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Pharma & Biotech

Technology Selection for Bioavailability Enhancement

The increasing prevalence in pharmaceutical pipelines of active compounds with low solubility has led to the proliferation of approaches to increase oral drug absorption and bioavailability. Selection of the proper technology can make the difference between development success or failure.

Technology Selection for Bioavailability Enhancement

Careful selection of the right technology to enhance bioavailability and oral drug absorption is essential in development programs from initial preclinical phases to commercialization. A science-based technology selection process is presented, based on a series of inputs including the target product profile, drug properties, extensive past project experiences, technology maps, and absorption modeling.

Introduction

Due to the growing incidence of compounds with low solubility in the pharmaceutical discovery and development pipeline, the number of enabling technologies that are employed to improve oral drug absorption and bioavailability (BA) is also growing. Commonly used technologies in this area have been extensively reviewed,[1] and include salts, cocrystals, amorphous solid dispersions, nano- and microcrystals manufactured by particle size reduction, cyclodextrin complexation, and lipid-based technologies.

Many of these technologies have been shown to enhance drug BA, but the most notable commercial products are those that utilize lipid-based technologies, amorphous solid dispersions, and nanocrystals: e.g., Neoral® (cyclosporine, Abbott), a liquid-filled capsule; Zepatier® (grazoprevir and elbasvir, Merck) and Simpirica (sarolaner, Zoetis), amorphous solid dispersions produced by spray drying for human and animal health, respectively; Kaletra® (lopinavir and ritonavir, Abbott), an amorphous drug dispersion produced by hot-melt extrusion (HME); and Emend® (aprepitant, Merck), a nanocrystal-containing tablet. The commercial precedence of these key enabling technologies supports their continued utilization in addressing the estimated 40% to 70% of the New Chemical Entity (NCE) development pipeline candidates that are regarded as poorly water-soluble. Enabling technologies are also widely explored in the 505(b)(2) product pathway to reformulate existing products on the market into products that are better performing (e.g., "supergenerics") or during the product patent life through life-cycle management approaches. Economic benefits are increasingly driving interest in the 505(b)(2) regulatory pathway, and include faster time to market, lower development costs by avoiding certain costly and repetitive preclinical and clinical trials, and 3 to 5 years of market exclusivity depending on the extent of change to the previously approved drug. One example of a marketed 505(b)(2) product is the lipid-formulation-containing hard capsule product Absorica™ (Ranbaxy), which provides higher drug absorption in the fasted state than the original Roaccutane®/Accutane® (Roche) products, thus offering consumers the potential to benefit from acne treatment independently from meals[2] and granting Ranbaxy the aforementioned commercial benefits.

Due to their wide applicability, from NCEs to off-patent drugs, the enabling technology field is innovative, dynamic, and highly competitive. Indeed, the prevalence of poorly soluble drugs in the development pipeline is a key focus for many contract research/development and manufacturing organizations (CRO/CDMO), supporting

[1] Williams, H.D., N.L. Trevaskis, S.A. Charman, R.M. Shanker, W.N. Charman, C.W. Pouton, and C.J. Porter, "Strategies To Address Low Drug Solubility in Discovery and Development." *Pharmacol. Rev.,* 65:315-499 (2013).

[2] Webster, G.F., J.J. Leyden, and J.A. Gross, "Comparative Pharmacokinetic Profiles of a Novel Isotretinoin Formulation (Isotretinoin-Lidose) and the Innovator Isotretinoin Formulation: A Randomized, 4-Treatment, Crossover Study." *J. Amer. Acad. Dermatol.,* 69:762-767 (2013).

drug development work with one or more BA enhancing technology approaches to advance such drug candidates. A much smaller number of companies have a broad range of technologies and/or the capacity to support these technology efforts from design and development to commercial-scale production. This latter point is particularly important as the need to partner with multiple companies during a drug development program can introduce complexity and risk into the development process, resulting in significant delays and additional costs in transferring technologies and knowledge. This can be critical in today's drug development environment, where 70% to 80% of investigational new drugs (INDs) are held by small biopharma firms that often do not have the in-house capabilities to develop and manufacture drug-product intermediates or drug products.[3]

Those working in the field will, of course, recognize several important facts.

- The diverse needs of all drug compounds currently in development across and within pharmaceutical companies cannot be addressed by a single enabling technology.

- Development success is more probable if a technology is appropriately matched to the compound properties and product needs.

- In many cases, more than one technology can be utilized successfully, and commercial considerations such as desired dosage format (e.g., tablets versus capsules) can play a decisive role.

