**Abstract**

Nowadays, the pharmaceutical industry is facing an increasing numbers of low solubility drug candidates and this issue often hinders those compounds from achieving sufficient oral bioavailability. In order to alleviate this challenge, many enabling formulation technologies have been developed. Of these, liquid-filled capsules have emerged as one of the key technologies for oral drug delivery of low solubility compounds. A liquid-filled capsule (LFC) is a liquid formulation encapsulated in a soft or hard capsule. In general, lipids and/or co-solvents are the most commonly solubilizing excipients in LFCs. Although developing and manufacturing LFCs is non-trivial and challenging, they possess distinct advantages over traditional solid dosage forms. For example, improving oral exposure (or faster on-set) of poorly soluble drugs, allowing the use of API with challenging solid state properties (i.e. hard to crystallize), overcoming content uniformity issues with low dose drugs, reducing exposure to dust from high potency compounds, and other specific purposes such as prevention of drug abuse. Therefore, despite the challenges associated with LFCs, they remain an important option for formulators. Three major types of liquid-filled formulations currently being employed in the industry will be briefly discussed in this article.

**Introduction**

Due to the ever-increasing ADME challenges encountered for new drugs, liquid-filled capsule (LFC) dosage form has gained significant popularity over the last several decades [1]. LFCs are generally applied to drugs with poor aqueous solubility or poor solid state properties (i.e. hard to crystallize). In general, the drug is first solubilized in the liquid vehicle, which is mainly composed of lipid, co-solvent, a co-solvent/surfactant mixture, or a co-solvent/lipid/surfactant mixture, and then encapsulated in a soft or hard capsule for oral delivery. For drug absorption that is dissolution rate limited, dissolving the drug in solution can help to eliminate the rate-limiting dissolution step and to boost the oral bioavailability or to achieve faster on-set with higher Cmax and shorter Tmax in both pre-clinical and clinical settings [1-4]. Other specific applications such as abuse resistance and combination therapies that utilize LFCs further expand the utility of this technology [4]. Since these applications of LFCs are considered non-traditional, they are beyond the scope of this review.

In order to be successfully formulated as a LFC, the drug candidate should satisfy three major requirements: (i) the drug must have high solubility in the formulation vehicle, (ii) drug must have good physical and chemical stability in the formulation vehicle and (iii) the formulation must be compatible with the capsule shell. Usually, a solubility requirement (based on 70% of saturation solubility) can be used to calculate the desired solubility using the following equation:

$$S = \frac{D}{0.7V_f}$$

where $S$ is the desired solubility, $D$ is the dose, and $V_f$ is the fill volume. For example, if the required dose is 50 mg per capsule with a fill volume of 0.6 mL (this depends on the capsule size), then the desired solubility of the drug in formulation vehicle will need to be greater than 119 mg/mL. The high solubility requirement is usually the limiting factor in development of LFCs and maximum achievable dose is typically less than 100 mg/capsule.

However, LFC provide unique advantages when compared with other enabling delivery technologies such as amorphous solid dispersion and micro/nanoparticle formulations. For example, for a high potency (low dose) compound, high homogeneity of the drug in the solution can be easily achieved thereby ensuring excellent content uniformity (CU). For other solid dosage based delivery methods achieving good CU at low doses are challenging as solid blending steps are utilized. In addition, for high potent compounds exposure to dust during the manufacturing process is reduced since the drug is dissolved at the first step. Alternatively,
LFCs are a great solution for compounds with challenging solid form landscape or when it is difficult to control the final solid form of the API. Based on the composition of formulations, three of the most commonly used liquid-filled formulations are discussed in this article. They are co-solvent (water miscible) based, lipid-based (water insoluble), and self-emulsifying (SEDDS) formulations.

**Co-solvent (water miscible) based formulations**

Many drugs have higher solubility in the co-solvent vehicle than pure aqueous medium. Co-solvents are widely used in the preparation of drug solutions in different dosage forms in both pre-clinical and clinical setting [5-6]. Thus, for compounds with solubility and dissolution rate limited absorption, bioavailability (or faster on-set) may be achieved when co-solvents or other liquid-based formulations are used. However, since the co-solvent dose has the potential of creating supersaturation in the gastrointestinal (GI) track upon dosing, drug precipitation may happen in the GI. The potential of in vivo precipitation becomes more significant when the drug solubility ratio (i.e. Solubility in vehicle/ solubility in aqueous) is high. A formulation with a higher solubility ratio is likely to create higher supersaturation ratio upon dosing, hence increasing the possibility of in vivo precipitation. Due to the above reasons, the exposure improvement of the co-solvent formulations may be restricted and highly variable. These major drawbacks of the co-solvent formulation often limit the use of this technology and require the inclusion of other excipients such as surfactants (to form micelles) or a precipitation inhibitor to improve their performance [7]. Typically high throughput screening methodologies and solubility parameter based approaches have been used to select the appropriate solvent mixture for formulation.

