Softgels

Lipid formulation development: Why softgels are the technology of choice

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As biotech and pharmaceutical organizations focus on bringing life-changing therapies to patients as quickly as possible, they must also determine the needs of their proprietary molecules and the market. Today, many companies are prioritizing patient-friendly drug formats, such as oral solid dose (OSD) drugs or sterile injectables, in order to deliver safe and effective therapies to patients in need.

However, within the pharmaceutical industry, the development of new OSD drugs is fraught with challenges, one of the most significant being the issue of low bioavailability. This problem is particularly prevalent during the early stages of drug development and is a recognized reason why many drugs fail to progress beyond preclinical stages[1].

Despite the risks that stem from low bioavailability, many pharma and biotech organizations continue to opt for standard OSD forms, such as tablets and capsules. In fact, there are several factors in choosing a final formulation that will offer precise control of the drug release rate, content uniformity, and site of absorption. Lipid formulations, particularly softgels, offer a compelling solution to the bioavailability challenge and present several key advantages that make them worth considering from the outset.

Why companies opt for standard oral solid dosage forms

Despite the known risks associated with low bioavailability, many pharmaceutical companies continue to choose standard OSD forms for several different reasons. The first stems from the familiarity of traditional dosage forms. Companies are often more comfortable with conventional formulations like tablets and capsules, which have well-established manufacturing processes and regulatory pathways.

Additionally, during the early stages of development, the primary goal is to demonstrate that the drug is effective. At this point in the timeline, formulation scientists are often more focused on clinical proof of concept, rather than formulation optimization.

Finally, developing alternative dosage forms, such as lipid formulations, can be perceived as more costly and time-consuming. Companies may be concerned about the potential impact on development timelines and budgets.

Of course, bioavailability challenges can be overcome by developing formulations for intravenious administration, such as sterile injections. However, in general, this route of administration is less patient-friendly and more expensive. Because of these considerations, OSD drug formulations are widely accessible, making up for 84% of drugs on the current market[2].

The challenge of low bioavailability

Bioavailability refers to the proportion of a drug that enters the systemic circulation and is available to exert its therapeutic effect. Solubility plays a critical role in influencing a drug's bioavailability. Poorly soluble compounds often demonstrate lower bioavailability, which can reduce drug efficacy[3]. This is a prevalent concern affecting around 80% of active pharmaceutical ingredients (APIs).

For many drugs, particularly those that have poor water solubility, achieving adequate bioavailability can be a significant hurdle. Poor bioavailability can lead to suboptimal therapeutic outcomes, necessitating higher and/or multiple unit doses to achieve the desired exposure, which in turn can increase the risk of side effects and toxicity. However, without addressing bioavailability issues early on, promising drug candidates may fail to progress[4], resulting in wasted resources and lost opportunities.

Recent innovation has enabled scientists to develop a toolbox of technologies to help overcome solubility issues. Some of these technologies include:

- Particle size reduction, which reduces the particle size to a micronized form and helps the molecules to dissolve more rapidly, resulting in quicker absorption into the bloodstream when compared to larger particles[5].
- Solid dispersion—when a drug is dissolved into a solvent and then sprayed or melted with excipients that stabilizes the amorphous drug which is obtained—creating a formulation which ultimately leads to a higher absolute bioavailability.
- Complexation of drugs with excipients like cyclodextrins/mesoporous silica, which can wrap around drug molecules to make them more water-soluble and stable, improving how well the body absorbs them.

While largely effective, these approaches can be limited by stability concerns, material requirements, or cost. This is where lipid formulations, and specifically softgels, come into play.

The case for lipid formulations

Lipid formulations have been well-established and proven to overcome bioavailability challenges[6]. In fact, there is growing evidence that suggests this process is predictive, effective, and offers several key advantages.

Firstly, as mentioned, lipid formulations can enhance the solubility and absorption of poorly water-soluble drugs, leading to improved bioavailability. Lipid formulations have the advantage of leveraging the body's natural digestive processes. By utilizing the digestive tract's mechanisms for lipid digestion and absorption, these formulations can enhance the solubility and bioavailability of poorly soluble drugs. This approach allows for more efficient drug delivery and improves therapeutic outcomes. This can result in more consistent therapeutic outcomes and potentially lower required doses. At the same time, initial formulations can be screened using very limited amounts of API, typically between 10 to 40 grams. This is particularly preferable during the early stages of development when API availability may be limited.

It is necessary to also note that the benefit of lipid formulations is advantageous throughout the entirety of the drug development cycle, from preclinical studies and clinical Phase I trials to subsequent clinical stages and commercialization. This continuity can simplify the development process and reduce the need for formulation changes. In fact, the manufacturing process for lipid formulations, particularly softgels, is semi-continuous, making it relatively straightforward to scale up from small-scale laboratory batches to commercial production. This can help streamline the development process and reduce time to market.