In other words, programs where a technology approach does not best suit the compound are more likely to falter in their progression due to feasibility/stability/scalability reasons or due to poor *in vivo* biopharmaceutical performance. Unfortunately, this is a common occurrence and highlights the clear need for appropriate technology selection to increase the level of success during drug development, particularly when absorption is low in the absence of an enabling technology. While often sought, effective technology selection can remain elusive since it relies on many inputs, not least of which is access to alternative or complementary technologies and a clear understanding of the science governing the mechanisms of drug solubilization, absorption, and metabolic fate.

The purpose of this article is to highlight key physicochemical and biological obstacles to drug exposure following oral intake and then describe how a technology selection process factors in these basic properties. We will then discuss the technology selection tools that have been developed from a deep investigation of key technologies and leveraging experience of hundreds of BA enhancement projects

Physicochemical obstacles to BA

Physicochemical obstacles to oral drug BA include low aqueous solubility (a thermodynamic and form-dependent property) and a slow rate of dissolution (a kinetic property). Low drug solubility can limit the maximum drug concentration that can be obtained in the small intestine (the primary site for drug absorption) and, therefore, drug absorption since a high concentration gradient between drug in the intestinal lumen and drug in the intestinal wall is needed to drive passive diffusion to (through the unstirred aqueous mucus layer) and across the intestinal membrane. A slow dissolution rate is nearly always associated with low drug solubility, but is compounded in instances where drug surface area and/or diffusion rates are also low. A slow dissolution rate can also limit absorption, particularly where the solubility of the drug form so low that the concentration of drug must be maintained near its solubility limit for drug absorption to be complete over the limited time that the drug transits the GI tract.

Low drug solubility is a property common to drugs that are Class II and IV of the Biopharmaceutical Classification System (BCS). Factors underpinning the property of low solubility are well described[4] and include

- a high crystal lattice energy, which generally increases with increasing melting temperature (T_m) of a compound;

- a low energy of aqueous solvation, which generally decreases with increasing Log P value of a compound (i.e., lipophilicity)—often referred to as "grease-ball" compounds; and

- a combination of both, where the impact of a high crystal energy on solubility is exacerbated by a low

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3   Citeline and internal Lonza analysis (2019).

4   Grant, D., and T. Higuchi, *Solubility Behavior of Organic Compounds.* Wiley-Interscience, New York, 1990.

solvation energy—often referred to as "brick-dust" compounds.

Through an appreciation of these obstacles, it is possible to rationalize the principal means by which enabling technologies increase solubility and dissolution rate— namely by either reducing the drug lattice energy, increasing available drug surface area, or increasing the energy of solvation. For example, lipids, surfactants and cosolvents increase the volume and character of hydrophobic microphases of GI fluids, such as vesicles and micelles. Most low-solubility compounds have much more favorable intermolecular interactions with such hydrophobic colloids, leading to increased drug solubilization in the GI fluids.

To elucidate this distinction, Figure 1 provides a simplified separation of key enabling technologies according to the primary mechanisms of solubility/dissolution rate enhancement. For example, nanocrystals increase dissolution rate by increasing the available surface area of drug and, potentially, by increasing drug solubility if particles are <100 nm in diameter and/or show some change in crystalline structure, particularly at the crystal surface. Spray drying and HME solid dispersion approaches increase apparent drug solubility and, therefore, dissolution rate by isolating the higher-energy amorphous form, showing reduced solid-state obstacles to solubility, which is maximized in instances where a drug is dispersed in a matrix material at a molecular level.[5] On the other hand, lipid-based technologies are effective in augmenting drug solubility as dispersed and digested lipid components mix with endogenous bile salts and phospholipids to form a range of colloidal species. (i.e., "like dissolves like").[6]

In many cases, however, clear distinctions cannot be made because some technology approaches have the capacity to increase drug solubility through both solid-state and solvation effects: e.g., salts and cocrystals where the introduction of a counterion or conformer (respectively) can alter the solid-state energy (by changing molecular packing in the crystal) and solvation energy (by changing the nature of the local solvent [e.g., pH in the case of a

salt counterion] or by changing the drug to the ionized form) to increase solubility. In addition, solid dispersions that utilize amphiphilic polymer materials such as hydroxypropyl methylcellulose acetate succinate (HPMCAS)[7] or nonionic surfactants[8] may also affect solvation, while predissolving a drug within a lipid-based formulation will eliminate the solid-state-related obstacles to solubility and dissolution and, if properly formulated, will maintain the compound in solution throughout the GI tract (albeit, with a high proportion of the drug solubilized in a colloidal state rather than in the aqueous phase of the GI fluid).

