J-STAR RESEARCH, Inc

Process Simplification Series No. 7

Lipid-Based Formulations of Liquid-filled Capsules for Poorly soluble Drugs to Stay Away from Potential Manufacturing Issues of Oral Solid Dosages

Drug Product Group at J-Star Research
drug.product@jstar-research.com

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Process Simplification Series No. 7:

Lipid-Based Formulations of Liquid-filled Capsules for Poorly soluble Drugs to Stay Away from Potential Manufacturing Issues of Oral Solid Dosages

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Outlines:

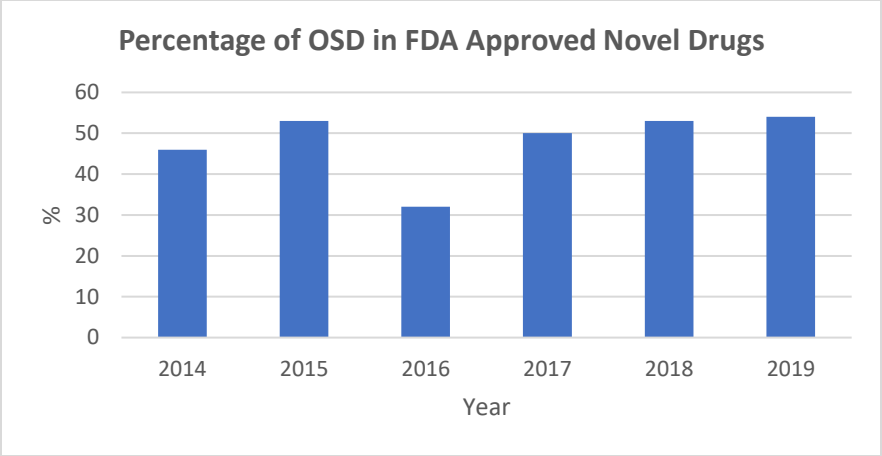
- The reasons of solubilization of drug substances
- The OSD is still a dominant forms of drug products
- Main issues during the manufacturing of OSD
- Solubilized formulations for liquid-filled capsules to get around the OSD manufacturing issues
    - Comparison of performance of OSD vs LBF in poorly soluble drugs
    - Different processing steps, OSD vs LBF, to show the advantages of LBF in simplifying the process and avoid the OSD issues

For a drug substance administered via oral route, it should possess adequately aqueous solubility before passes through the gastrointestinal tract to complete the absorption, and then enters the blood steams for the pharmacological actions. Hence the solubility of a drug substance is one of the most important physicochemical properties to determine the drug's fate to be developed the drug product for clinical applications.

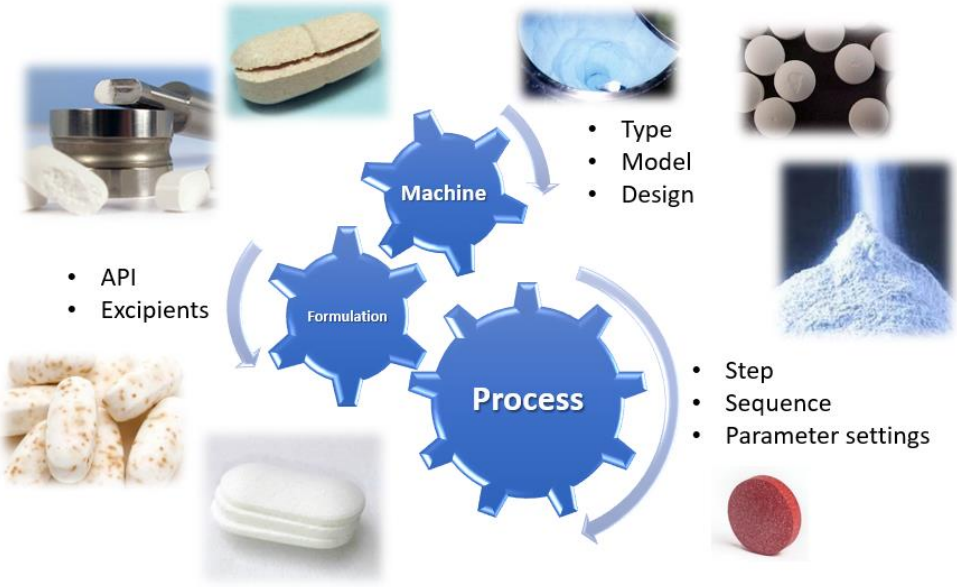
Unfortunately, it has been found that as many as 70% of new chemical entities (NCEs) have poor aqueous solubility. It is a big challenge to deliver this kind of drug candidates to the drug substances and then the drug products. Different drug solubilization approaches have been developed which includes pH control, salt formation, complexation, surfactants, cosolvents, and etc.

