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Lipid-Based Formulations for Early-Stage Clinical Trials
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A large majority (80% or more) of drug candidates currently under development are poorly water-soluble and experience bioavailability challenges, leading to difficulties in drug product formulation. Drug developers today also face accelerated development timelines, often due to specialized medicines and regulatory pathways such as orphan drugs, break-through and fast-track designations and NDA 505(b)2 programs. Both of these challenges are especially pressing for small or emerging pharma and biotech companies, which tend to lack resources in-house for bioavailability enhancement or rapid drug development.

Several technologies, including particle size reduction and nano-milling, salt formation, amorphous solid dispersions and lipid-based drug delivery systems, have extensive track records in enhancing oral bioavailability. These technologies can also be used in the context of accelerated drug development. But not all technologies are appropriate for all molecules, and developers can benefit from avoiding spending time and API testing different technologies.

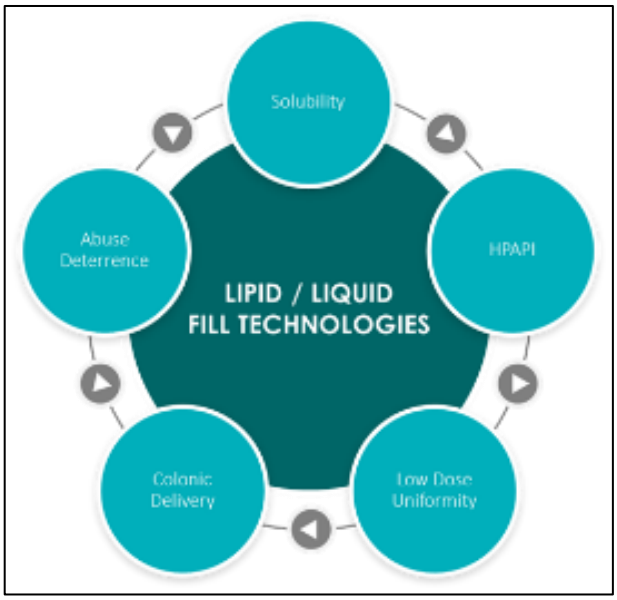
The choice between enabling technologies depends on physicochemical and biologic parameters, as well as the target product profile of the candidate drug. One effective approach to technology selection relies on using in silico and in vitro formulation and testing methodologies that are highly correlated to in vivo performance. Such R&D-derived capabilities may help drug developers quickly and accurately select the most effective bioavailability-enhancing technologies for candidate molecules, avoiding a lengthier trial-and-error approach. For certain molecules, the most appropriate technology for bioavailability enhancement and accelerated development will be lipid-based formulations (LBF), supported by in silico development tools.

When are lipid-based formulations the appropriate technology?

Lipid-based formulations are widely used in drug development to improve the oral absorption of Biopharmaceutical Classification System (BCS) Class II or IV molecules, which have a high/low permeability and a low aqueous solubility, respectively. The use of LBFs can aid development of “grease ball”-type molecules that exhibit slow dissolution and poor oral absorption, by retaining them in a solubilized state during gastrointestinal transit.

In addition to improving drug solubilization, LBFs can also increase drug absorption for “grease ball”-type compounds by circumventing the drug dissolution step, recruiting endogenous solubilizers to effectively shuttle the drug to the absorption site and by promoting the uptake of certain drugs into the lymphatic system. Moreover, lipid- and liquid-based formulations are highly versatile (see Figure 1) and can provide acceptable content uniformity of high-potency/low-dose drugs, achieve a fast onset of action, prevent interaction with food, reduce inter-/intrahuman variability, produce modified/targeted release profiles or use a combination of these qualities to meet market and patient needs.

Figure 1: Potential benefits of lipid-based formulations



The Lipid Formulation Classification System (LFCS) classifies LBFs into four main types based on the relative proportions of included lipids, surfactants and co-solvents (see Figure 2). Type I formulations, due to their rich content of lipids, require digestion to allow for dispersion into intestinal fluids, whereas Type II-IV contain sufficient surfactants to promote spontaneous dispersion. Increasing quantities of surfactants and co-solvents in Type IIIB & IV usually increase the potential for drug loading since, with the exception of the most lipophilic drugs, the majority of poorly water-soluble drugs are more soluble in surfactants and co-solvents than in glyceride lipids.