Co-solvent-based formulations have traditionally been encapsulated in gelatin capsules. Glycerin, propylene glycol, Ethanol, and PEG are the most widely acceptable co-solvents for formulation and PEG 400 is the most commonly used solvent that is compatible with softgel capsules. The level of ethanol in the formulation is usually limited to less than 15% by weight because of its volatility, ability to diffuse out of a capsule and cause capsule softening. Examples of marketed products that have used co-solvent based formulations are Acetaminophen softgel, Ibuprofen softgel, Naproxen softgel, Nimodipinesoftgel, and Nifedipinsoftgel.

**Lipid (water-insoluble) based formulations**

For compounds with poor water solubility but good lipid solubility, lipid-based formulations can be used to solubilize the compound for drug delivery in both pre-clinical and clinical setting. The formulation vehicle is primarily composed of lipids such as corn oil, peanut oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides derived from coconut and palm oil. Other water-insoluble solvents such as Vitamin E TGPS and oleic acid are also commonly used as solvents for drugs.

Similar to the co-solvent based formulation, drug solubility in the lipid is a major formulation parameter that has to be optimized. Here again screening approaches are used to determine the lipid composition that is ideal for a given drug.

The neutral form of the drug is often the best for this application as it usually gives the best solubility in the lipids. A lipid-based formulation may introduce a higher degree of potential for a food effect [8]. The primary reason for this is that if no surfactants are added to the lipid, the formulation will need to rely on digestion in the GI tract in order to emulsify the lipid formulation. Thus, higher levels of bile acid, which present in the small intestine in the fed state, expedite this process and may lead to large food effect [7]. In addition manufacturing considerations should also be taken into account when using lipid-based vehicles. These vehicles tend to be highly viscous liquids and higher temperatures are required to reduce viscosity during capsule filling. Examples of marketed products that have used lipid-based formulations are Rolcatrolsoftgel, Progesteronesoftgel, Valproic acid softgel, Doxercalciferolsoftgel, Colpermin® hard gelatin capsule, Isotretiloin hard gelatin capsule, and Fortovaseosoftgel.

**Self-emulsifying drug delivery system (SEDDS)**

Self-emulsifying formulations (SEDDS) and supersaturated self-nano emulsifying drug delivery systems (Super-SNEDDS) are subsets of lipid co-solvent based formulations that have gained popularity in recent years [9,10]. For this type of formulation, the drug is dissolved in the vehicle containing co-solvent, lipid, and surfactant. When dosed, a spontaneous formation of an emulsion or microemulsion (or a mixture) will take place when formulation comes in contact with the fluids of the GI tract. The drug is solubilized in the emulsion droplets and is supersaturated with respect to the aqueous milieu. The formation of emulsion can improve oral absorption of the drug. For this type of formulation, high surfactant levels in the formulation are required to achieve a microemulsion state as the formulation comes into contact with the GI fluids. Thus, it is possible that this type of formulation may reduce the positive food effect since high levels of surfactant are already present in the drug product and the bile acid effect on micelle formation may become less significant [11-12]. The design of SEEDS and SNEEDS systems are more complex than the co-solvent or lipid-based systems previously discussed. Special attention needs to be paid to choice of surfactant as this will govern the propensity for emulsification and the particle size of the emulsion droplets formed. Examples of marketed products that have used lipid-based formulations are Cyclosporine A softgel, Ritonavir softgel, and Kaletra (lopinavir and ritonavir) softgel.

**Conclusion**

The advantages and limitations of LFC were discussed. While there are instances where LFC technology is superior to other enabling oral delivery technologies, there are some unique
challenges for this technology. The manufacturability, stability, storage conditions and quality (i.e. leakage, capsule shell brittleness), of the final dosage form and suitable systems for high dose drugs remain a challenge. Furthermore, the selection of the pharmaceutically acceptable co-solvents and surfactants is rather limited. These limitations constrain the application of this technology. Other factors such as lack of good prediction tools for compound solubility (under various conditions) in co-solvents, surfactants, lipids, and mixtures force formulators to determine them manually which is both time and resource consuming. In this regard high throughput screening approaches are recommended for identifying the appropriate formulation composition.

Finally, the IVIVC (in vitro in vivo correlation) between formulation and performance in vivo is hard to predict. While this is true for all enabling formulation technologies, it is especially challenging for the liquid-filled formulations that produces supersaturation in vivo which could lead to precipitation and can result in variable exposures. The balance between supersaturation/ precipitation and permeability of the drug becomes critical for this type of formulation and it needs to be further studied.

References