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Science-Based Technology Selection And Formulation Development For Oral Bioavailability Enhancement

Capsugel Dosage Form Solutions

White Paper

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Capsugel

Introduction

The increasing fraction of poorly water-soluble compounds in pharmaceutical discovery is leading to significant growth in the use of enabling technologies to improve oral drug absorption and bioavailability (BA). Commonly used technologies in this area have been extensively reviewed (1) and include salt selection, cocrystals, amorphous solid dispersions, particle size reduction, cyclodextrins, amorphous/lipid micro- and nanoparticulates, adsorbents and lipid-based technologies. Many of these technologies have been shown to enhance drug BA, with most commercial products utilizing solid amorphous dispersion, nanocrystalline drug or lipid-based technologies. Examples include Neoral® (cyclosporine, Abbott), a lipid-based liquid-filled capsule; Incivek® (teleprevir, Vertex), an amorphous drug dispersion produced by spray drying; Kaletra® (lopinavir and ritonavir, Abbott) an amorphous drug dispersion produced by hot-melt extrusion (HME); and Emend® (aprepitant, Merck), a nanocrystal-containing tablet.

Increasing use of such enabling technologies will be driven by the need to deliver the estimated 40% to 70% of the NCE pipeline candidates that are 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., "super generics") or during the product patent life through life-cycle management approaches. Drivers toward the 505(b)(2) regulatory pathway 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 dependent upon the extent of change to the previously approved drug. One example of a marketed 505(b)(2) product is Absorica™ (Ranbaxy), a hard capsule product containing a lipid formulation. This product, provides higher drug absorption in the fasted state than the original Roaccutane®/ Accutane® (Roche) softgel product, thus offering patients the potential to benefit from acne treatment independently from meals (2) and granting Ranbaxy the aforementioned benefits of a 3-year period of market exclusivity.

Due to the wide applicability of enabling technologies to NCEs and off-patent drugs, the BA enhancement landscape is innovative, dynamic and diverse. Indeed, the formulation of poorly water-soluble drugs is a key focus for many contract research/development/manufacturing organizations (CROs/CDMOs), supporting drug

development work with one or more BA-enhancing technology approaches to advance such drug candidates. A much smaller number of companies have both a broad range of technologies and the capacity to implement and scale them from design and development to commercial scale production. Having the ability to understand and provide multiple technology or formulation approaches under one roof is extremely advantageous, since the need to partner with multiple companies during a drug development program results in higher costs, significant program delays and inefficiencies and increased risk in the development process.

Optimal application of enabling technologies is based on key principles, including the following.

- 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 early in the development process.
- In many cases, more than one technology can be utilized successfully and commercial considerations such as desired dosage format can play a decisive role.

Using a technology ill-suited to a compound or problem statement often results in development delays, additional costs or even failure, due to poor manufacturability, stability, performance, or shortcomings in some other aspect of the target product profile. Appropriate application of technology is therefore critical to achieve success for development projects where achieving adequate oral absorption is required. Effective application of technology for enabled formulations can remain elusive, since it relies on many inputs, not the least of which is expertise with a range of alternative or complementary technologies, involving a clear understanding of the fundamental science governing the mechanisms of drug solubilization, absorption and metabolic fate.

The purpose of this article is therefore to *highlight* key physicochemical and biological obstacles to drug exposure following oral administration and how effective use of formulation technology relies on an understanding of the drivers to oral BA. We will then discuss the formulation development tools that have been developed from a deep investigation of key technologies and leveraging experience of hundreds of BA-enhancement projects.

Physicochemical Obstacles to Oral 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). The drug concentration gradient from the intestinal lumen across the unstirred mucus layer and into the intestinal wall is the driving force for passive absorption of drugs. Low aqueous solubility of a drug can therefore limit this gradient and result in low absorption from the intestine. A slow rate of dissolution can also limit absorption, particularly where the solubility of the drug form is sufficiently

low that it is necessary to maintain the concentration of drug near its solubility limit in order 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 in Class II and IV of the Biopharmaceutical Classification System (BCS). Factors underpinning the property of low solubility are well described (3) and include:

- A high crystal lattice energy (which generally increases with increasing melting temperature of a compound) and results in low solubility in essentially all solvents, sometimes referred to as "brick dust";
- a low energy of aqueous solvation (which generally decreases with increasing Log P value of a compound, i.e., lipophilicity), often referred to as "greaseball" compounds; and
- a combination of both, where the impact of a high crystal energy on solubility is exacerbated by a low solvation energy.