Figure 2: Lipid Formulation Classification System

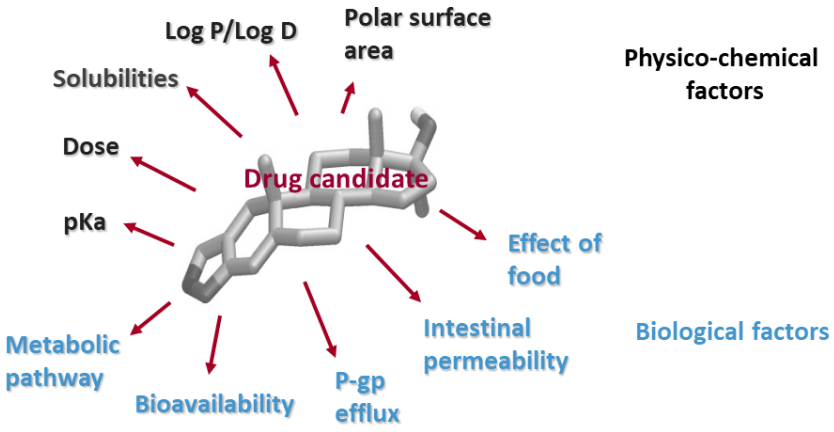
	Type I Oils e.g. Prometrium®	Type II SEDDS e.g. Roaccutane®	Type IIIA and IIIB SEDDS/SMEDDS e.g. Neoral®, Gengraf®	Type IV Lipid-free e.g. Prograf®
	Lipids, no surfactant	No water-soluble components	Includes lipids and water-soluble surfactants and possibly co-solvents	Comprises only water-soluble surfactants and co-solvents
Physical performance criteria	No/limited dispersion	Emulsion	IIIA: Fine emulsion IIIB: Transparent dispersion	Micellar solution
Biological performance criteria	Requires digestion	Will be digested	Digestion may not be necessary	Limited digestion

A Lonza analysis of the physicochemical and biological parameters and the available in vitro/in vivo data generated from 20 New Chemical Entities (NCEs) over a decade confirmed that Type IV LBFs' typical attributes, including a molecular weight of 400-750 g/mol, a cLog P of 3 or higher, a high permeability and a polar surface area, in almost all cases, of less than 100 Å², can significantly increase molecules' oral bioavailability.

Using in silico methods to accelerate LBF development

Developing a robust LBF that helps shorten development timelines depends on the candidate's physicochemical and biopharmaceutical drug properties, as well as its Target Product Profile (TPP), which refers to the desired characteristics of the drug being developed. The use of digital tools, databases and in silico analysis is increasingly important for rapid LBF development. The analysis process involves understanding the underlying drug-LBF structure at the molecular scale, as well as extensive knowledge of lipidic excipients and their behavior in the gastrointestinal tract. Other aspects like manufacturing, compatibility, stability and regulatory acceptance also need to be considered at the early stage of development.

Figure 3: Key physicochemical and biopharmaceutical factors of drugs for LBF development



The first step is drug selection, which refers to evaluating the drug molecule in relation to its stability, physicochemical and biopharmaceutical properties (Figure 3). This assessment, along with the TPP, can be used to develop the initial framework of the LBF design approach. The next step is consideration of appropriate excipients from a wide range of oils, surfactants, co-surfactants and co-solvents, based on their structures and properties, regulatory acceptance for oral delivery and commercial availability. Lipid excipients with high affinity and solubility for the drug product tend to be effective.

