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Strategies at the Interface of Drug Discovery and Development: Early Optimization of the Solid State Phase and Preclinical Toxicology Formulation for Potential Drug Candidates

Michael Palucki,* John D. Higgins,* Elizabeth Kwong, and Allen C. Templeton

Basic Pharmaceutical Sciences, Merck Research Laboratories, Merck & Co., Inc., West Point, Pennsylvania 19486

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Introduction: Rationale for Early Pursuit of an Optimal API Phase and Preclinical Toxicology Formulation

Over the past decade, scientific and business needs have driven the pharmaceutical industry to more closely align drug discovery and drug development efforts. Likewise, medicinal chemists now routinely impart a cognizant effort to incorporate drug-like properties into their chemical scaffolds, with the prevailing goal of not only identifying a compound that can advance into development, but also identifying an associated solid state phase that has appropriate physicochemical characteristics that allow for optimal in vivo performance.[1,2] Hence, medicinal chemistry efforts in the lead optimization space routinely focus not only on structure−activity relationship (SAR[a]) studies but on structure−property relationship (SPR) studies as well. As a result, a combined strategy of "structure-based design", which focuses on biological activity/potency, and "property-based design"[3], which focuses on optimizing structural features of the candidate in efforts to optimize absorption and pharmacokinetics has now become the preferred approach in lead optimization.[4]

In order to effectively progress property-based-design efforts during lead optimization, animal studies are routinely performed to evaluate a compound's oral absorption and pharmacokinetic (PK) parameters. Two key factors that can affect the outcome of such studies are the drug candidate's solid state phase and the formulation.[5] It is well-known that a compound's phase (i.e., salt or neutral, crystalline or amorphous) can have profound effects on solubility and subsequent oral absorption. Similarly, the nature of the formulation, whether a standard vehicle such as methylcellulose or an enabling technology such as nanoparticles or an amorphous dispersion, also can have a profound effect on absorption and PK.[6] Unfortunately, appropriately addressing these factors at the drug discovery stage is a difficult endeavor because of the limited availability of active pharmaceutical ingredient (API), the strict timelines that are routinely imposed based on priority, and the availability of resources. In turn, missed opportunities in addressing phase and formulation early can lead to potential delays in drug candidate identification and in drug development timelines.

It follows that early engagement of pharmaceutical development scientists on the identification of an optimal phase and formulation during the drug discovery stage can lead to significant benefits not only in drug discovery efforts but downstream in drug development as well. One of the most important benefits of applying efforts toward early optimal phase and formulation identification is the potential for reducing preclinical candidate attrition. From demonstration of dose limiting toxicity to establishing acceptable and reproducible safety margins in preclinical toxicity studies, realistically achieving the desired absorption and PK in animal studies is critical in the early part of drug development.

Early identification of an optimal phase and formulation also minimizes the potential for multiple changes in phase or formulation during development, which in turn reduces resource expenditures directed toward in vitro physicochemical studies and in vivo biocomparison studies. Regardless of the potential for downstream benefits of early phase/formulation optimization, efforts must be balanced in the broader context and risks of drug development, as multiple factors ultimately impact survival of a molecule to market. The objective of this article is to share some of our perspectives on how pharmaceutical scientists transplanted from development into discovery can effectively contribute to the pursuits described above. In addition to the collaborative strategies described herein, several other useful reports have also been communicated on this topic.[7]

Benefits of API Phase Optimization in Drug Discovery and Development

Example in Drug Discovery. Salt formation of drug candidates is often employed for improving physicochemical properties such as solubility as well as associated biopharmaceutical attributes such as oral absorption.[8] While it is standard in the pharmaceutical industry to conduct salt screens/selection in the drug development arena, earlier application of salt formation in drug discovery also can be beneficial. A recent example at Merck involved a program

*To whom correspondence should be addressed. For M.P.: phone, 215-652-7016; fax, 215-652-7310; e-mail, michael_palucki@merck.com. For J.D.H.: phone, 215-652-3669; fax, 215-652-7310; e-mail, john_higgins3@merck.com.