Figure 1 is an attempt to match compound solubility/dissolution obstacles to a respective formulation technology. Where low solubility stems primarily from a high crystal lattice, solubility will benefit most from a reduction in solid-state interactions (e.g., solid dispersions), whereas those compounds that show limited affinity for aqueous solvents would benefit most from approaches that enrich the GI environment with exogenous solubilizers (e.g., lipid-based formulations). This relatively simple differentiation is simply based on the physicochemical properties of the drug.
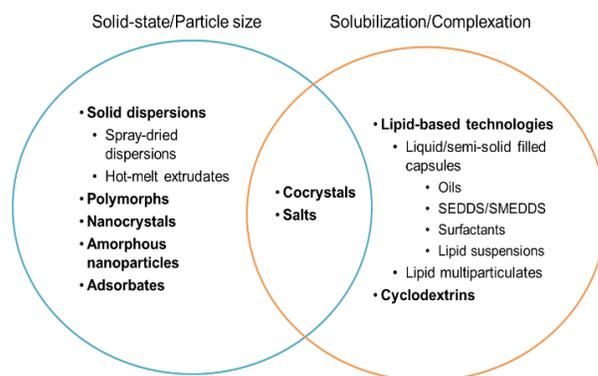
Figure 1
Simplified diagram illustrating the principal mechanisms by which various enabling technologies increase drug solubility/dissolution rate to likely enable faster and more successful development with reduced costs to lead to improved oral absorption. See the supporting text for a more detailed description of some of these enabling technologies.

[5]   Leuner, C., and J. Dressman, "Improving Drug Solubility for Oral Delivery Using Solid Dispersions." *Eur. J. Pharm. Biopharm.,* 50:47-60 (2000).

[6]   Porter, C.J.H., N.L. Trevaskis, and W.N. Charman, "Lipids and Lipid-Based Formulations: Optimizing the Oral Delivery of Lipophilic Drugs." *Nature Rev. Drug Disc.,* 6:231-248 (2007).

[7]   Friesen, D.T., R. Shanker, M. Crew, D.T. Smithey, W. Curatolo, and J. Nightingale, "Hydroxypropyl Methylcellulose Acetate Succinate-

Based Spray-Dried Dispersions: An Overview." *Mol. Pharm.,* 5:1003-1019 (2008).

[8]   Sjökvist, E., C. Nyström, M. Aldén, and N. Caram-Lelham, Physicochemical Aspects of Drug Release. XIV. The Effects of Some Ionic and Non-Ionic Surfactants on Properties of a Sparingly Soluble Drug in Solid Dispersions." *Int. J. Pharm.,* 79:123-133 (1992).

Biological obstacles to BA

In some cases, overcoming the physicochemical obstacles to low absorption may not yield the level of BA that is desired. In these cases, biological obstacles to exposure may be apparent, which are known[9] and include

- efflux of absorbed drug back into the intestinal lumen (often P-gp or BCRP transporter mediated),

- presystemic drug metabolism in the intestine (principally via cytochrome P450 enzymes), and

- extensive hepatic first-pass drug metabolism.

A good example highlighting the possibility of achieving high drug absorption yet low BA is testosterone. Despite its low relatively low aqueous solubility (<25 μg/ml), testosterone is well absorbed from the intestine, but shows extremely low BA following extensive first-pass metabolism.[10] Thus, extensive formulation work may be undertaken to improve drug physicochemical properties in an attempt to improve intestinal absorption only for intrinsic biological processes to render the drug still poorly bioavailable.

Critically in the context of this article, certain enabling technologies may have the capacity to attenuate these biological obstacles to BA, particularly by reducing efflux and metabolism in the intestine. Indeed, fatty acids and nonionic surfactants (typically, polyethoxylated esters/ethers of oils/fatty acids) commonly used in lipid-based technologies have frequently been shown to inhibit

P-gp and BCRP efflux transporters in intestinal cell models[11] or increase transcellular permeability,[12] with evidence that these effects may also manifest *in vivo,* leading to higher drug exposure.[13] These same excipients are also increasingly implicated in the inhibition of a variety of cytochrome P450 enzymes that have the potential to metabolize drug in the intestinal wall.[14,15]

Beyond events in the enterocyte, there is a possibility that a lipid-based enabling technology may, for highly lipophilic drugs, increase the fraction of absorbed drug that enters the lymphatic system, where hepatic metabolic pathways are avoided.[16,17] For example, the undecanoate ester of testosterone exhibits much lower aqueous solubility than the native form (<1 ng/ml versus ~25μg/ml) yet demonstrates higher oral BA due to a greater lipophilicity and a greater propensity to enter the systemic circulation via the lymphatic system particularly when formulated as a lipid solution[18] (Andriol Testocaps®). Indeed, lipidic excipients have repeatedly been shown to increase the BA of highly lipophilic drugs (i.e., those with Log D values >5 and solubility in long-chain triglycerides >50 mg/g) via the lymphatic system.[19]

Certain enabling technologies, particularly lipid-based formulations, therefore have the capacity to address both physicochemical and biological obstacles to achieving satisfactory drug exposure. This highlights the value of understanding what factors limit the absorption of the compound of interest and impartially selecting an appropriate technology, particularly when biological

9   Wuand, C.-Y., and L.Z. Benet, "Predicting Drug Disposition Via Application Of BCS: Transport/Absorption/Elimination Interplay And Development Of A Biopharmaceutics Drug Disposition Classification System." *Pharm. Res.,* 22:11-23 (2005).

