Introduction

It is estimated that more than 70% of new chemical entities (NCEs) within the current drug discovery process exhibit poor biopharmaceutical properties, such as low aqueous solubility (BCS class II), poor permeability (BCS class III), or both (BCS class IV). These suboptimal properties pose significant challenges for the oral absorption of the compounds and for the development of orally bioavailable dosage forms. As a consequence, the development of the soft gelatin capsule (softgel) dosage form is of growing interest for the oral delivery of poorly water soluble compounds (BCS class II or class IV) as it provides several unique advantages over traditional oral tablets. Specifically, the softgel dosage form offers advantages which include the ability to deliver a liquid or semi-solid matrix containing high levels of solubilizers, penetration enhancers, in a range of solubilizing media that span from hydrophilic to hydrophobic. Moreover, the ability to accurately dispense liquids into the softgel form offers unique quality advantages over solids manufacturing, as well as the ability to effectively deliver highly potent drugs. However, due to the very dynamic nature of the softgel dosage form, its development and stability throughout its shelf life are fraught with a multitude of unique challenges.

Historically, softgels were originally developed to dose oils commonly used today in dietary supplements, such as borage oil, fish oil, and vitamin E. Over time, softgel formulation strategies have evolved to incorporate hydrophilic fills, predominately used in polyethylene glycol (PEG)-based solutions, thus allowing for the encapsulation of drugs with wide ranging chemical properties. In addition, the flexibility of the softgel even allows for the dosing of a combination of lipophilic and hydrophilic APIs. Currently, there are a multitude of softgel formulation strategies that can be utilized to solve the complex needs of the pharmaceutical industry, including: solubilized APIs or pure APIs, self-emulsifying systems, encapsulated microsuspensions, nanosuspensions, solid dispersions, or multiphase-fill systems, which involve the dosing of a combination of two liquids and/or solids within the same softgel. A variety of prescription softgels are on the market today, such as Omega-3 extracts like Lovaza/Omacor, Vascepa, Epanova, and hormones like Prometrium, and poorly soluble compounds such as Procardia, Amitiza, and Neoral. In addition, softgels are often used as a line extension or specifically marketed for over the counter (OTC) use. These include Advil, Aleve, Colace, and various cough and cold products such as Dayquil. As a dietary supplement, there are several single-ingredient and combination softgel products, such as Omega-3 conjugated linoleic acid, CoQ10, and other vitamins, as well as combination products specifically for pre-natal care or complex diseases like Cystic Fibrosis.
• Despite the wide range of capabilities available through the use of softgels, in all cases, the drug release rate is entirely governed by the dissolution and release rate of the gelatin which can only directly be modified by the use of a functional coating. While coating tablets is a relatively mature science, the coating of softgels offers several unique challenges, including: The surface of the softgel tends to be smoother than that of a tablet, which can make it more difficult for the coating to stick
• Softgels are flexible and some coatings can be brittle, which can lead to coating integrity issues
• Softgels have water and plasticizer in the shell, as a result the moisture content will fluctuate throughout the manufacturing process and shelf life of the product
• Softgel seams can be a point of failure
• Softgels will soften at low temperatures (-40°C/104°F).

While the aforementioned coating challenges associated with softgels are difficult to overcome, companies like BASF have developed specific technical strategies to address and conquer these obstacles.

The Softgel Composition
The typical composition of a softgel contains a shell, most often made from gelatin, the liquid or semi-solid fill, and finally the coating. The shell is roughly 35% by weight of the total softgel and contains about 45% gelatin, a high concentration of moisture, 30% plasticizer (typically made from sorbitol or glycerin), and 1% pigment and/or opacifier that protects the API from ultraviolet rays.

The fill is roughly 65% by weight of the total softgel, and contains the bulk of the API or dietary supplement. The API or supplement is dissolved in, or suspended in a matrix of solubilizers, antioxidants, and viscosity modifiers. The solubilizers are selected specifically to dissolve and maintain the stability of the API throughout the course of the product shelf life. Antioxidants prevent the oxidation of the pharmaceutical compound, the viscosity modifiers increase the viscosity and maintain the suspension if it is a suspension type product; and finally, humectants and plasticizers regulate moisture flux.

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Criteria for Selecting Proper Softgel Fill
A better understanding of a softgel’s composition will help when selecting the proper fill and how that fill subsequently affects the coating. The fill must be made from pharmaceutically acceptable and compendial materials, adequately dissolve or suspend the actives, and have minimal interaction with the ac-
tive and the gelatin shell. In addition, certain excipients such as low molecular weight povidones may be required to maintain drug solubility or prevent recrystallization throughout the shelf life of the compound. In addition, protective compounds like antioxidants can reduce the degradation of the pharmaceutical compound.

Fill selection is crucial for both moisture regulation and gelatin compatibility. With regard to moisture regulation, it is important to understand that the softgel is a dynamic, non-steady state product where there is a constant flux of moisture. The moisture will flow from the air to the coating, to the gelatin, to the fill, and then back out again. It is important to note that the fill composition is highly influential in determining this moisture flux.