[a] Abbreviations: API, active pharmaceutical ingredient; AUC, area under the curve; BCS, biopharmaceutical classification system; DMPK, drug metabolism and pharmacokinetics; DLT, dose limiting toxicity; DSC, differential scanning calorimetry; ETPGS, vitamin E−PEG−succinate conjugate; FaSSIF, fasted stated simulated intestinal fluid; FIH, first in human; GI, gastrointestinal; GLP, good laboratory practices; HT, high throughput; ip, intraperitoneal; LI, lead identification; LO, lead optimization; PK, pharmacokinetic; PSD, particle size distribution; SAR, structure−activity relationship; sc, subcutaneous; SMEDDS, self-emulsifying drug delivery system; SGF, simulated gastric fluid; SPR, structure−property relationship; TGA, thermogravimetric analysis; XRPD, X-ray powder diffraction.

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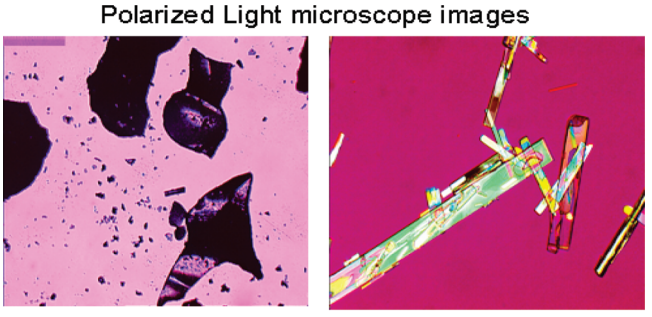
Table 1. Solubility of Two API Phases in FaSSIF and SGF

	solubility, μg/mL	
biological relevant solution	in FaSSIF	in SGF
targeted exposure	>40	high
API neutral phase	25	2
API sulfate salt	410	450

with an existing lead compound in development that displayed low solubility in both fasted state simulated intestinal fluid (FaSSIF)[9] and simulated gastric fluid (SGF) media (2 and 25 μg/mL, respectively). As a result, oral absorption observed in the clinic was poor. A discovery team was charged with identifying a backup candidate against the target with increased solubility in both media (see Table 1) in order to achieve adequate exposure in the clinic using a conventional formulation. Through arduous SAR studies focused on incorporating solubility optimization, a lead was identified that contained an ionizable amine that still retained adequate potency. A subsequent salt screen identified a scalable crystalline sulfate salt phase with significantly improved solubility and favorable physicochemical properties (Table 1). This compound was very well absorbed in preclinical animal models and is currently under development using a conventional formulation.

Example of the Impact of a Poorly Defined Phase on Drug Development. One of the most notorious solid state challenges in drug development arises when an amorphous drug phase is converted to a crystalline phase, resulting in a significant drop in solubility and oral exposure. The potential for phase changes such as these is important to consider, since this can make or break the preclinical toxicology program. This situation is illustrated in Figure 1. In this case, the amorphous phase of a preclinical candidate was used for all PK studies throughout discovery, where adequate exposures were achieved and the compound was progressed. Later in development, the chemical and physical stability of the amorphous phase was determined to be unacceptable and a crystalline phase was identified. The crystalline phase drastically reduced solubility, and the resulting lower oral exposures in preclinical safety studies could not provide adequate margins to support the clinical program.



API Phase	Solubility (mg/mL)	AUC (750 MPK, μM h)
Amorphous (Discovery)	>25	~200
Crystalline (Development)	<0.01	<30

Figure 1. Crystallization of an amorphous drug phase and the impact on solubility and oral exposure (AUC, area under the curve). Reprinted with permission from *American Pharmaceutical Review*. [5]Copyright 2009 Russell Publishing.