Enabling technologies increase solubility and dissolution rate by reducing the drug lattice energy, increasing drug surface area, or increasing the energy of solvation. For example, lipids, surfactants and cosolvents increase the volume and character of hydrophobic micro-phases of GI fluids, such as vesicles and micelles. Many low solubility compounds have favorable intermolecular interactions with such hydrophobic colloids, leading to increased drug solubilization.

Nanocrystals enhance the dissolution rate by increasing the drug surface area and may increase drug solubility if particles are very small (~<100 nm) and/or show change in crystalline structure, particularly at the crystal surface. Spray drying and HME solid dispersions increase apparent drug solubility and, therefore, dissolution rate by molecularly dispersing a high energy amorphous form in a matrix material (4). 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 such that the dissolving "solvent" is more favorable to the drug (i.e., "like dissolves like") (5).

In many cases, technology approaches have the capacity to increase drug solubility through both solid-state and solvation effects. For example, the introduction of a counterion or conformer in salts and cocrystals, respectively, can increase solubility in two ways: first, by altering both the solid-state energy through changes in molecular packing in the crystal; and second, by increasing the solvation energy by changing the nature of the local solvent, i.e., by changing pH in the case of a salt counterion, or by changing the drug to the ionized form (1). In addition, solid dispersions that use amphiphilic polymers such as hydroxypropyl methylcellulose acetate succinate (HPMCAS) (6) or nonionic surfactants (7) may also affect solvation. Finally, predissolving a drug within a lipid-based formulation can eliminate the solid-state 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 matches compound solubility/ dissolution obstacles to formulation technology, which forms the foundation of a science-based technology selection process. Where low solubility stems primarily from a high crystal lattice energy, solubility will benefit most from a reduction in solid-state interactions (e.g., solid dispersions) while 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 based on the physicochemical properties of the drug, while well recognized, is often overlooked in utilizing what is known, available and, in some cases, proprietary. As discussed throughout this article, technology selection and formulation development based on scientific understanding of mechanistic barriers to absorption is likely to result in more rapid and successful development with reduced costs.

Biological Obstacles to BA

In some cases, it is necessary to overcome not only physicochemical obstacles to absorption, but also biological barriers, which include (8):

