



PATENTED TECHNOLOGY IN SOFT GELATIN CAPSULE: A REVIEW

ABSTRACT

Since the introduction of Soft Capsule Making Machine in the 1970s, formulations have continually become more popular with rapid developments in recent years. Soft Gelatin Capsules (Softgel) were developed in the 19th century to mask unpleasant taste and odour of drug substances. After then, many improvements have been made with respect to the production of these soft capsules. In the pharmaceutical field, the softgel dosage forms are increasingly being preferred. Technologically with Softgel, content uniformity of low-dose drugs has been achieved and also has consumer preference as is easy to swallow. Interesting advances have recently been made in the area of developing liquid and semi-solid formulations in a soft gelatin capsule to address particular bio-performance issues. The Softgel dosage form therefore offers several advantages over other oral dosage forms, such as delivering a liquid matrix designed to solubilize rapidly. This improves the oral bioavailability of poorly soluble compounds. Delivery of low and ultra-low doses of a compound using softgel also ensures decreased plasma variability. However, due to the dynamic nature of the softgel dosage form, its development and shelf-life stability optimization are fraught with several challenges. This has led to the commercial pharmaceutical and nutraceutical industries opting for the development of alternative shell forming materials instead of the traditional capsule shell material gelatin. This review discusses establishment and the on-going development of the manufacturing technology for liquid fill capsules with focus on progress and challenges of soft gelatin capsules formulation in oral administration for improved solubility and as an absorption-enhancing technique. This considerations form a basis for new applications in oral drug delivery.

Keywords: Soft gelatin capsules, oral administration, drugs formulation

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INTRODUCTION

The softgel dosage form has been around for many years. The earliest softgels date back to the 19th century. Since then, many improvements have been made with respect to the production of these soft capsules. Softgel manufacturing still requires special skills and equipment that less than a handful of companies can offer to pharmaceutical clients.

Notwithstanding the progress that has been made in softgel manufacturing, the softgel as a dosage form has remained largely unchanged over the years. As a result, patent protection on the technology was lost, which is a disadvantage in the era of pharmaceutical life-cycle management. For that reason, Banner has developed new softgel variants that not only offer specific benefits over the standard softgel, but also provide additional patent protection to the compounds they deliver.

Since the introduction of Soft Capsule Making Machine in the 1970s, formulations have continually become more popular with rapid developments in recent years. This could be illustrated by emergency of a more than 560 sets of Soft Capsule Making Machine with transfer mode having a production rate of up to 60 billion pills/year (i.e. more than 3600 kinds of drugs) in the world³. Up to now, there are more than 30 manufacturers producing more than 40 kinds of soft capsules by using over 60 sets of advanced machines. Softgels' ability to enhance bioavailability not only makes them the preferred dosage form for new chemical entities with poor oral bioavailability, they can also be used for reformulation of existing drugs, with the purpose of life-cycle extension.

SOFTGEL: A BRIEF REVIEW

Soft gelatin capsules¹ (referred to as soft elastic gelatin capsules, liquid gels or softgels) are a unique drug delivery system that can provide distinct advantages over traditional dosage forms such as tablets, hard gelatin capsules and liquids. However due to economic, technical and patent constraints there are relatively a few manufacturers of softgels in the world. Softgel is a hermetically sealed, one-piece capsule with a liquid or semisolid fill. The softgel consists of two major components, the gelatin shell and the fill. In the finished product gelatin shell is primarily composed of gelatin, plasticizer and water. The fill material can include a wide variety of vehicles and can either be a solution or a suspension. Softgels may be coated with suitable exterior coating agents such as Cellulose acetate phthalate (CAP) to obtain enteric release of encapsulated material. The standard softgel shape of oral pharmaceutical products is oval, oblong and round, though softgels can be manufactured in many shapes.

Soft gelatin capsules (softgels) offer the possibility of delivering a liquid in a solid oral dosage form. The softgel can therefore contain the active ingredient in solution, suspension or emulsion, which will inherently lead to better absorption of the active ingredient as compared with delivery in a tablet or as a powder. Softgels are therefore the ideal solution –and sometimes the only solution – for delivery of compounds with poor oral bioavailability. Other properties that make softgels a useful and frequently applied dosage form include their aesthetic properties and ‘swallowability’, their tamper-resistance, their protection of the active ingredient from light and oxidation, their taste-masking of ingredients and their masking of unpleasant odours of ingredients.