The development then progresses into testing a series of LBF compositions, the step where in silico methods play the largest role. A software platform such as Lipidex® , Lonza's library management and data-processing tool for lipids, can help speed the transition from excipient screening into the development phase. Lipidex® and in silico tools can also help sidestep a time-intensive trial-and-error approach that would otherwise involve screening dozens of different formulation compositions. The Lipidex® tool contains hundreds of phase diagrams for one-, two- or three-excipient LBFs and, based on a series of drug-specific inputs, can rapidly identify candidate LBFs that meet criteria such as the target LBF dispersibility (i.e., microemulsion), the ability to solubilize the target dose and/or percentage of excipients known to inhibit intestinal efflux transporters. The subsequent LBF experimental testing phase will consist of evaluating the pre-selected LBF compositions, namely formulation performance, stability and processability.

The primary goal of in silico testing during early LBF development is to evaluate the properties of the LBF and the fate of the drug following oral administration, rather than mimic in vivo performance. This may be achieved through a combination of in vitro dispersion tests (in conditions simulating the fasted/fed stomach) and digestion tests (in conditions simulating the upper small intestine). The findings are used to identify the formulation compositions that match it most closely.

Figure 4: Digital tools and databases: Molecular Dynamic Simulations (MDS) and in silico tools (Lipidex®)

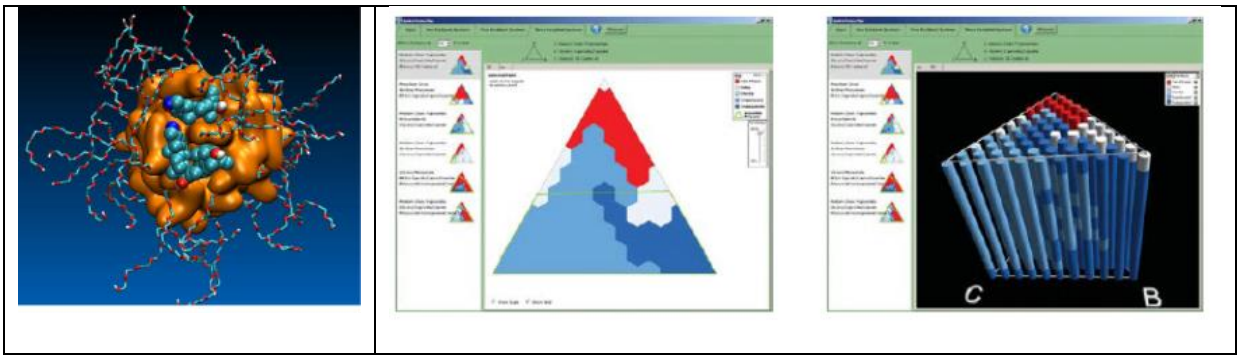
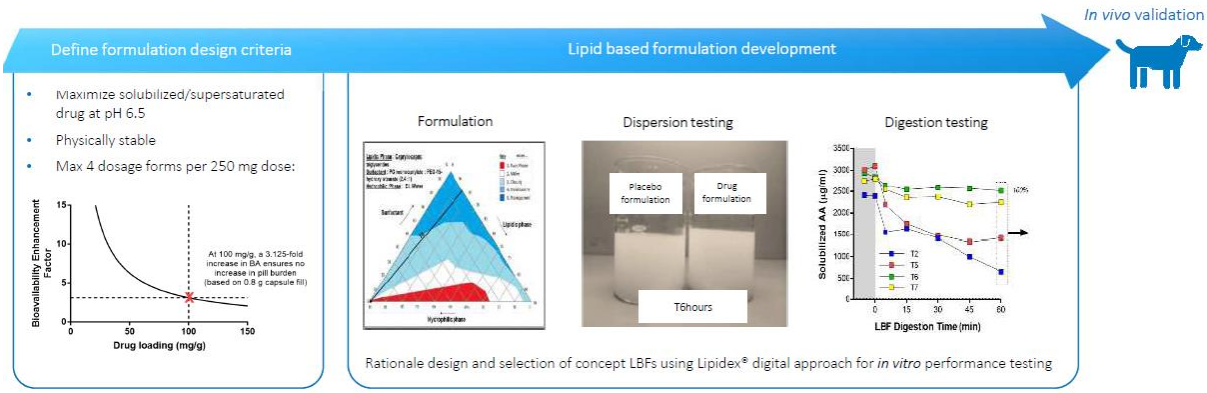


Figure 5: Overview of a rational approach to formulation development



The future of LBF development

For pharmaceutical and biotech leaders evaluating more and more low-solubility molecules with a growing focus on rapid development, lipid-based formulations can be a helpful tool. A rational approach to technology selection is critical to use time and resources optimally. LBF technology advancements and formulation guidance tools such as Lipidex® can shorten timelines and increase the success rate in reaching the TPP in early development.