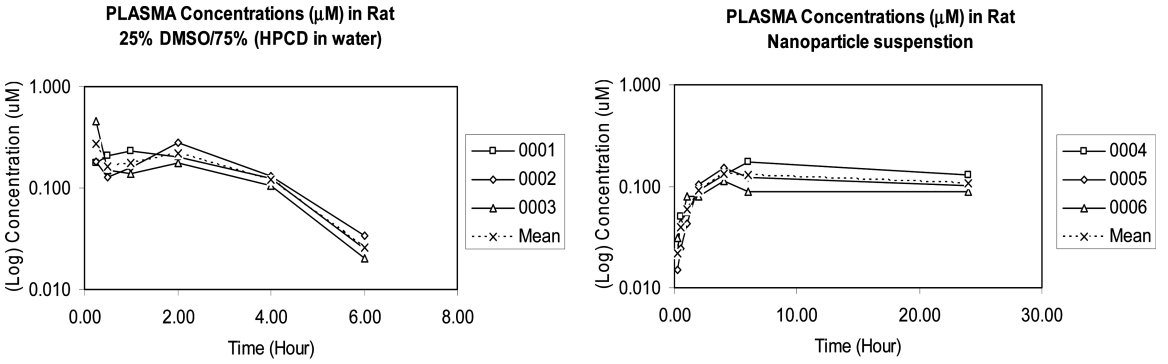
This risk alone provides significant justification for identifying a suitable crystalline API phase by the late discovery stage, *before* a candidate is nominated for development, thus setting realistic solubility/exposure expectations for downstream development activities. Note that the goal is not to identify the final phase to be used for a preliminary market formulation but rather to minimize the gap of physicochemical and biological characteristics between discovery/early development phases vs late development phases.

An Example of the Benefit of Formulation Optimization in Drug Discovery.[10] A lead compound in a Merck early drug discovery program was being evaluated for further consideration, and a key aspect for the decision making process was the ability to obtain sustained exposure in rats. By use of a standard subcutaneous (sc) formulation (25% dimethyl sulfoxide (DMSO)/75% aqueous hydroxylpropylcylcodextrin (HPCD)), plasma concentrations of the drug declined precipitously 2 h after dosing (Figure 2). On the basis of these data and the criteria for further consideration, one might conclude that the compound had limited potential to move forward. However, after several enabled formulations were screened, a sc nanoparticle suspension was identified that was well tolerated and provided the desired sustained exposure and increase in AUC. Accordingly, the compound progressed into the next phase of the drug discovery program. Without the added investment of drug delivery efforts, a missed opportunity would have resulted.

Identifying an Effective API Phase and Formulation Workflow

Identification of an efficient workflow for selecting a suitable API phase and formulation is not straightforward given the complexity of the process. Assignment of dedicated resources and the engagement of scientists from different disciplines with the appropriate skill sets are needed. For each phase and formulation under consideration, a number of parameters must be evaluated when trying to select the optimal combination (Figure 3). These parameters can be grouped into three general categories: (1) solid state properties wherein crystallinity, all aspects of solid state stability, and morphology are the key parameters, (2) solution/formulation properties wherein solubility and all aspects of solution stability are the key parameters, and (3) biopharmaceutical properties, wherein absorption and PK are the key parameters. The biopharmaceutical performance is the final vindication of the process, wherein selecting an optimal phase and formulation is validated against the targeted exposure goals.

Traditionally, for compounds that move from discovery into development, more resources, technologies, and rigorous testing are applied toward API phase and formulation optimization. A depiction of this overall process is highlighted in Figure 4. It is evident that as a molecule proceeds through the drug discovery/development continuum, there is emphasis on optimal API phase and formulation, with the majority of optimization occurring in drug development. As a result, several functional areas in development (for example, process chemistry research, pharmaceutics, drug delivery, high throughput screening groups, analytical chemistry, etc) often have the expertise and technology to inform and execute the phase and formulation optimization process. Consequently, moving development resources into the discovery arena may seem to be the most obvious and simple solution for pursuing optimal phases and formulations early; however, the *how*, *when*, and *where* to do this are not easily discernible.



Formulation	Cmax (μM)	AUC (μM.hr)	Tmax (h)
DMSO	0.3	0.90	1.1
Nanoparticle Suspension	0.2	2.7	4.7

Figure 2. Plasma concentration comparisons using conventional aqueous sc formulation and nanoparticle formulation.