10 Täuber, U., K. Schröder, B. Düsterberg, and H. Matthes, "Absolute Bioavailability of Testosterone After Oral Administration of Testosterone-Undecanoate And Testosterone." *Eur. J. Drug Metab. Pharmacokinet.,* 11:145-149 (1986).

11 Yamagata, T., H. Kusuhara, M. Morishita, K. Takayama, H. Benameur, and Y. Sugiyama. "Improvement of the Oral Drug Absorption of Topotecan through the Inhibition of Intestinal Xenobiotic Efflux Transporter, Breast Cancer Resistance Protein, by Excipients," *Drug Metab. Dispos.*, 35:1142-1148 (2007).

12 Aungst, B.J., "Absorption Enhancers: Applications and Advances," *AAPS J.,* 14:10-18 (2012).

13 Martin-Facklam, M., J. Burhenne, R. Ding, R. Fricker, G. Mikus, I. Walter-Sack, and W.E. Haefeli, "Dose-Dependent Increase of Saquinavir Bioavailability by the Pharmaceutic Aid Cremophor EL." *Br. J. Clin. Pharmacol.,* 53:576-581 (2002).

14 Christiansen, A., T. Backensfeld, K. Denner, and W. Weitschies. Effects of Non-Ionic Surfactants on Cytochrome P450-Mediated Metabolism *In Vitro*." *Eur. J. Pharm. Biopharm.,* 78:166-172 (2011).

15 Mountfield, R.J., S. Senepin, M. Schleimer, I. Walter, and B. Bittner, "Potential Inhibitory Effects of Formulation Ingredients on Intestinal Cytochrome P450." *Int. J. Pharm.,* 211:89-92 (2000).

16 Noguchi, T., W.N.A. Charman, and V.J. Stella, "The Effect of Drug Lipophilicity and Lipid Vehicles on the Lymphatic Absorption of Various Testosterone Esters." *Int. J. Pharm.*, 24:173-184 (1985).

17 Shackleford, D.M., W.A. Faassen, N. Houwing, H. Lass, G.A. Edwards, C.J.H. Porter, and W.N. Charman, "Contribution of Lymphatically Transported Testosterone Undecanoate to the Systemic Exposure of Testosterone after Oral Administration of Two Andriol Formulations in Conscious Lymph Duct-Cannulated Dogs." *J. Pharmacol. Exp. Therapeut.,* 306:925-933 (2003).

18 Nieschlag, E., J. Mauss, A. Coert, and P. Kićović, "Plasma Androgen Levels In Men After Oral Administration of Testosterone or Testosterone Undecanoate." *Acta Endocrinol.,* 79:366-374 (1975)

19 Trevaskis, N.L., W.N. Charman, and C.J.H. Porter. "Lipid-Based Delivery Systems and Intestinal Lymphatic Drug Transport: A Mechanistic Update." *Adv. Drug Delivery Rev.,* 60:702-716 (2008).

processes may limit the overall gain in exposure using technologies that affect only drug solubility and dissolution.

Defining the product needs

Besides physicochemical and biopharmaceutical properties of a compound, a number of other considerations typically affect technology selection for a particular application, including target dose, preferred final dosage form and size, frequency of administration, specific storage and/or packaging requirements, excipient acceptance, and potential intellectual property rights (IPR). In some cases, these factors play an important part in the technology selection process. It is, however, important to note that many if not all of these "technology restraints" can often be identified before development work is initiated, and such considerations can therefore prove valuable by reducing the risk of pursuing certain technologies that are later deemed to be unsuitable.

Technology selection in BA enhancement

Lonza's Dosage Form and Delivery Solutions offers development capabilities (GMP/non-GMP) in amorphous spray-dried dispersions (SDDs), hot melt extrudates, nanocrystals, and liquid/semisolid filled capsules, and multiparticulates utilizing lipid-based technologies. Each of these enabling technologies has proven capacity to increase drug absorption and BA via several different mechanisms, which have been deeply investigated and form the basis of our technology selection process and tools. Collectively, the utility of these respective technologies now covers a broad space in terms of drug properties and target performance. A broad range of complementary technologies and capabilities is critical for optimal drug development, enabling both impartiality and flexibility in selecting the optimal technology platform for a particular compound.