Most of these solubilization methods can be used in oral solid dosage form development. However, the lipid-based formulations are a unique approach, which can be in the form of liquid filled capsules, to take advantages over solid dosage forms for patients with difficulty swallowing tablets and capsules and to produce rapid therapeutic effects. Moreover, it simplifies the manufacturing process and stay away from the potential manufacturing issues of oral solid dosage forms.

It is true that oral solid dosage forms dominate the pharmaceutical product market for their advantages in convenience to take and store, easy to administer without professional assistance, economical and safe to the patient. On the other hand, it always a challenge for a formulator while designing and developing the oral solid dosage forms, especially the tablets.



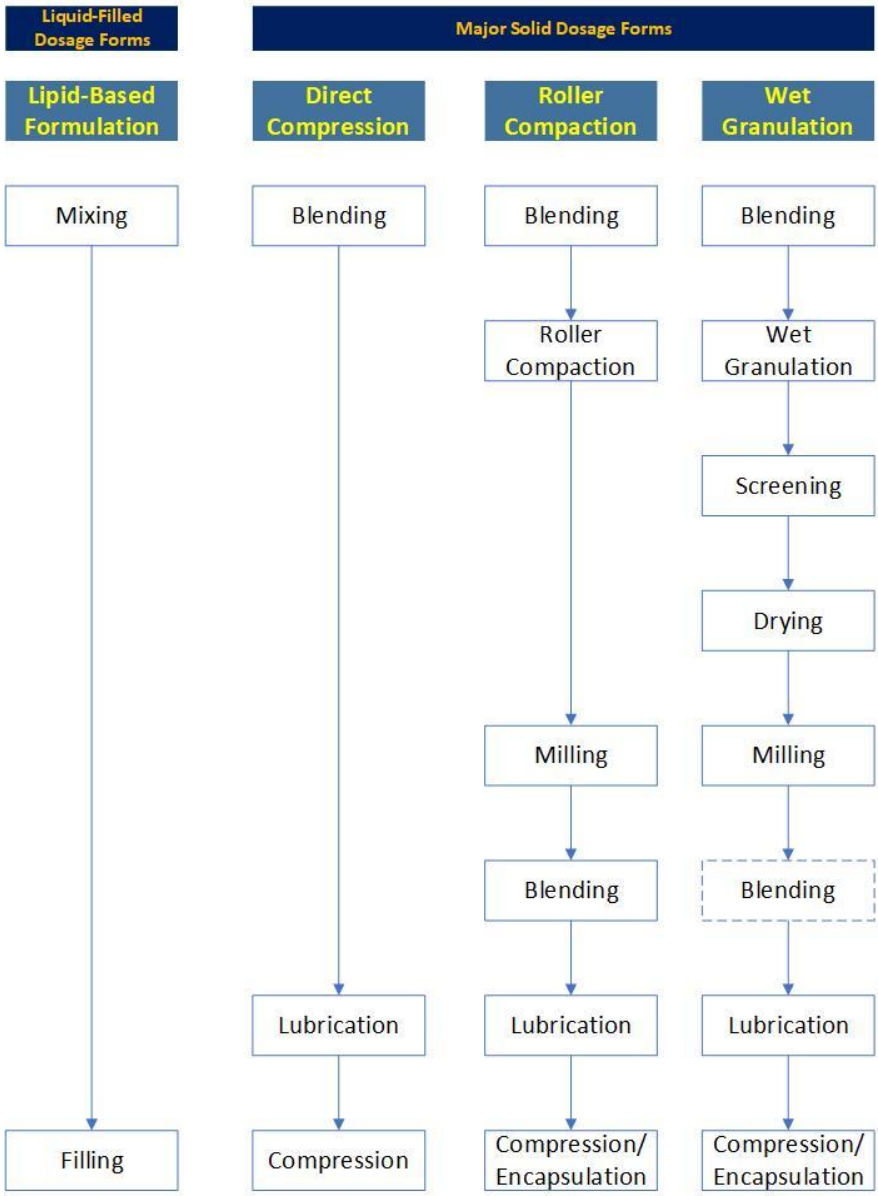
Many technical issues related to the formulation, processing method, and manufacturing equipment settings may occur at the different drug product development stages. Let's take tablets as the example, the common defects of tablets include: capping and lamination, picking and sticking, tablet hardness variation, tablet weight variation, mottling, chipped edge, soft tablet, poor powder flow, etc. Some issues may occur at the early development stage, but sometimes, the issues are batch size and manufacturing time dependent which happen in large or commercial scales—a number of defect samples over the acceptable quality limit (AQL) will cause a failure of a whole batch of manufacturing. According to the specific issues, troubleshooting may lead to reformulation, redevelopment of processing method, and parameters adjustment of processing equipment, which are time, materials, and funds costly.