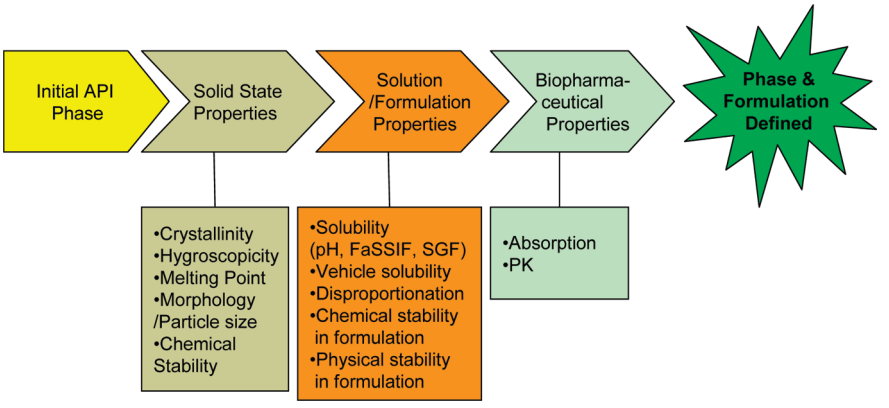


Figure 3. Workflow and properties associated with phase and formulation definition.

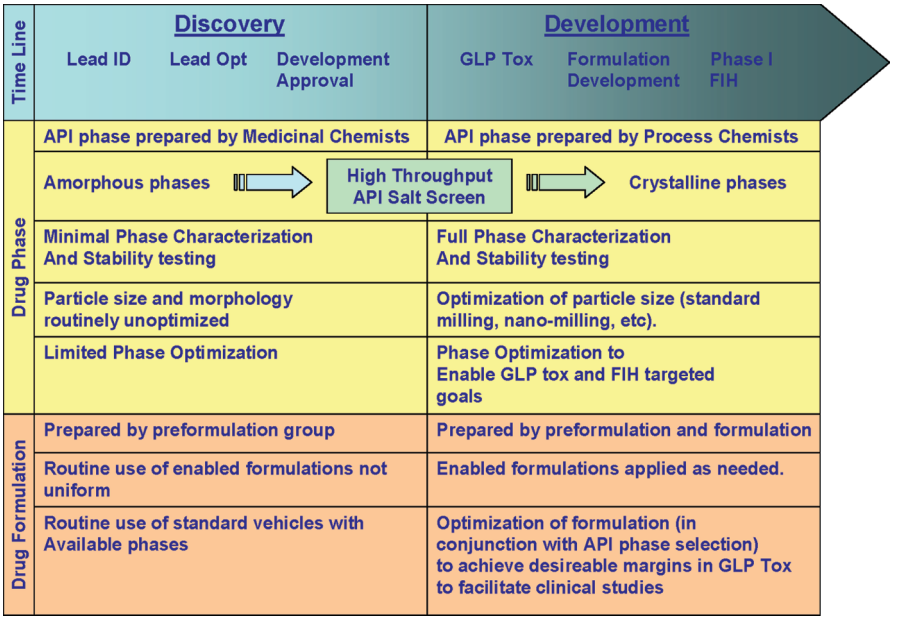


Figure 4. Traditional drug phase and formulation activities from drug discovery through first in human (FIH) development.

As programs progress in lead optimization, the number of chemical series and leads under investigation decreases until at a certain point a preclinical candidate is nominated for development. During this process, one of the key questions to address is *when* to initiate API phase optimization. Ideally, an internal trigger such as a key toxicology study, PK study, or