The technology selection process is governed by multiple inputs (shown in Figure 2) to ensure that an informed decision is made for each new compound and associated target product profile. Ensuring that a particular technology is well matched to a drug compound enables easier feasibility assessment, better performance *in vivo*
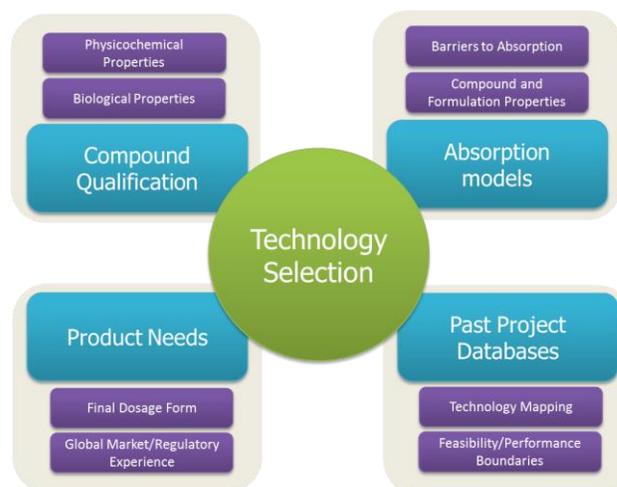
Figure 2
Schematic summarizing the various inputs required for optimal enabling technology selection

of early concept formulations, and ultimate success in reaching the target product profile.

As evident from Figure 2, this selection process considers the overall product needs. Robust dialogue with customers is needed to ensure that this input receives a sufficient amount of attention. Aspects that require consideration here will include the target dose and client expectations concerning the final dosage form size, shape, appearance, and packaging. These discussions are critical to technology selection, as well as preclinical and early clinical development, since they may affect critical elements of ultimate success, such as compliance. Within Lonza, such discussions are greatly supported by experience developing formulations in the North America, Europe, and Asia, across which there may be significant variation in both regulatory requirements and patient preferences. Technology selection should also draw upon compound-specific elements in the Compound Qualification input area of Figure 2—that is, a consideration of all drug physicochemical and biological properties that may constitute obstacles to drug BA and those properties that experience has taught are essential to feasibility and scale-up of robust SDD, HME, nanocrystal, and lipid-based technologies. Again, essential to the collection of these properties is an effective dialogue and exchange of information, and, if needed, access to *in silico* tools that may be used to predict how certain compound properties (e.g., Log P and solubility)

are expected to impact performance, although experimental measurements are always preferred.

From a fundamental understanding of enabling technologies and past development work, two additional dimensions have been introduced to the technology selection process: predictive physiological-based pharmacokinetic models and technology maps.

First, physiologically based pharmacokinetic (PBPK) models are useful for evaluating hypotheses about barriers to absorption, whether that is dissolution rate, solubility and/or permeability. A formulator can use absorption modeling to understand existing *in vivo* data for a formulation of interest or establish a framework for predicting *in vivo* performance with existing *in vitro* data. These models may also be useful for predicting specific formulation attributes from enabled formulations (e.g., amorphous solid dispersions, lipid-based formulations) such as drug speciation and how undissolved species—nanocolloids or bile-salt micelles—may contribute to absorption.[20,21]

In our experience, the best approach to using absorption modeling in formulation development is through hypothesis testing and understanding parameter sensitivity (i.e., critical bioperformance attributes). This involves careful consideration of assumptions (e.g., can a physical interpretation be provided to support assumptions?), *in vitro* data incorporated into the model, as well as avoiding "curve fitting" and performing iterations to understand different *in vivo* scenarios that may ultimately impact performance of your formulation.

Second, following a retrospective analysis of our past development projects, we have produced conceptual technology maps centered on how key physicochemical drug properties impact oral absorption. This effort is aided by our extensive experience, such as in developing SDD formulations, with more than 5,000 compounds evaluated *in vitro*, more than 1,500 compounds in preclinical studies, and more than 300 compounds in clinical studies. One such example of a technology map is illustrated in Figure 3, where data points in this graph denote some of
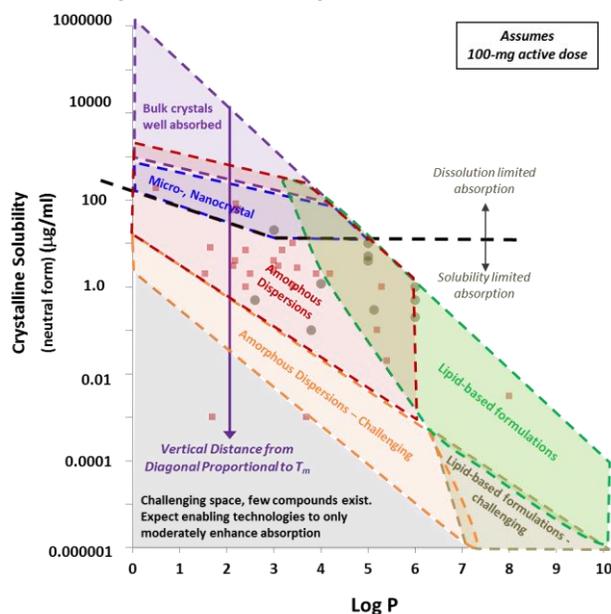