Soft gelatin capsules generally contain the drug in a non aqueous solution or suspension. The vehicle may be water immiscible liquid, such as PEG, and non ionic surface active agent, such as Polysorbate 80. Hydrophobic drugs dissolved in a lipophilic solvent such as vegetable oil would generally demonstrate poor bioavailability compared to the same drug given as a powdered solid, suspension or hard gelatin capsules. However, a drug dissolved or dispersed in a water miscible solvent may have better bioavailability than a compressed tablet of the same drug.

ADVANTAGE

1. Softgels ability to enhance bioavailability not only makes them the preferred dosage form for new chemical entities with poor oral bioavailability, they can also be used for reformulation of existing drugs, with the purpose of life-cycle extension. Two of such applications are briefly described here.
2. Pharmaceutical compounds delivered in tablets or regular two-piece hard shell capsules first need to dissolve before they can be absorbed. When delivered in a softgel, the active ingredient – being solubilised already – will be more readily available for absorption and therefore may reach its target receptor more quickly. This can result in a more rapid onset of therapeutic effect. This has been demonstrated clearly with ibuprofen softgels, which give a significantly faster onset of pain relief than analgesic tablets (see *References*).
3. Compounds that are currently being delivered in a tablet or a capsule could be reformulated in a softgel so as to improve their bioavailability. The compound would then exert the same therapeutic effect at a lower dose level. As a result, the reformulated drug can be promoted
 - with a new brand-name;
 - for a new indication;
 - in a new, more appealing dosage form; and
 - at a dose level that is not easily copied by generic versions of the original dosage form. With this metamorphosis, the chemical entity can start a new period of its life-cycle.

The following new dosage forms have been developed at Banner: enteric softgel, controlled release softgel, chewable softgel and gelatin-free softcapsule. Patent applications have been filed for all drug delivery systems. Banner's dosage forms can therefore offer additional market exclusivity to pharmaceutical and consumer products.

ENTERIC COATED

In contrast to existing enteric dosage forms, Banner's new enteric softgel is not coated. The enteric features of the dosage form reside in the shell itself. The result is a clear enteric dosage form with the exact same appeal and patient benefits that the standard softgel offers. Banner's enteric softgel meets all Pharmacopoeial (American, European, Japanese and British) standards for enteric delivery. Banner's enteric softgel technology is unique in that it offers a one-step process to manufacture enteric softgels. Traditionally, enteric softgels were prepared by coating with enteric polymers using traditional coating technology. Coating has its own disadvantages such as unsuccessful adhesion of the enteric polymer onto the soft gelatin shell due to the shell's inherent flexible nature. This can lead to chipping and peeling of the coat. Enteric coating also results in a hazy and opaque appearance of the capsule and is an additional step of manufacturing.

Advantages of the enteric softgel over other enteric dosage forms can be summarised as follows:

1. Banner's enteric softgel technology provides enteric properties more consistently than other products because the enteric system is built into the gelatin shell, not just as a coating on top;
2. clear, transparent dosage form, as opposed to coated enteric dosage forms;
3. offers the exact same advantages as standard softgels, including improved 'swallowability' taste-masking and protection against light or oxygen degradation; and
4. no leaking problems, as opposed to regular two-piece hard shell capsules.

Candidates for enteric delivery include:

- compounds that are unstable in gastric acid, for example proton pump inhibitors, certain antibiotics, triptans and dideoxyinosine (ddI);
- compounds that are irritating or damaging to the gastric mucosa, for example bisphosphonates, non-steroidal anti-inflammatory drugs, certain antibiotics and carbamazepine;

- compounds targeted at the small intestine, e.g. drugs for the treatment of Crohn's disease or other intestinal disorders, and drugs that are preferentially being absorbed in the small intestine; and
- compounds that may cause belching, regurgitation or other gastrogenic discomfort.

Banner has comprehensively designed and optimised the new enteric technology to suit a wide variety of products. We have applied the new technology on different drugs and have generated accelerated stability data. Banner is currently working on an existing drug for scale-up purposes. For this compound, the enteric softgel formulation has successfully passed accelerated stability testing as well.



Figure 1: Banner's enteric softgels are as clear as regular softgels because the enteric properties are incorporated in the shell.

CONTROLLED RELEASE SOFTGEL

Banner's scientists have developed a controlled release technology that is able to achieve a large variety of release patterns. The controlled release softgel can be applied to a wide range of active molecules. Banner's controlled release softgel technology uses a lipid matrix in a standard softgel shell. Depending on the physicochemical properties of the active molecule, an emulsion or a suspension is chosen as a matrix. By applying these, or combinations of these, almost any release profile can be engineered simply by varying the formulation. The result is an oral dosage form offering controlled release of the active moiety, combined with all the benefits that the softgel dosage form offers.