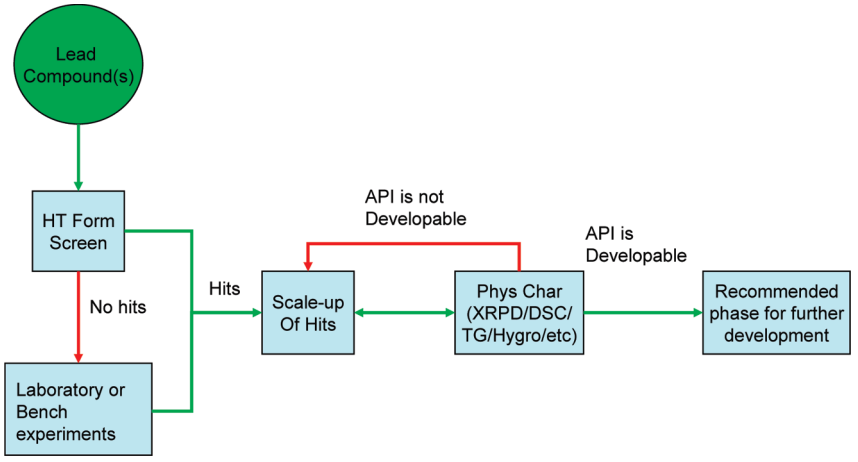


Figure 5. Initial workflow for phase identification (HT, high throughput; DSC, differential scanning calorimetry; TGA, thermogravimetric analysis).

efficacy study will determine *when* resources should be applied toward identifying an optimal API phase and formulation. The *how* and *where* of applying this effort require more in-depth discussion.

A common difficulty in the identification of a suitable solid state phase is the management of the limited amount of experimental compound available in discovery with respect to the physical and biological studies required to progress the compound through lead optimization and into development. Similarly, the time available between triggering the search for a suitable phase and the need to lock into the phase for development purposes is shrinking.

To address the often limited API availability and timing constraints, automated miniaturized high-throughput methods have provided significant benefits to the phase screening process by providing rapid turnaround of results using minimal drug.[11] This methodology is routinely applied by pharmaceutical scientists working in the discovery space. For pharmaceutical scientists, the question is not how to apply these approaches but when. Thus, maintaining close ties between pharmaceutical scientists and medicinal chemists is critical.

One way to address API availability is to bring in process chemistry into drug discovery in order to engage resources for preparing larger quantities of key leads. While medicinal chemists primarily focus on using chemistry as a tool to produce smaller quantities of a large number of structurally diverse compounds, process chemists typically focus on optimizing synthetic chemistry on a single or more limited subset of development candidates, with the goal of identifying cost-effective and green synthetic routes that produce the requisite API in large quantities in high yield. Of note is that drug discovery scale-up groups can be effectively deployed to provide the requisite API needed during drug discovery efforts; however, discovery scale-up groups may or may not have the appropriate connectivity with development groups and/or the skill set or background to effectively participate in phase selection. The process chemist also is keen on preparing a final phase (salt and/or polymorph) that can be reproducibly delivered from the synthetic process irrespective of batch scale. This mind-set can prove to be beneficial, for example, when scaling up hits from a high throughput salt screen.

Identification and Criteria of a Suitable API Solid State Phase. Before a detailed work flow (Figure 5) for identifying a "suitable" solid state phase is described, the definition of "suitable" should be established. In past decades, the traditional drug discovery view of a "suitable" solid state phase was often one that achieved acceptable exposures in early in vivo studies and was stable enough to be handled and weighed. At the opposite end of the spectrum, the customary definition of a "suitable" solid state phase from a pharmaceutical development scientist's perspective is a stable, reproducible crystalline phase in which the inherent physical properties are amenable for use in a conventional formulation. Clearly, these expectations contained minimal overlapping characteristics, which in turn often led to misaligned risks and resources in both parties.

There are three generally accepted properties that should be considered when attempting to identify a suitable solid state phase for development: solid state properties, solution properties, and biopharmaceutical properties. Solid state properties are noted first simply for the fact that if there is no stable API solid state phase that allows for basic handling and storage, it would be extremely difficult for the compound to move forward to any degree. Consequently, initial efforts typically focus on identifying viable solid state phases, whether they are salts or neutral phases.[12] This is routinely accomplished through either manual or high throughput screening protocols of salts, polymorphs, or both.[13] It is prudent to first obtain an accurate pK_a determination of the parent API, as this is crucial in guiding the selection of potential conjugate acids or bases. High throughput workflows routinely incorporate X-ray powder diffraction (XRPD) as the initial means of confirming crystallinity. This output, coupled with 2−4 mg per well in a 48- or 96-well plate screen, provides a significant return on the investment of 100−400 mg of API required.