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

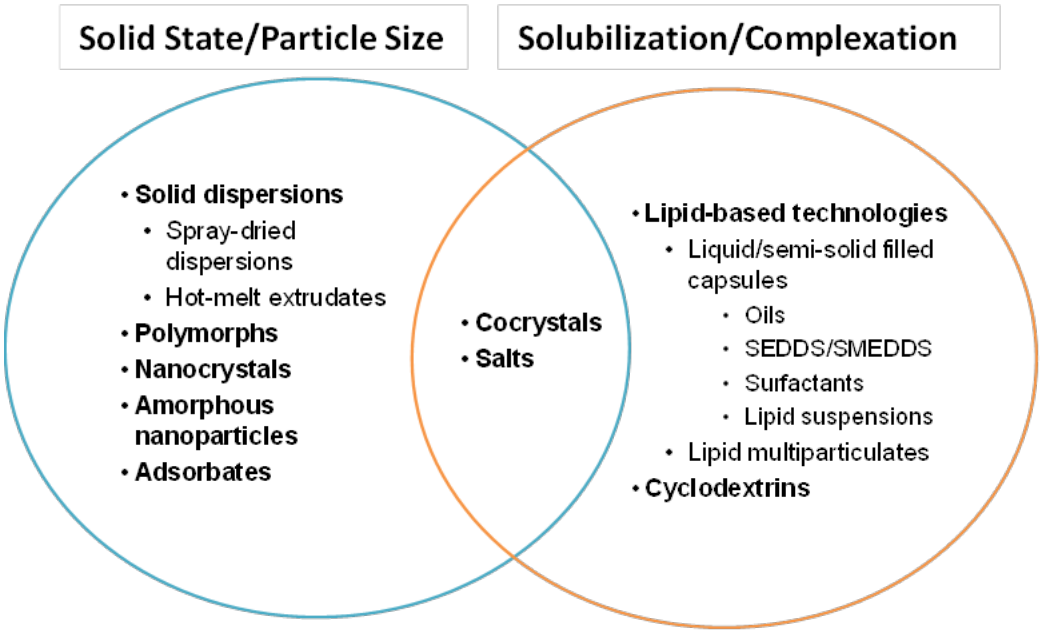

Figure 1: Simplified diagram illustrating the principal mechanisms by which various enabling technologies increase drug solubility/dissolution rate to lead to improved oral BA. See the supporting text for a more detailed description of some of these enabling technologies.

- presystemic drug metabolism in the intestine (principally via cytochrome P450 enzymes); and
- extensive hepatic first-pass drug metabolism.

A good example of high drug absorption accompanied by low BA is that of testosterone. (<25 µg/ml), testosterone is well absorbed from the intestine, but shows extremely low BA due to extensive first-pass metabolism (9). Thus, formulation work to alter drug physicochemical properties to improve intestinal absorption would be ineffective to improve BA in this case. Certain enabling technologies have the capacity to attenuate these biological obstacles to drug 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 (10) or increase transcellular permeability (11), with evidence that these effects may also lead to higher *in vivo* exposure (12). These same excipients are also increasingly implicated in the inhibition of a variety of cytochrome P450 enzymes, which have the potential to metabolize drug in the intestinal wall (13, 14).

For highly lipophilic compounds, lipid-based formulations can also increase the fraction of drug that enters the lymphatic system, avoiding hepatic metabolic pathways (15, 16). For example, the undecanoate ester of testosterone exhibits much lower aqueous solubility than the native form (<1 ng/ml cf. ~25 µg/ml) yet demonstrates higher oral BA due a greater lipophilicity and a greater propensity to enter the systemic circulation via the lymph, particularly when formulated as a lipid solution (Andriol Testocaps®) (17). 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 triglyceride >50 mg/g) via the lymphatic system [reviewed in (18)].

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 the key determinants of low oral BA of a compound of interest and selecting an appropriate technology that overcomes the rate-limiting barrier.

Beyond Physicochemical and Biopharmaceutical Properties

Besides the physicochemical and biopharm-aceutical properties of a compound, there are a number of other considerations that may impact technology selection and formulation development 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. These factors may play an important part in the technology selection process. These constraints can often be identified prior to the initiation of development work and therefore

reduce the risk of pursuing certain approaches that are later deemed to be unsuitable.

Technology Selection in BA Enhancement

Capsugel Dosage Form Solutions offers development capabilities (GMP/non-GMP) in amorphous spray-dried dispersions (SDDs), HME, nanocrystals, liquid/semi-solid filled capsules and lipid multiparticulates. Each of these enabling technologies has a proven capacity for increasing drug absorption and BA via several different mechanisms, which have been deeply investigated and form the basis of our drug development capability. Collectively, the utility of these respective technologies covers a broad space in terms of drug properties and target performance. Access to such a broad range of complementary technologies and capabilities is critical for optimal drug development, enabling flexibility in selecting an optimal technology platform for a particular compound.

The process for developing formulations based on appropriate technologies is governed by multiple inputs (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 ensures rapid and efficient feasibility assessment, better performance *in vivo* of early concept formulations and ultimate success in reaching the target product profile.