Figure 3

Graphic plotting compound aqueous solubility with respect to Log P for a range of compounds previously developed into SDDs (squares) or lipid formulations (circles) at Lonza, with subsequent overlay of the optimal space(s) for nanocrystal, amorphous (including SDDs and HME) and lipid-based technologies at a standardized 100-mg dose (per dosage unit). This visualization provides a simplistic 2D insight into how drug physicochemical properties can affect the feasibility and performance of various enabling technologies, but should not be looked in isolation as it does not consider other important properties such as biological obstacles to drug exposure.

the compounds that have been successfully developed over the past few years. In this graph, compound solubility in aqueous media (lowest energy crystalline form; no micelles in the media) is plotted with respect to Log P. The solid diagonal line in this map traces the maximal solubility of the lowest-energy, neutral form of the compound, calculated via a modified general solubility equation that assumes that compound solid-state interactions are negligible (i.e., the compound is a liquid at ambient temperature). Decreasing aqueous solubility at a constant Log P value therefore is driven primarily by an increase in the overall solid-state interactions, which is directly proportional to compound T_m. Thus, in general,

20   Stewart, A.M., et al., "Impact Of Drug-Rich Colloids of Itraconazole and HPMCAS on Membrane Flux *In vitro* and Oral Bioavailability in Rats." *Mol. Pharm.,* 14(7): 2437-2449 (2017).

21   Stewart, A.M., and M.E. Grass, "Practical Approach To Modeling the Impact of Amorphous Drug Nanoparticles on the Oral Absorption of Poorly Soluble Drugs." *Mol. Pharm.,* 17(1):180-189 (2020).

the further a compound falls below the diagonal line, the higher its T_m.

In the upper region of this map, crystalline solubility is sufficiently high that the BA of a 100-mg compound dose is high when using simple, nonenabling formulations. With increasing Log P and/or increasing T_m, however, the decrease in solubility creates the need for enabling technologies to maintain good *in vivo* performance. Particle size reduction technologies (e.g., micronization, nanocrystals) can offer acceptable BA at a 100-mg dose when solubility falls below 1 mg/ml, resulting in the dissolution rate of unprocessed drug becoming too slow to maintain the drug concentration at its equilibrium level while it is being absorbed. However, as the solubility decreases further (i.e., below 10 to 100 µg/ml, depending on the Log P of the compound), the utility of such technologies will typically diminish as solubility reaches the point at which absorption is inadequate even if high dissolution rates are achieved. At these low solubilities, it is necessary to utilize technologies that improve drug concentration in the GI lumen above its equilibrium solubility and/or drug transport across the unstirred water layer via submicron colloids. Amorphous solid dispersions (including SDDs and hot-melt extrudates) are highly effective across a broad Log P range (i.e., Log P 0 to 6), but at increasing compound lipophilicities (i.e., >Log P 6), additional excipients provided by lipid technologies are often necessary to solubilize and enhance transport of the compound through the aqueous boundary layer (also called the unstirred water layer), which can be slow and potentially limit absorption when the drug is lipophilic. Lipid technologies are typically applicable when Log P 5, so there is some overlap for the amorphous and lipid approaches. Notably, the optimal utility of lipid technologies in Figure 3 corresponds to the space below the solid diagonal line (where T_m is effectively at ambient temperature or less), reflecting the fact that compound solubility in oil will decrease with increasing T_m. Indeed, lipid formulations have proven utility in delivering low-T_m compounds, but development of lipid solutions becomes challenging with high-T_m compounds unless the compound dose per dosage unit is low (i.e., <25 to 50 mg). In other cases (i.e., where lipidic excipients are still needed), suspensions are a viable option to improve BA. Similarly for solid dispersions, a high T_m can be limiting to feasibility, for example, by requiring the use of higher process temperatures in HME, which in turn increase the

risk of compound and/or excipient degradation. For SDDs, a high T_m can limit solubility in commonly used organic spray solvents, resulting in an inefficient process with low throughput. To efficiently process such high-T_m compounds, a high-temperature spray-drying process (i.e., the "temperature- shift process") has been developed,[22] which allows a drug suspension to be heated to high temperatures—often well above the ambient-pressure boiling point of the solvent—to dissolve the drug immediately before it is introduced into the spray dryer.