From an expediency standpoint, it is tempting to try and rationally design a standardized platform that can be applied toward all high throughput phase screening. However, maintaining flexibility in the design of the screen can ensure that the data obtained will provide the highest probability of success for generating a suitable phase. The screen should be tailor-made for an individual compound based on pK_a, as well as existing polymorph or salt history. For example, if it is known that various crystalline neutral phases and an amorphous hydrochloride (HCl) salt have been prepared previously, all of which have shown to give adequate exposure in an animal study, this should be taken into consideration when designing the high throughput screen. Hence, a 96-well

Table 2. Desirable Solid State Characteristics of an API Phase

parameter	desired attribute/criteria
solid state phase	crystalline with minimal polymorphism or amorphous with T_g > 100 °C[a]
chemical stability	<2% degradation under stressed conditions[b]
physical stability	no phase changes under stress conditions
hygroscopicity	<2% water adsorption at 75% RH
hydration state	anhydrous form preferred; hydrated form with acceptable thermal/environmental lability

[a] T_g: glass transition state temperature. [b] Typical stress conditions: 40 °C, 75% RH.

plate screen might consist of 24 wells dedicated to a polymorph screen for the HCl salt, another 24 wells dedicated to a polymorph screen for a neutral form, and 48 wells dedicated to a general acid salt screen.

Although it provides a good starting point, a hit from a high throughput screen does not necessarily lead to a scalable process to prepare the phase. The procedure conducted in a high throughput screen is often designed for processing via an automated protocol and may not be amenable to standard process chemistry crystallization techniques. Consequently, it is imperative that chemists perform scale-up experiments to confirm that the phase is reproducible and provide material for further physicochemical characterization. Classic manual crystallization efforts also can provide suitable hits that may not be observed in a high throughput screening mode.

Even if a suitable crystalline phase is not identified after executing both high throughput and manual screens, options still exist for progressing the compound. Advancing an amorphous phase is accompanied by certain risks, primarily that a crystalline phase can emerge with lower solubility and resultant oral absorption, as described earlier. If reasons are compelling enough to progress an amorphous drug phase into development, it is prudent to stabilize the phase via dispersion in a polymer in order to avoid unexpected crystallization. Milligram-scale technologies for preparation of amorphous dispersions are described briefly in a later section.

Once a chemist is able to scale up a hit from the high throughput screen (100 mg to 1 g if API is available), adequate API supplies should be available from the scale-up study to appropriately evaluate the solid state properties. Some desirable characteristics of a stable phase are shown in Table 2.

Once a phase(s) with acceptable solid state properties has been identified, the next stage is to evaluate the solubility/solution properties of that phase. Establishing the solubility properties of an API phase(s) is one of the central elements of physicochemical characterization, as this can directly correlate to oral absorption. While the solid state properties of API phases are used as contributing factors of which phase to move forward, the solubility and solution properties of various API phases under consideration can play an even more decisive role in API phase and formulation selection.[14]

The process of evaluating physicochemical properties of leading API phases is multifaceted (Figure 6). From determining API phase solubility in biorelevant media to evaluating particle size effects on oral absorption, the various parameters of API solubility/solution properties will affect the decision on which phase and formulation is selected for development. Dedicated time and resources are required to support both preparations of viable API lead phases on a reasonable scale and the necessary characterization studies for phase selection. The identification and optimization of these parameters increases the probability