As evident from Figure 2, this selection of approaches takes into consideration compound qualification and the overall product needs, which

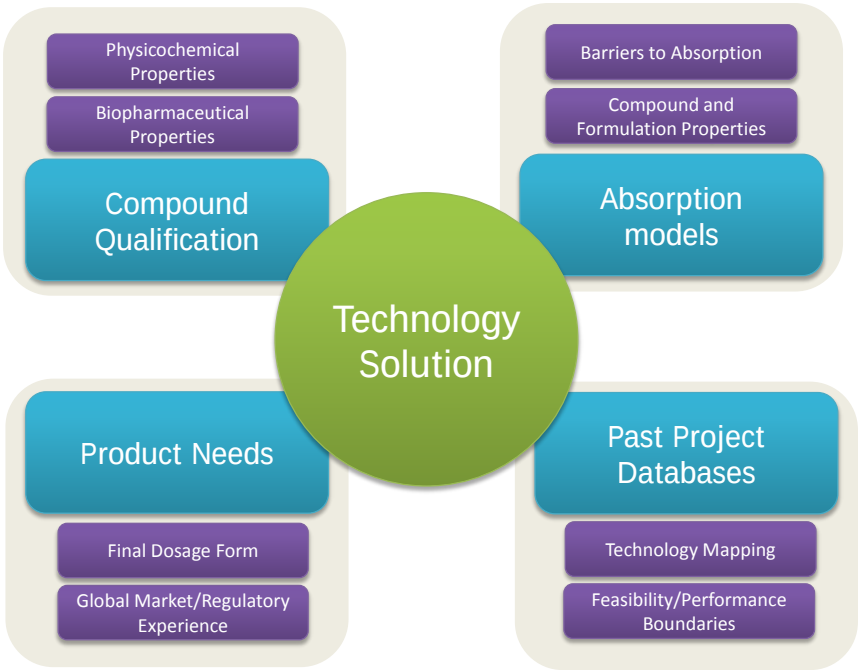

Figure 2: Schematic summarizing the various inputs required for optimal enabling technology selection.

in turn necessitates a thorough dialogue and teamwork with the customer. "Product needs" that require consideration include the target dose and client expectations concerning the final dosage form size, shape, appearance and packaging. Detailed target product understanding based on extensive client discussions is critical to technology selection, and preclinical and early clinical development, since they may affect critical elements of ultimate success, such as compliance. Within Capsugel, such discussions are greatly supported by experience developing formulations in the US, Europe and Asia, across which there may be significant variation in both regulatory requirements and patient preferences.

Technology selection and formulation development should also draw upon compound-specific elements in the "Compound Qualification" input, 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 for exchange of information. If needed, *in silico* tools may be used to predict how certain compound properties such as Log P, solubility and compound ionization are expected to impact performance (though experimental measurements are always preferred).

From a deep fundamental understanding of enabling technologies and past development work, two additional tools are employed in the formulation development process — internal predictive physiological-based pharmacokinetic (PBPK) models and technology maps. Firstly, we use PBPK models based on mass transport under physiologically relevant conditions to support formulation development. These models are often useful in predicting pharmacokinetic (and, potentially, pharmacodynamic) performance based on compound and formulation properties (19). Originally developed for our SDD capabilities but translatable to other enabling technologies, these models are based on the assumption that the time-concentration profile of all drug species — dissolved free drug, drug in natural or formulation-derived micelles and various undissolved but "high-energy" particulates — drive the extent of intestinal absorption of a poorly water-soluble drug. Although these models were developed primarily for solid dosage forms (SDDs, amorphous or crystalline nanoparticles, or salt forms), we are in the process of adapting these models to account for the performance of lipid-based formulations — including the incorporation of important attributes such as the impact of formulation dispersion, digestion, supersaturation and overall capacity to increase dissolved drug above its equilibrium level in lipid colloids and in free solution.

Secondly, a retrospective analysis of our past development projects had been used to produce technology maps that relate key physicochemical drug properties to oral absorption. The maps are based on our extensive formulation experience, including evaluation of >1000 compounds *in vitro*,

>500 compounds in preclinical *in vivo* studies and >100 compounds in clinical studies using SDD technology. The graph of Figure 3 is an example of a technology map, in which data points denote 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 (S_{max}) of the lowest-energy, neutral form of the compound, calculated via a modified general solubility equation (S_{max} (mg/ml) = 1000 * $10^{(-LogP)}$) that assumes that compound solid-state interactions are negligible (that is, the compound is a liquid at ambient temperature).