Its release properties, combined with the advantages of a softgel, make the CR-softgel a preferred form for those insoluble compounds that require enhanced absorption as well as a prolonged and controlled release.

CHEWABLE SOFTGEL

The chewable gelatin dosage form offers excellent mouth feel and chewing experience as compared with other chewable dosage forms. Chewable soft gels are particularly suitable for pediatric populations, where swallowing whole tablets or capsules is often a problem, and chewable tablets are often rejected.

Consumer preference testing with Banner's new chewable gels showed that three out of four parents would buy this product for their children (Tragon Research, data on file). In the adult population, chewable gels are convenient because they can be taken easily on the run, without the need for water. Lipid-coating of the active ingredient has been used and tested as a means to mask the taste of bitter active ingredients. This approach has resulted in a highly acceptable end-product. Other taste-masking technologies can be combined with the chewable softgel.



Figure 2: Banner's chewable softgels provide a gel-like mouthfeel and texture very different from chewable tablets.

Gelatin-free soft capsules:

Gelatin-free soft capsules are made from vegetable ingredients. They have all the advantages of standard softgels, but do not contain gelatin. Gelatin-free soft capsules are particularly suitable for vegetarians or other populations that prefer non-animal products.

Some patented capsule technology:**1. Soflet® Gelcaps:**

Soflet Gelcaps is a patented technology that enrobes tablets with either a gelatin or non-animal film, resulting in a preferred dosage form that's easy to swallow. Our unique, patented manufacturing process allows us to create one or two-toned color dosage forms that can be easily printed on, offering distinctive opportunities to brand and differentiate your product. And since Soflet Gelcaps are tamper-evident in finished form, they deliver increased consumer safety.

Soflet® Gelcaps represent a patented technology whereby tablets are enrobed with gelatin. Soflet® Gelcaps are a dosage form preferred by consumers because of the ease of swallowing as well as the taste and odour-masking properties imparted by the gelatin coating. The unique, patented manufacturing process of Soflet® Gelcaps results in a single or two-toned colour dosage form that can be imprinted upon. These features offer distinctive opportunities for product branding. Soflet® Gelcap technology is therefore widely used in over-the-counter products, both branded and private label. In addition, Soflet® Gelcaps are ideal for clinical trial blinding. Banner now also has the capability of manufacturing gelatin-free Soflet® Gelcaps.

Features of Soflet® Gelcaps:

1. Improves swallowability, masks unpleasant odors and tastes
2. Provides a multitude of color combinations; allows surface printing
3. Patented technology is difficult to mimic, providing easy recognition of tampering or counterfeiting by consumers or pharmacists
4. Soflet Gelcaps are ideal for clinical trial blinding
5. Also available in EcoCaps™ non-animal formulation
6. Technology is widely used in over-the-counter products, both branded and private label
7. Three out of four consumers prefer Soflet Gelcaps over tablets – so much so that respondents would purchase Soflet Gelcaps over tablets at a 10% premium

BENEFITS

1. Increases patient compliance
2. Enforces your brand identity and ensures recognition
3. Technology design minimizes tampering and counterfeiting
4. Provides life cycle extension possibilities
5. Increases sales and profits



Figure 3: Banner-patented Soflet® Gelcap Technology

2. Versatrol™:

Versatrol™ is a unique oral controlled release technology for the pharmaceutical market place. When combined with softgels, controlled release technology provides a consumer-preferred dosage form with the ability to tailor release profiles for a wide variety of drugs. Versatrol™ offers controlled release formulations with the benefits of greater effectiveness in the treatment of chronic conditions by reducing side effects through minimizing peak plasma concentrations, and greater convenience leading to higher levels of patient compliance due to a simplified dosage schedule. Versatrol™ technology can be applied early on in pharmaceutical product development, leading to the parallel development of immediate release and controlled release formulations to maximize market exposure.