Softgels: The technology of choice

Softgels offer a particularly attractive option for addressing bioavailability challenges. These drug formats consist of a gelatin-based shell filled with a liquid or semi-solid formulation, which can include lipids, surfactants, and other excipients designed to enhance drug solubility and absorption.

Softgels offer several key features like enhanced solubility and absorption, meaning the lipid-based fill material in softgels can improve the solubility of poorly water-soluble drugs, facilitating their absorption in the gastrointestinal tract. This can lead to higher bioavailability and more consistent therapeutic effects.

Additionally, the encapsulation of the API within the softgel shell can protect it from degradation from factors like light, oxygen, and moisture. This can enhance the stability and shelf life of the drug product.

From a patient compliance perspective, softgels are generally easier to swallow than tablets and capsules, particularly for patients who have difficulty swallowing solid dosage forms. The smooth, gelatin-based shell can also mask the taste and odor of the API, improving medication adherence.

Softgels have long been depicted as a product most applicable for vitamins, fish oils, and herbal supplements, or over-the-counter (OTC) medications, such as, nonsteroidal anti-inflammatory drug (NSAID), ibuprofen (IBU). Indeed, softgels are widely accepted by consumers, and features such as improved bioavailability (e.g., diclofenac softgels) and quicker onset of action (e.g., IBU softgels) that are achieved for these OTC drugs are, of course, equally applicable for prescription drugs. Greater familiarity and adaptation of soft gelatin capsules for prescription drugs could help address bioavailability challenges that are currently unmet.

However, despite their slower rate of adoption, softgels are technically excellent for most molecules and offer improved bioavailability, especially when applied to the delivery of lipid-based formulations.

Lipid formulation: A staged development approach

An early-phase lipid-based fill formulation development program consists of several stages that ultimately result in identification of lead candidates for pharmacokinetic study. One of the key criteria to determine is the drug loading feasibility in lipid formulations for the drug candidate. Therefore, drug developers typically start with a solubility assessment in single vehicles, followed by prototype selection and emulsion characterization in water.

Then, a formulator assesses characteristics such as the speed and quality of emulsion formed, droplet size, dispersion behavior, and recovery from the biorelevant fluids over time. They study *in-vitro* digestion models in biomimicking fluids like simulated gastric fluid (SGF) or simulated intestinal fluid (SIF), to generate the drug recovery profile in the aqueous phase of the digested component. Next to all *in-vitro* data, short-term chemical stability data on the fill formulation is collected under accelerated conditions.

Based on the *in-vitro* characterization outcome coupled with chemical stability data from previous stages in the process, final selection of lead candidates is made for pharmacokinetic study. This general approach requires limited quantities of API and generates a comprehensive formulation package in just a few months. To provide more context on the described approach, some case studies where these screening tools and techniques were used to design lipid formulations targeting bioavailability enhancement are outlined in the next section.

Case studies and examples

Lipid-based self-microemulsifying drug delivery system (SMEDDS) formulation of IBU and phenylephrine (PE) for softgels[7]

A lipid-based formulation for a cough and cold medication containing 200 mg of IBU and 5 mg of PE was developed. Using a streamlined approach, the solubility of IBU in various excipients was assessed. Due to the differing properties of IBU and PE, their solubility profiles varied significantly.

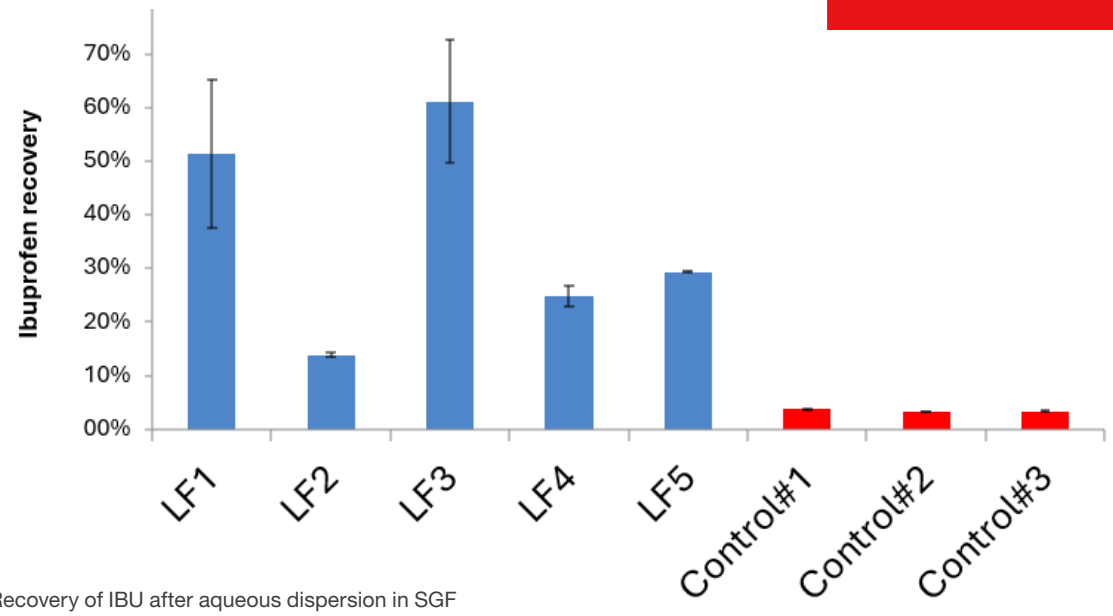
Propylene glycol monocaprylate (type II) and Caprylocaproyl macrogol-8 glycerides were selected after initial testing, with Vitamin E TGPS added as a co-surfactant and antioxidant, and Propylene Glycol for PE. Five lipid formulations with different ratios of these ingredients were created and tested against three PEG-based control formulations. These samples were dispersed in water and SGF to observe their behavior.