Table 1 lists specific compounds that exemplify the relationship between drug physicochemical properties and the enabling capacity of amorphous and lipid-based technologies. For example, Compounds 1 to 6 were all successfully formulated as amorphous SDDs, and all six provided the targeted exposure when dosed in the clinic. The Log P values for these compounds ranged from about 2 to about 10, aqueous solubility of the neutral crystalline form ranged from less than 0.01 µg/ml up to ~100 µg/ml, and the T_m ranged from ~80°C up to about 230°C. It is clear from this broad range of properties that formulation as SDDs can be successful for compounds with a broad range of properties. Compound 6 was particularly challenging to formulate due to its high T_m and strong tendency to recrystallize from amorphous or solution states. By using a low (10% w/w) active loading, SDDs were developed that stabilized the amorphous form and performed well *in vivo*, but solid nanocrystalline dispersions with higher active loadings were developed for this compound that performed as well or better than the SDD. Compounds 7 and 8 also had a strong tendency to crystallize. In the case of Compound 7, the nanocrystalline formulations that did not generate highly supersaturated solutions upon dissolution performed the best *in vivo*. In the case of Compound 8, an acid-soluble base, using a nonenteric dispersion polymer, polyvinylpyrrolidone vinyl acetate (PVP/VA) made via HME promoted gastric dissolution and though it precipitated rapidly at intestinal pH *in vitro*, it nonetheless performed the best *in vivo*. Finally, Compound 9, a high Log P liquid (T_m <20°C) was formulated as an amorphous dispersion adsorbed to a high-surface-area silicon dioxide carrier. This formulation provided rapid dissolution of the compound and, in the clinic, resulted in near complete absorption at doses up to greater than 1 gram. Compounds 10 to 18 in Table 1 represent past development projects where it was possible to develop

[22]   Friesen, D.T., D.D. Newbold, J.M. Baumann, D.B. Dubose, and D.L. Millard. Spray-drying process, WO 2010 111132 A3

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Table 1

Selected physicochemical properties of 18 past compounds in relation to the performance of the developed formulation (**These compounds had proven biological barriers to BA, namely susceptibility to P-gp efflux*)

Compound No.	T_m (°C)	Log P/Log D	Aq. Solubility (µg/ml)	Technology/Formulation	*In Vivo* Performance Notes (Clinical data unless stated otherwise)
1	80 – 100	6 – 7	0.01 – 0.1	HPMCAS SDD	6-fold increase in fasted exposure compared to softgel reference. Crystalline exposure in animals near zero
2	90 – 100	~3	50 – 100	HPMCAS SDD	6-fold increase in fasted exposure compared to crystalline at 300-mg dose
3	150 – 170	~4	1 – 5	HPMCAS SDD	25% increase in AUC, 50% reduction in T_{max}
4	$T_g = 80$	~8	0.01 – 0.001	HPMC SDD	Near complete absorption at therapeutic dose
5	~250	~1.5 – 2	~10	HPMCAS SDD	Large enhancement versus bulk crystals in dogs
6	210 – 230	4 – 5	0.1 – 0.5	HPMCAS SDD / nanocrystal	Both formulations were well absorbed, limiting recrystallization following dissolution
7	150 – 160	4 – 5	~1	HPMCAS SDD granules and nanocrystals	All formulations had improved *in vivo* absorption in dogs relative to bulk; nano-crystal suspension performed best
8	200 – 220	~3	~5	PVP/VA HME dispersion	PVP/VA HME dispersion (particles <10 µm) fully dissolved in gastric; performed better than HPMCAS dispersions in dogs
9	<20	9 – 10	<0.01	Amorphous PVP dispersion adsorbed to SiO_2	Near-complete absorption up to doses >1 gram
10	~150	~5	~4	Self-emulsifying lipid solution	4-fold increase in AUC and 7-fold increase in C_{max} compared to reference tablet dosage form in dogs
11	Not determined	3 - 5	<1	Self-emulsifying lipid solution	>3-fold increase in fasted exposure compared to powder-based dosage form in dogs
12	~140	>5	~5	Self-emulsifying lipid solution	>2-fold increase in fasted exposure compared to reference tablet dosage form in dogs
13	~90	>5	<1	Self-emulsifying lipid solution	Increase in fasted exposure compared to reference dosage form in dogs
14	Not determined	>5	~5	Self-emulsifying lipid solution	Significant increase in fasted exposure compared to powder-based dosage form in dogs
15	~160	3 – 5	<1	Self-emulsifying lipid solution	Significant increase in exposure compared to reference powder-based dosage form in dogs
16	160 – 190	5 – 7	<1	Self-emulsifying lipid solution	Good oral exposure in monkeys and in clinical trials
17	150 – 220	2 – 3	10	Oil/surfactant self-emulsifying lipid solutions**	>2-fold increase in exposure compared to an aqueous suspension in dogs. Lipid formulation AUC at 30-mg compound dose was higher than 300-mg compound dose as a powder in capsule
18	Not determined	2 – 3	<10	Self-emulsifying lipid suspension**	2-fold increase in fasted exposure compared to powder in capsule