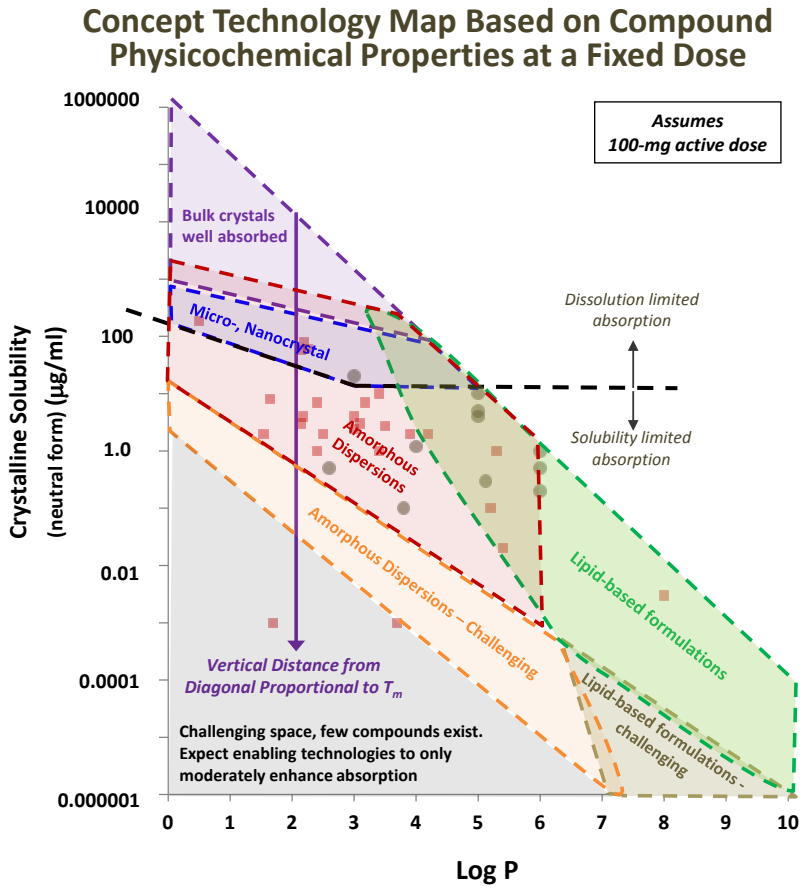

Figure 3: Graphic plotting compound aqueous solubility with respect to Log P for a range of compounds previously developed into SDDs (squares) or lipid formulations (circles) at Capsugel, with subsequent overlay of the optimal space(s) for nanocrystal, amorphous (including SDDs and HME) and lipid-based 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 viewed in isolation because it does not consider other important properties such as biological obstacles to drug exposure.

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 melting temperature (T_m). Thus, in general, the further a compound falls below the diagonal line, the higher its T_m value. In the upper region of this map, crystalline solubility is sufficient that high BA of a 100 mg dose can be achieved 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 (i.e., micronization, nanocrystals) can offer acceptable BA at a 100 mg dose when solubility falls below 1 mg/ml, by overcoming instances where the dissolution rate of unprocessed drug is too slow to maintain the drug concentration at its equilibrium level in the intestine. As the solubility decreases further, the utility of such technologies diminish as solubility reaches the point at which absorption is inadequate even if high (even instantaneous) 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 sub-micron colloids. Amorphous solid dispersions (including SDD and HME) are highly effective at raising the concentration of dissolved drug above its equilibrium solubility across a broad range of Log P values (~0 to 6). For compounds with high lipophilicity (i.e., Log P >~6), additional excipients provided by lipid technologies are necessary to solubilize and enhance transport of the compound through the (unstirred) aqueous boundary layer — a process that can be slow and often limit absorption for lipophilic drugs. Lipid technologies also cover a broad Log P range of ~3 to 10, hence there is overlap region of amorphous and lipid approaches between Log P 3 and 6 values, with progressively greater applicability of lipid approaches with increasing compound lipophilicity. 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 to moderate melting compounds (e.g., oily compounds to T_m <200°C), but development of lipid solutions becomes challenging with high melting compounds unless the compound dose per dosage unit is low (i.e., <50 mg). In such cases lipid suspensions are a viable option to improve BA when lipidic excipients are still needed. 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 increases the risk of compound and/or excipient degradation. For SDDs, a high T_m can be limit solubility in commonly used organic spray solvents resulting in an inefficient, low throughput process. In order to efficiently process such high T_m compounds, a high-temperature spray dry process ("hot process") has been developed (20). In this process, the drug suspension is 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. Compounds 1 through 9 utilized either nanocrystal or amorphous dispersion technology, while Compounds 10 through 18 utilized lipid-based technology, all for the purpose of BA enhancement. The developed formulations have been subsequently assessed as optimal to sub-optimal based on their location on the technology map in Figure 3 (i.e., the physicochemical properties of the compound). In some cases, more than one technology was utilized for comparative purposes.