Common issues in manufacturing processes of oral solid dosage forms

In traditional oral solid dosage form, the processing approaches commonly include: blending, dry/wet granulation (with screening, milling and/or drying), lubrication, and tablet compression or encapsulation. Direct compression can eliminate the granulation step. But considering the drug solubilization approaches, the entire processing steps should be more complicated than traditional ways. The details of the solubilization approaches will be introduced in other tech bulletins.

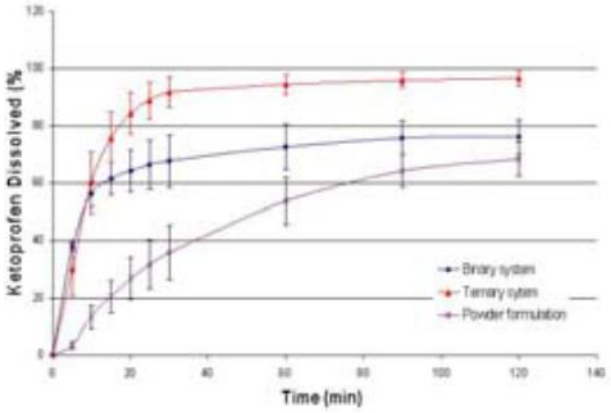
In contrast, liquid filled capsules, lipid-based formulations as an example, can take all the advantages of the oral solid dosage forms, at the same time, due to the unique formula and simplified preparation, it can avoid the potential manufacturing issues occurred in traditional tablets and capsules. The manufacturing processes will be very simple and straight forward: mixing the drug substance with the selected liquid system (see figure below), and encapsulating the drug solution to liquid-filled capsules to satisfy the quality target profile of the drug product.



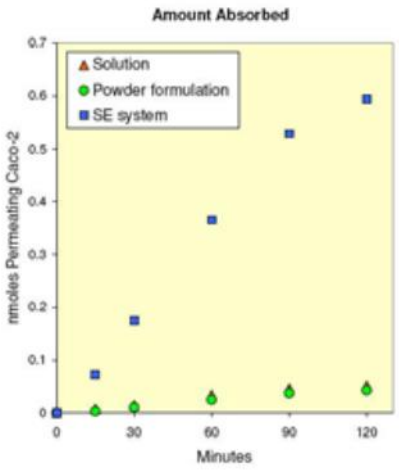
Comparison of manufacturing Processes of liquid-filled capsules and most solid dosage forms

Here is an example of a liquid filled capsule self-emulsifying system developed by A. Igonin and colleagues from Capsugel. Ketoprofen was used as the model drug which is a class II active compound with a LogP at 3.12, and has a low solubility (0.06 µg/mL in pH 1.2 buffer) and a high apparent permeability (> 1 × 10-6 cm/s). In their study, the developed ternary self-emulsifying system and binary self-emulsifying system were compared to the conventional powder filled capsule.

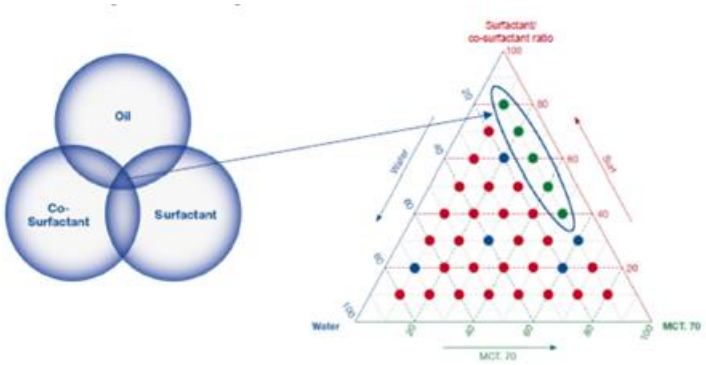
A significant improvement of the dissolution rate was seen in both liquid-filled self-emulsified formulations compared to the conventional powder formulation. And the ternary formulation is even better than the binary formulation.