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lipid formulations for compounds showing a broad range of Log P values (i.e., between 3 and 10, with proven *in vivo* capacities to enhance the BA compared to dosage forms based on crystalline drug. Compounds 10 to 16 were good candidates for lipid formulation technology based on their respective physicochemical properties, and robust performance (both *in vitro* and *in vivo*); self-emulsifying lipid solutions were developed in each case. Compound 17 had both physicochemical (i.e., low solubility) and biological (i.e., P-gp efflux, CYP P450-mediated intestinal metabolism) obstacles to exposure. Several two-component (oil/surfactant) self-emulsifying formulations incorporating excipients with capacity to impact these biological barriers were subsequently designed, developed, and later characterized in a series of *in vitro* tests, from which lead formulations were identified—namely, those that effectively solubilized the compound as the formulation was dispersed and digested in simulated gastric/intestinal conditions. In fasted dogs, the lead lipid formulations provided over a 2-fold increase in exposure over an aqueous suspension and gave a higher exposure at a 30-mg compound dose than that of a powder-in-capsule formulation at a 300-mg compound dose.

The physicochemical properties of Compound 18 were such that it was not possible to completely dissolve the target dose in the lipid vehicle; however, a lipid suspension was progressed and, in a clinical study, showed better performance than a powder-in-capsule formulation due, at least in part, to the formulation addressing some biological barriers to absorption (e.g., efflux, metabolism).

Similar graphics to that in Figure 3 have been created using the T_m or T_m/glass-transition temperature (T_g) ratio (for SDDs) versus Log P. Such technology maps assist in the selection of the appropriate enabling technology when the physicochemical properties of a drug are the critical factor impacting oral absorption.

By utilizing predictive PBPK and mapping, formulators can focus initial experiments on the technology that is most likely to be optimal – an approach much more efficient than parallel empirical formulation screening, since it can minimize compound usage and accelerate formulation development.

Future outlook
Lonza's absorption models and technology maps are continuously updated and refined through data and experience gained through an ever-expanding project pipeline with NCEs and existing compounds. We continue to invest in our fundamental understanding and are currently performing a deeper scientific analysis of all our development projects to establish better relationships between drug properties and

development success using SDD, HME, nanocrystal, and lipid-based technologies.

Conclusions

The legacy companies that make up Lonza's Dosage Form and Delivery Solutions (DFDS) have been at the respective forefronts of amorphous dispersion, nanocrystal, and lipid-based formulation development, expanding these technologies' application and range in overcoming the physicochemical and biological drug properties that negatively impact BA.

The fundamental understanding derived from this collective investment across the key enabling technologies has facilitated advances in science-based technology selection for BA enhancement, with clear benefits in minimizing the complexity, time, and cost of the drug development process. Our technology selection process has been summarized in this article and relies on a series of inputs, ranging from product needs, drug properties, past project experiences, technology maps, and absorption modeling.

The advantages of this science-based approach have been discussed and can be contrasted to instances where a drug is progressed down a specific technology path, or parallel paths, where drug properties and product needs stretch that technology's range.

It is also important to note that the Lonza DFDS approach to technology selection relies on (1) compound properties, which are often already available (or otherwise measurable *in silico*); and (2) an in-depth understanding of the technology constraints in relation to product needs. Thus, our approach is in sharp contrast to more empirical approaches that focus on "screening" various technologies. In addition to delaying development and requiring what may be a substantial amount of compound to effectively evaluate several technology paths, the risk in empirical screening is that a compound fails to perform across all technologies (i.e., the compound is considered "undeliverable"). In many cases, however, this lack of success may stem from a lack of appropriate formulation design/manufacture, rather than fundamental technology ineffectiveness.

At Lonza DFDS, we believe that the best enabling technology for a particular drug can often be predicted based on a detailed understanding of the compound properties, product needs, and our extensive past experience in drug delivery. The scientific understanding of the key BA enhancement technologies, intellectual property, and scale-up/manufacturing experience has been integrated into a full design, development,

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and commercial manufacturing offering for pharmaceutical clients facing BA challenges with new or existing compounds. This collective capability and infrastructure further reduces development time, risk, and complexity by giving pharmaceutical clients the option of dealing with a single partner at all stages of the drug development process.

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