Nanocrystal and Amorphous Dispersions

Compounds 1 through 6 were all successfully formulated as amorphous SDDs and all six provided 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 to ~100 µg/ml and the T_m ranged from ~80°C to about 240°C. It is clear from this broad range of properties that SDDs can be successfully formulated for compounds having a broad range of properties. Compound 6 was particularly challenging to formulate due to its very high T_m and strong tendency to recrystallize from amorphous or solution states. Despite this, low (10% w/w) active loading SDDs were developed that stabilized the amorphous form and performed well *in vivo*. Additionally, solid nanocrystalline dispersions with higher active loadings were developed that performed as well or better than the SDD. Similarly, 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, 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) that would not normally be considered ideal for solid dispersions, was formulated as an amorphous dispersion adsorbed to a high-surface-area silicon dioxide carrier. This formulation provided very rapid dissolution of the compound and, in the clinic, resulted in near complete absorption at doses up to greater than 1 gram.

Lipid-Based Formulations

Compounds 10 to 18 in Table 1 cover a broad range of Log P values (i.e., between 3 and 7), though all showed enhanced BA when formulated with lipids, compared to that obtained with dosage forms based on crystalline drug. Compounds 10 through 16 were good candidates for lipid formulation technology based on physicochemical properties, and robust-performing (both *in vitro*

Table 1: Selected physicochemical properties of 18 past compounds in relation to the performance of the developed formulation. Cells are color coded based on suitability for the respective technology based on the physicochemical properties shown (green = optimal, orange = moderate, red = nonoptimal) ***These compounds had proven biological barriers to BA, namely susceptibility to P-gp efflux*

Compound #	Melting Temperature (°C)	Log P/ Log D	Aq. Solubility (µg/ml)	Technology / Formulation	In Vivo Performance (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 @ 300 mg dose
3	150 – 170	~4	1 – 5	HPMCAS SDD	25% increase in AUC, 50% reduction in Tmax
4	T_g = 80	~8	0.01 – 0.001	HPMC SDD	Near complete absorption at therapeutic dose
5	~250	~1.5 – 2	~10	SDD	Large enhancement versus bulk crystals in dogs
6	210 – 230	4 – 5	0.1 – 0.5	HPMCAS SDD/nanocrystal	Both well absorbed; limiting recrystallization following dissolution the challenge
7	150 – 160	4 – 5	~1	SDD granules & nanocrystals	All formulations had improved in vivo absorption in dogs relative to bulk; nanocrystal suspension performed best
8	200 – 220	~3	~5	PVP/VA HME dispersion	PVP/VA HME dispersion (particles <10 micron) fully dissolved in gastric; performed better than HPMCAS dispersions in dogs
9	<20	9 – 10	<0.01	Amorphous 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 Cmax compared to reference tablet dosage form in dogs
11	nd	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	nd	>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°C	5 – 7	<1	Self-emulsifying lipid solution	Offering good oral exposure in monkeys and in clinical trials
17	150 – 220°C	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 higher than 300 mg compound as a powder in capsule
18	Nd	2 – 3	<10	Self-emulsifying lipid suspension**	2-fold increase in fasted exposure compared to powder in capsule

and *in vivo*) self-emulsifying lipid solutions were developed in each case. Compound 17 exhibited both physicochemical (i.e., low solubility) and biological (i.e., P-gp efflux, CYP P450-mediated intestinal metabolism) obstacles to exposure. Several oil/surfactant two-component 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 these tests, lead formulations were identified that were effective in solubilizing 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 relative to 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 dose. The physicochemical properties of Compound 18 were such that it was not possible to completely dissolve the target dose in the lipid vehicle. A lipid suspension, however, was developed and later showed better performance than a powder-in-capsule formulation in the clinic due, in part, to the formulation addressing biological barriers to absorption (i.e., efflux, metabolism).