The evaluation on Caco-2 cells showed a significant increase in the absorption of ketoprofen.



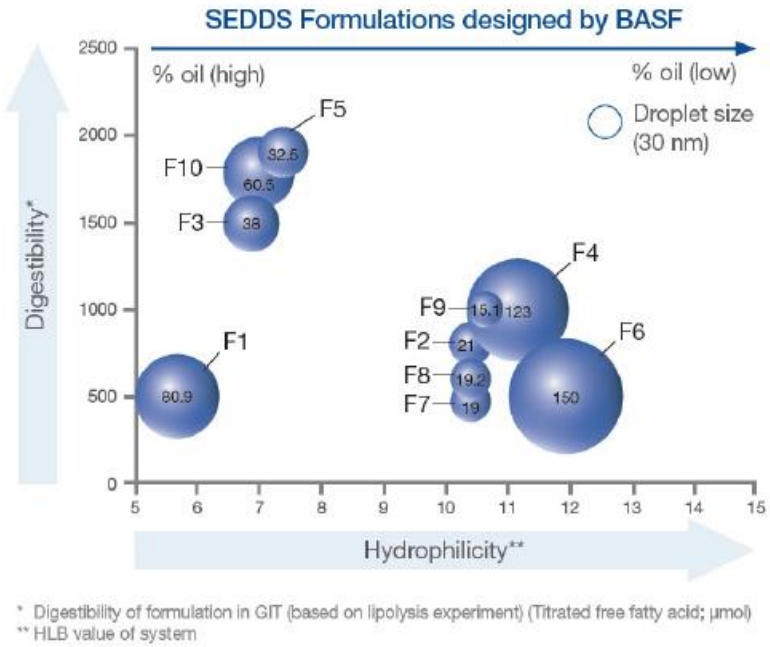
Typically, a drug substance specified homogeneous monophasic liquid system consisted of various lipid-based excipients is built up based on the drug's aqueous solubility, logP, and the solubility in the lipid-based excipients. This kind of lipid-based excipients normally include surfactants, cosurfactants, solvents and/or cosolvents.



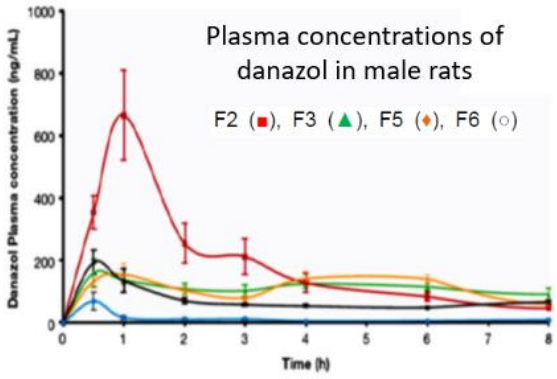
Components and screening of solubilization formulations using a ternary system (cited from BASF)

The biggest challenge is to screen the lipid-based excipients and find the optimized liquid system for the specific drug substance. Starting with the 10 lipid-based solubilization formulations for poorly soluble drugs below, the solubilization system screening work becomes much easier.

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Kollisolv MCT 70		x	x	x	x	x			x	x
Soybean Oil	x						x			
Maisine 35-1	x									
Corn Oil								x		
Glycerol Monocaprylocaprate									x	x
Kolliphor RH 40	x	x	x				x	x	x	x
Kollisolv P124						x				
Kolliphor EL				x	x					
Glyceryl Monooleate		x	x	x	x	x	x	x		
Water		x	x	x	x		x	x	x	x
Ethanol	x					x				



After evaluating the solubilization performance and stability of the drug candidate, a suitable solubilization liquid system is selected for desirable therapeutic outcome. Below is an example of in vivo performances of danazol prepared with SEDDS formulations by BASF.



For decades, lipid-based formulations, especially the self-emulsifying drug delivery systems, have been shown to significantly enhance the oral bioavailability of poorly water-soluble drugs via several mechanisms.

Overall, there is a rising tendency for liquid filled formulation. Europe is the leader in LFHC technology with a 20 percent annual growing rate. In the US, it is commonly found in the dietary supplement products, but expected to see more in pharmaceutical industry for it potentially satisfies therapeutic needs that solid dosage form cannot.

References:

1. Developing solid oral dosage forms: Pharmaceutical theory and practice. Y. Qiu et al, Academic Press, 2009.
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