In the future, lipid-based formulations will remain an important tool for bioavailability enhancement of certain molecules. Contract development & manufacturing organizations can help pharmaceutical & biotech companies with limited internal expertise and/or resources for drug development and manufacturing advance bioavailability-challenged molecules and meet their development timelines.

To learn more, please visit our website.

References

[1] Lonza webinar titled “Lipid-based formulations for early stage clinical trials”- November 2019

[2] H.D. Williams, N.L. Trevaskis, S.A. Charman, R.M. Shanker, W.N. Charman, C.W. Pouton, C.J. Porter, Strategies to address low drug solubility in discovery and development, Pharmacological Reviews, 65 (2013) 315-499.

[3] R. Holm, Bridging the gaps between academic research and industrial product developments of lipid-based formulations, Advanced Drug Delivery Reviews, 142 (2019) 118-127.

[4] O.M. Feeney, M.F. Crum, C.L. McEvoy, N.L. Trevaskis, H.D. Williams, C.W. Pouton, W.N. Charman, C.A. Bergström, C.J. Porter, 50 years of oral lipid-based formulations: provenance, progress and future perspectives, Advanced Drug Delivery Reviews, 101 (2016) 167-194.

[5] D.J. Hauss, Oral lipid-based formulations, Advanced Drug Delivery Reviews, 59 (2007) 667-676.

[6] J. LaFountaine, P. Gao, R.O. Williams III, Lipid-Based Formulations, in: R.O. Williams III, A.B. Watts, D.A. Miller (Eds.) Formulating poorly water soluble drugs, Springer 2012, pp. 295-382.

[7] H. Williams, M. Morgen, E. Jule, J. Vertommen, H. Benameur, D. Friesen, D. Vodak, Science-Based Technology Selection And Formulation Development For Oral Bioavailability Enhancement.

[8] E.T. Cole, D. Cadé, H. Benameur, Challenges and opportunities in the encapsulation of liquid and semi-solid formulations into capsules for oral administration, Advanced Drug Delivery Reviews, 60 (2008) 747-756.

[9] R.G. Strickley, R. Oliyai, Solubilizing vehicles for oral formulation development, Solvent systems and their selection in pharmaceutics and biopharmaceutics, Springer2007, pp. 257-308.

[10] A. Igonin, J. Vertommen, H. Benameur, Physical and biological parameters of poorly bioavailable compounds that influence the development of lipid-Based Oral Drug Delivery Systems, Annual Academy of Pharmaceutical Scientists Annual Chicago, 2012.

[11] C.W. Pouton, C.J. Porter, Formulation of lipid-based delivery systems for oral administration: materials, methods and strategies, Advanced drug delivery reviews, 60 (2008) 625-637.

[12] E. Jule, Accelerating Lipid-Based Drug Formulation Through Application of an Expert System, Capsugel White Paper, 2013.

[13] H.D. Williams, E. Jule, A. Igonin, H. Benameur, Drug permeability and metabolism for in silico formulation of lipid-based systems, Annual Academy of Pharmaceutical Scientists Annual Meeting San Antonio, 2015.

[14] H.D. Williams, P. Sassene, K. Kleberg, M. Calderone, A. Igonin, E. Jule, J. Vertommen, R. Blundell, H. Benameur, A. Müllertz, C.J. Porter, C.W. Pouton, Toward the Establishment of Standardized In Vitro Tests for Lipid-Based Formulations, Part 15: Proposing a New Lipid Formulation Performance Classification System, Journal of Pharmaceutical Sciences, 103 (2014) 2441-2455.