3. Licaps® Liquid - Filled Capsules®:

Licaps® two-piece gelatin capsules with liquid formulations containing pumpkin seed; pumpkin seed oil or herbal extracts such as saw palmetto or hop extract. The filled capsules are then sealed using Capsugel's LEMS® automated capsule sealing system and the finished capsules are marketed by GSK as pharmaceuticals to treat several types of urological conditions or as nutraceuticals. Licaps® Liquid Delivery System doesn't just offer better bioavailability. It's also fast-acting and gentle on the stomach. The capsule protects against degradation and oxidation to preserve the efficacy of your formulation. Liquid capsules are also visually appealing, and offering a liquid option sets your brand apart from your competition. Licaps® Liquid Delivery System is available in liquid-filled gelatin or vegetarian HPMC-based capsules. Every Licaps® capsule is sealed with our proprietary LEMS sealing process and fused with nitrogen to protect your supplement against oxidation. Innovative multi-phase capsule designs are also available. Like all of Capsugel's capsules, Licaps® can be colored and printed to reflect your brand.

Capsugel is meeting growing demand for liquid filled capsules with Licaps®, a two piece hard capsule specially designed for secure containment of liquid and semi-solids.

Some of the benefits of using Licaps® capsules include:

1. Visually appealing liquid formulation.
2. Proprietary Liquid Encapsulation Microspray Sealing (LEMS®) sealing process means no balancing and outstanding product integrity.
3. Available in both gelatin and non animal capsules and a wide variety of sizes and colors.
4. Opportunity for improved absorption and bioavailability over the tablets.
5. Improved time-to-market versus tablet due to less complex formulation and development processes.
6. Improved content uniformity over tablets against degradation helps, protects the potency of ingredients.
7. Helps to mask taste and unpleasant odors better than softgel capsules.



4. Chewels

Chewels are suitable for both adult and pediatric populations and offer a more palatable replacement for gritty, chalky chewable tablets or liquid doses. The excellent mouth feel and convenience versus similar forms make Chewels chewable gels a favorite among adults and children



5. EcoCaps:

Finally, the non-animal alternative to gelatin has arrived - EcoCaps non-animal softgels. EcoCaps are made from botanical ingredients, so they have all the advantages of standard softgels without using gelatin. Thus, they appeal to a wide range of consumers seeking non-animal alternatives for health, dietary, religious, or animal-rights reasons. Extend your product appeal to new audiences and see more green with EcoCaps non-animal softgels.

1. Formula is based on plant carbohydrates, manufactured into encapsulating films using patent-pending process
2. Capsules are compatible with current softgels with several types of fill materials
3. Delivers the advantages of standard softgels but does not contain gelatin
4. Manufactured using a unique, patent-pending technology
5. Technology may be applied to Soflet® Gelcaps as well as softgels



6. Enteri Care

Our clear EnteriCare enteric softgels provide an advanced alternative to unattractive spray-on coatings that can flake or crack. This unique dosage form maintains the benefits of a standard softgel while delivering enteric properties within the gelatin shell. As a dosage form preferred by consumers¹, EnteriCare enteric softgels increase the likelihood of compliance with dosing regimens and repeat sales.²

- Patent-pending technology
- Enteric properties of the dosage form are built into the shell itself; it is not coated
- Clear, elegant appearance
- Site-specific dosage delivery
- Delivers acid labile molecules directly to the small intestine
- Two different formulas: one to meet the regulatory standards for pharmaceutical products and another for nutritional supplements using GRAS ingredients
- Hermetic seal masks unpleasant tastes and odors
- Consumer-preferred choice - studies indicate consumers prefer softgels - perceived as being easy to swallow, better performing, and having an attractive appearance
- Ideal for reduction of reflux and gastric irritation

- Ideal for compounds targeted at the small intestine, such as drugs to treat Crohn's disease and other intestinal disorders or compounds causing belching, regurgitation, or other gastrointestinal discomfort
- Softgel formulation allows for efficient/optimized physico-chemical properties of the compound
- Shell can be UV-formulated for photosensitive compounds
- EnteriCare technology creates a seamless, one-piece design that is uniquely tamper-evident
- Uncoated - to remove the risk of flaking or cracking
- Encapsulated formulation may enhance bioavailability and absorption



7. Solvatrol technology:

Solvatrol technology provides an effective method for enhancing solubility of active pharmaceutical compounds. Poorly water-soluble drugs can be formulated with Solvatrol, leading to improved absorption following oral administration.

- Suitable for lipophilic and hydrophilic formulations
- Provides a stable solvent system
- Eliminates dissolution rate limitations
- Delivered in a softgel dosage form

- Increases speed of onset
- Enhances solubility of compounds
- Improves bioavailability
- Reduces variability
- Delivered in a consumer preferred dosage form



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