on choice of excipients	Hygroscopic excipients can be tolerated because of the presence of plasticiser in the shell	High concentrations of hygroscopic excipients, such as glycerol, propylene glycol, or liquid polyethylene glycol (PEG) can be avoided
Risk of active compound migration	High for compounds soluble in plasticiser	Low

# Liquid fill combinations in hard capsules: combining innovation with aesthetics

Compared to softgel capsules, another lucrative aspect of liquid-filled hard capsules is their ability to be formulated as combination fill capsules. The different types of combination fill in liquid-filled hard capsules not only adds to increased consumer appeal, but also creates a strong brand differentiation. Since hard capsules can be easily imprinted, this further serves as a measure for anticounterfeiting and brand security. It also offers other benefits, as detailed below.

# Consumer preference

The nutraceutical industry uses a wide selection of commercial approaches to provide innovations in oral drug delivery systems. To a certain extent, it was the nutraceutical sector that led to the early adoption of liquid-filled hard capsule products to market. Since the nutraceutical industry is in close contact with consumers, it understands the consumers' needs. Lately, consumers have been seeking more benefits from delivery systems beyond those possible through traditional (tablet and capsule) technologies. As a result, formulators need to work harder to cater to increasing consumer demands. As the nutraceutical industries look to carve a niche of their own and create a differentiated product, an important trend is the growth and diversity of new dosage forms that enjoy consumer preference. Consumers prefer liquid-filled capsules as they are easier to swallow. These capsules are also considered to work faster and more effectively. Moreover, capsules can also be made visually attractive to guarantee instant consumer appeal.

# Commercial benefits

Novel formulations combining two or more compounds are an excellent lifecycle management strategy to revitalise product pipelines. Combining existing compounds is less expensive, hastens the speed to market, and makes development less risky.

**Table 2. A few examples of marketed nutra products formulated into liquid-filled capsules**

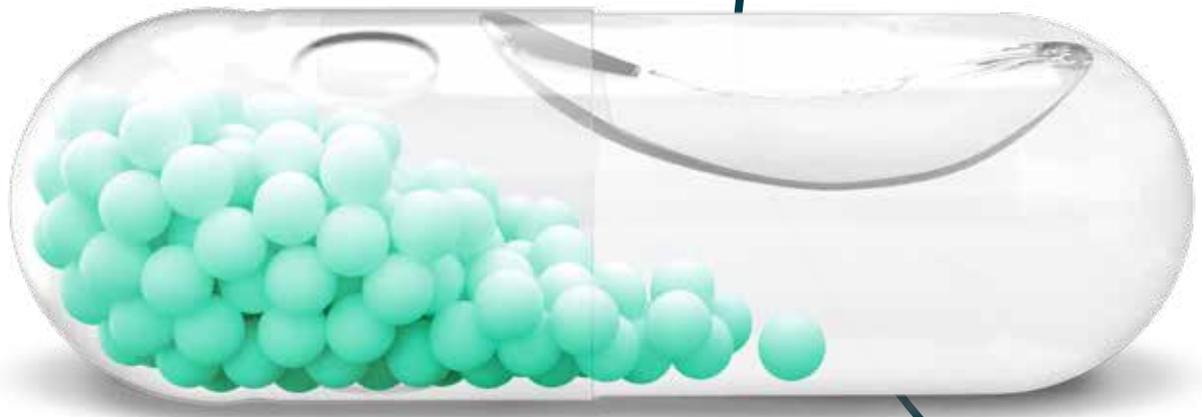
Active ingredient	Brand	Dosage form	License holder
Krill oil	Cardiosteroil	Hard capsule	Altacare
Flaxseed oil	Omega Flax	Hard capsule	Curegarden
Caffeine, safflower oil	Termolen	Hard capsule	Equaliv
Coenzyme Q10*	CoQ10	Hard capsule	Vantage Nutrition

\*Vantage Nutrition has completed stability study for 6 months and is ready to offer this product.

## The way forward for liquid-filled hard capsules

There is a strong need to develop a superior and viable alternative to softgel capsules, because of the inherent challenges in softgel capsule processing. With evolving technology, newer and more sophisticated capsule-filling techniques are flooding the market. Liquid-filled hard capsule encapsulation is probably the strongest contender amongst these, as this process offers an entire bouquet of advantages to both nutra manufacturers and consumers and is therefore, here to stay.





## Benefits of liquid-filled hard capsule encapsulation for nutra

Consumer-friendly dosage form

Convenience

Ideal for lipophilic compounds

Protection and taste-masking of ingredients

Aids bioavailability

Product differentiation

Brand life cycle extension

Stronger anti-counterfeiting

### References:

1. Grand View Research. [Internet] [updated 2017 Dec; cited 2018 Jun 15]. Available online at: <https://www.grandviewresearch.com/press-release/global-nutraceuticals-market>
2. Crane M. Majority of Consumers Willing to Pay More for Recognizable Ingredients, Survey Suggests [Internet] [updated 2016 Dec 22; cited 2017 May 29]. Available online at: <http://www.nutritionaloutlook.com/trends-business/majority-consumers-willing-pay-more-recognizable-ingredients-survey-suggests>
3. Brox W, Zande H, Meinzer A. Soft gelatin capsule manufacture. EP 1993: 0 649- 651.



# Vantage Nutrition

Vantage Nutrition is one of the first companies in India to offer a unique solution to nutraceutical brand owners for the introduction of new products that allow them to expand their product portfolios and drive business growth. Its V-Fill technology is setting a new standard for nutritional ingredients in hard capsules. Its novel formulations allow nutraceutical companies to incorporate liquids, pellets, tablets, and powders in capsules.

**If you'd like to learn more about nutrition and supplements, visit our [Instagram page](#).**

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