Moisture content will also affect the drying time and the physical properties, such as hardness or the seams of the soft gelatin capsule. Slide 15 shows a hydrophilic fill made from polyethylene glycol (PEG), such as BASF’s Kollisolv® E400 NF LA, which is a low-aldehyde, low-molecular weight liquid PEG. Typically, when the softgel is filled with this, a high level of water flux is maintained, even after the softgel has been completely created and coated. This results in a high amount of water retention between 5% and 10% in the fill.

The same figure also shows a hydrophobic fill that is lipid-based, such as BASF’s Kollisolv® MCT 70, which is a medium chain triglyceride and retains significantly less water, resulting in a faster drying system, lower water flux, and low water retention in the fill of less than 1%, despite the presence of the gelatin barrier between the coating and the fill. Again, the fill will have a profound effect on the amount of moisture going in and out of the coating, as well as the equilibrium concentration of moisture, which in this case is at or less than 1%.

Regarding gelatin-compatible fill, the body gelatin is water soluble, therefore hydrophilic compounds like water, ethanol, and some glycols are important and must be limited to <10% to prevent premature dissolution or softening of the capsule. Failure to do this may result in degradation and softening, characterized by low glass transition temperature (Tg). Shell softening will weaken the seam and soften the overall capsule, resulting in poor coatings regardless of the coating parameters that were selected or the type of coating.

When considering fill and its relation to coating, pay additional attention to the presence of impurities, specifically the exposure of gelatin to aldehyde, which is a common impurity in various excipients and has been shown to produce irreversible crosslinking of the gelatin network. Slide 17 highlights what happens when a normally flexible hydrogen bonded network is covalently crosslinked, resulting in a rigid matrix that no longer behaves as desired. Crosslinking is also influenced by temperature, relative humidity, and pH. Crosslinking results in altered release rates, and sometimes preventing release entirely. This ruins the functional coating of the softgel and changes the release kinetics to an undesired property. Thus, maintain the use of high quality, proven low aldehyde fills in order to minimize crosslinking.

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In summary, the fill characteristics are crucial to softgel coatings in order to achieve desired functionality. Fill composition and polarity affect moisture flux and drying time as well as the seams of the softgel. Pharmaceutical-grade, low aldehyde fills of compendial materials prevent crosslinking, which is crucial to maintaining the physical properties of the capsule and improve release kinetics.

**Key Parameters of Softgel Coating**

As previously mentioned, the challenges of coating softgel capsules include: smooth surfaces make it hard for coating films to stick, the hygroscopic nature of the gelatin shell poses stability issues, the gelatin softens at 40°C, the shell is flexible and irregularly shaped, and that coatings tend to be brittle. The results are poor coating adhesion, cracking along the gel's seam, and storage agglomeration (Slide 21).

Poor adhesion of the coating film to the softgel surface happens when the coating polymer dries too fast (this often occurs during winter or in arid environments because the moisture in that air is very low). Coating failure cracks the film along the seam, which affects the quality of the coated softgels. In fact, when the coated softgels are dissolving, the cracking allows the dissolution media to get into the softgel, dissolve the shell, and the fill leaks.

On the other hand, there is also the issue of capsule agglomeration. If stored in a high-moisture environment, the capsules have a propensity to stick together. A slight tap can break the agglomeration, but sometimes the agglomeration is so severe that, if pulled, the coating and the capsules will be damaged, irreversibly ruin the product.

In addition, coating polymer selection also has a multitude of issues associated with proper coating. For example, when the polymer itself is brittle there are only a handful of options to improve the formulation. Specifically, Slide 22 illustrates an example of optimizing the coating dispersion formulation and the coating process for enteric coating fish oil softgels with Kollicoat MAE 30 DP, a pH sensitive enteric coating. Kollicoat MAE 30 DP is a 30% aqueous dispersion of methacrylic acid and ethyl acrylate copolymer, and will not dissolve at a pH below 5.5, thus offering enteric protection of the softgel. However, Kollicoat MAE is brittle with a Tg of 106°C, which requires coating at a relative high process temperature and the proper
use of a plasticizer to reduce the coating temperature.

It is known that a high coating temperature and high Tg causes adhesion and film cracking, so in response, it is important to add the right amount of the plasticizer to the coating formulation. This plasticizer lowers the minimum film forming temperature and reduces the coating temperature. A plasticizer also increases the flexibility of the film to reduce the tendency of cracking.

Finally, it is important to note that too much plasticizer can cause agglomeration during storage. One option for eliminating agglomeration is to add a moisture barrier coating, such as BASF Kollicoat® Protect, on top of the entire coating. In fact, using 5% of the Kollicoat® Protect top coat can completely eliminate the sticking, and stabilizes the coated softgels.

Summary

Softgel coating has many challenges stemming from the unique structure of the softgels and also from the nature of the coating polymers. Proper technical application of formulation strategies will result in the optimization of the coating formulation in order to overcome these challenges, and ensure a successful product.

BASF offers comprehensive solutions to the pharmaceutical industry, ranging from a broad portfolio of excipients to active ingredients and custom synthesis services. With its expertise in polymer chemistry and research and development capabilities around the globe and the company’s clear commitment to developing pharmaceutical excipients, BASF continuously creates solutions that contribute to its customers’ success. BASF’s high-quality ingredients and services can help with challenges related to Instant & Modified Release, Solubilization, Taste Masking, Soft Gels and Skin Delivery. BASF’s soft gel platform seeks to provide understanding, solutions and materials specifically targeted for soft gel application.

Reference