Graphs similar to that in Figure 3 have been created using the T_m or T_m/T_g (glass transition temperature) ratio (for SDDs) versus Log P, similar to the reference map depicted in Figure 3 for crystalline solubility versus Log P. Such technology maps assist experienced formulators in the selection of the appropriate enabling technology when the physicochemical properties of a drug are the critical factor impacting oral absorption. Such two-dimension maps are not the sole predictor of the ultimate formulation or commercial success, since there are not just two factors but many parameters that mechanistically affect BA. For example, the cyclic peptide cyclosporine (Log P 2.9: water solubility ~7 µg/ml) is available as a commercial lipid formulation (Neoral®) at 25 and 100 mg doses. According to our crystalline solubility versus Log P technology map (Figure 3), cyclosporine would not be considered an ideal candidate for a lipid formulation. Thus, while conceptual maps are powerful references to the experienced formulator, many considerations can come into play, requiring the use of complementary tests and analysis to optimally formulate compounds.

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, accelerate formulation development and, ultimately, increase the chance of technical and commercial success.

Conclusions and Future Work

The companies that comprise Capsugel's Dosage Form Solutions (DFS) — legacy Capsugel, Encap Drug Delivery and Bend Research — have been at the respective forefronts of amorphous dispersion, nanocrystal technology and lipid-based formulation, expanding these technologies' application and range in overcoming drug physicochemical properties and biological

interactions that negatively impact oral BA. The fundamental understanding derived from this collective investment across the key enabling technologies has facilitated advances in science-based technology guidance and formulation development selection for BA enhancement. Our development process, which relies on a series of inputs ranging from product needs, drug properties, past project experience, conceptual technology maps and absorption modeling, has been summarized in this article.

The advantages to this mechanistic science-based process have also been discussed and can be contrasted to instances when a drug has been progressed down a specific technology path, or parallel paths, where drug properties and product needs stretch that technology's range. This approach is common in the industry where a pharmaceutical company, CRO, or CDMO has strong expertise and experience in a specific technology. Based on past experiences, however, this strategy is likely to be sub-optimal or unsuccessful either early during initial feasibility assessment or later on during development. More empirical approaches that focus on "screening" various technologies are also considered suboptimal. In addition to delaying development and requiring what may be a substantial amount of compound to effectively evaluate several approaches, the risk in this screening approach is that a compound fails to perform across all technologies (i.e., the compound is considered "undruggable"). In many cases, however, this lack of success may stem from inappropriate or sub-optimal formulation design and development rather than fundamental technology limitations. Access to the range of key technologies, fundamental scientific understanding of each technology's application and limitations and extensive experience across the technology options are considered key in ensuring that an optimized, fit-for-purpose dosage form is rapidly identified and developed. It is also important to note that the Capsugel's approach to formulation work relies on compound properties that are often already known (or otherwise measurable *in silico*) but require the in-depth understanding of the technology constraints in relation to product needs.

We continue to expand our fundamental understanding and our absorption models and technology maps are routinely updated and refined through data and experience gained from an expanding product development pipeline of NCE's and existing drugs. Capsugel is 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. An initiative has been launched to further validate our technology selection/formulation develop-ment strategy: compounds are being progressed through our formulation development process, and SDD and lipid-based technologies will be tested *in vitro* and *in vivo* using both technologies for head-to-head feasibility and performance comparisons. A particular focus will be on compounds lying in areas of the maps between "adjacent" technologies, for which we will also

evaluate multiple enabling technologies to refine maps and models by identifying properties that are the best indicators of development success (performance, stability, manufacturability) for specific technologies/formulations.

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