The lipid formulations successfully formed nano-sized emulsions, keeping the active ingredients dissolved in SGF, unlike the PEG-based controls where the API precipitated. Further testing showed that lipid formulations (LF) LF1-LF4 formed nano-sized droplets, while LF5 and the PEG-based control did not.

Hence, the streamlined solubility screening led to effective lipid-based formulations that maintained the active ingredients in a dissolved state, showing promising results for IBU recovery in acidic SGF.

In PEG-based formulation (control), API crashes out in SGF

LFs can form S(M)EDDs, keeping the API solubilized in SGF



Recovery of IBU after aqueous dispersion in SGF

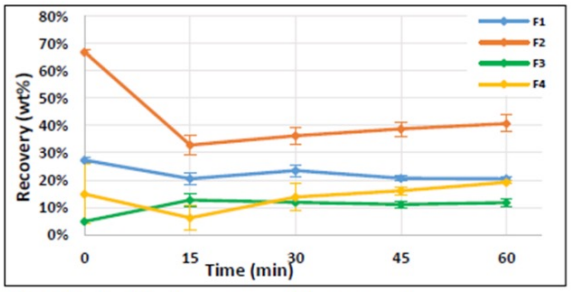
Relationship between *in-vitro* lipolysis release and *in-vivo* performance of lipid-based drug delivery systems (LBDDS) for a biopharmaceutics classification system (BCS) class II compound[8]

A study was conducted to link the *in-vitro* release of a BCS class II compound from LBDDS to its *in-vivo* bioavailability. The compound was formulated into four different LBDDS, each with varying combinations of excipients.

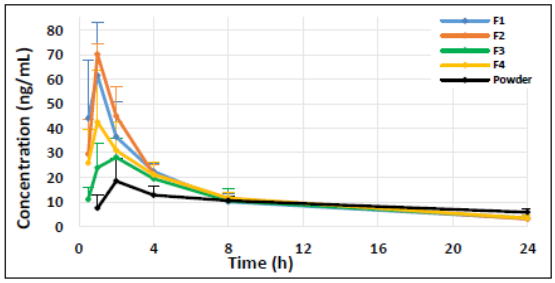
Using a methodology described in literature, the drug's release during *in-vitro* lipolysis was analyzed. Formulation (F) F2 showed the highest drug recovery, suggesting a potential for supersaturation that could lead to better absorption in vivo.

Testing these formulations revealed that lipid formulations significantly improved drug exposure compared to the drug in powder form. Formulations F1 and F2 showed the highest peak concentrations and faster absorption rates.

Therefore, a strong correlation between *in-vitro* lipolysis data and *in-vivo* performance was demonstrated, highlighting the value of the lipolysis model in selecting effective lipid-based drug delivery systems.



In-vitro lipolysis: Drug recovered over time in aqueous phase



In-vivo drug exposure of LBDDS measured against drug powder

Conclusion

Solubility and bioavailability in OSD formulations remain major challenges within the early stages of drug development. While technological innovations have allowed the pharmaceutical industry to make progress in solving this hurdle, choosing formulations that help achieve desirable solubility and bioavailability can help speed up development of the most promising molecules. Ultimately, lipid formulations, particularly softgels, offer a compelling solution.

The advantages of improved bioavailability, efficient use of API, ease of scale-up, versatility across development stages, and consumer preference make softgels a technology of choice. By addressing bioavailability issues early in the development process, companies can increase the likelihood of success for their drug candidates, bringing more effective therapies to market. As the pharmaceutical industry continues to evolve, embracing these innovative formulation technologies will be crucial in overcoming the challenges of drug development and improving patient outcomes.

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