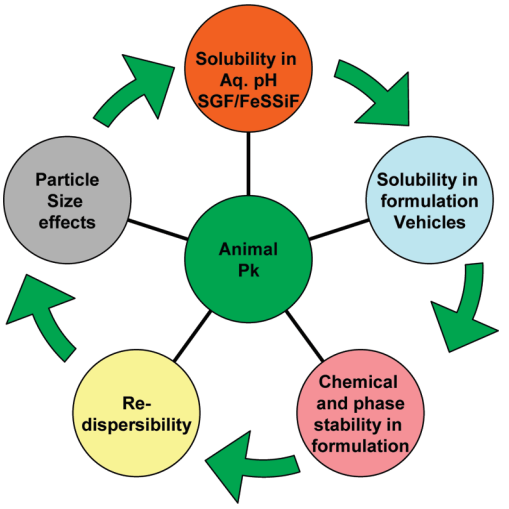


Figure 6. Process for phase selection based on physiochemical data and animal PK.

of achieving the desired PK outcome in preclinical and clinical studies.[15]

As shown in Figure 6, animal PK studies are the defining study for final evaluation of phase and formulation. Earlier in lead optimization, animal PK studies are performed on lead candidates in order to generate PK data that can help differentiate the potential candidates. At this stage, the studies are routinely conducted in rodents (usually rats) at low dose, the phases are often amorphous, and the formulation is simple. As the program progresses toward a selection of a candidate for development consideration, animal PK studies advance to include both rodents and nonrodents.[16] In addition, higher doses are often evaluated to ensure that appropriate exposures above the targeted PK parameter(s) are achieved. Hence, dose limiting toxicity studies or multiple rising dose studies often are conducted as the final study prior to development approval. Because the phase identity and formulation used plays a critical role in these key studies, prior optimization of phase and formulation is paramount, with final validation via an animal PK study.

Providing general guidelines or cutoff criteria for desirable solubility properties of leading phases is difficult, given the unique goals for each therapeutic program. Obviously, the more soluble is the phase, the better, although the solubility requirements for any particular program depend on a number of factors, including potency, PK profile, projected clinical dose, administration route, and permeability, to name a few.[17] In addition, the availability of enabling formulation technologies to poorly soluble compounds has resulted in loosening strict solubility criteria. Thus, a risk assessment that addresses the ability of a compound to achieve the desired oral absorption based on its intrinsic solubility properties provides a better means for determining the development potential of a compound.

In 1991, Oh et al. introduced the calculation of a "dose number" (D_o) as one means to assess the impact of solubility on oral absorption.[18] Dose number (eq 1),

$$D_o = \frac{M_o}{(C_s)(V_o)} \quad (1)$$

incorporates the saturation solubility in FaSSIF (C_s) along with mass of the dose (M_o) and the volume of the gastrointestinal (GI) media (V_o). This calculation is particularly useful in predicting oral drug absorption of poorly soluble compounds.[19] $D_o < 1$ indicates complete solubilization in intestinal media, whereas $D_o > 1$ indicates incomplete solubilization. At $D_o \gg 1$, the fraction of the absorbed dose declines with increasing dose because of solubility limitations (solubility limited absorption), and exposure consequently will reach a plateau. Hence, with a human dose prediction from DMPK colleagues in hand, calculation of D_o can help translate an in vitro solubility assessment in biorelevant media into the likelihood of developing a conventional clinical formulation.

API particle size reduction, often called micronization, is a standard practice for increasing dissolution rate via increasing the surface area of the particles. Increased dissolution rates often can lead to enhanced oral absorption. This is especially true for biopharmaceutical classification system (BCS) class II type compounds where solubility is low and permeability is high.[20] There are various milligram-scale milling techniques now available in a discovery setting (i.e., ball or jet milling). However, while milling has gained some acceptance as a tool for achieving enhanced absorption, there are still legitimate concerns with potential loss of the limited supply of compound, as well as the concerns with potential phase changes during the process. Consequently, a general guideline for micronization in discovery space that takes these aspects into consideration is useful.

Figure 7 shows a general approach for micronization in the discovery space. If the PSD is >25 μm, the compound should be milled, followed by a rat PK comparison of the milled vs unmilled API. Finally, after the milling is complete, the product should be characterized to ensure that agglomeration or a phase change has not occurred.

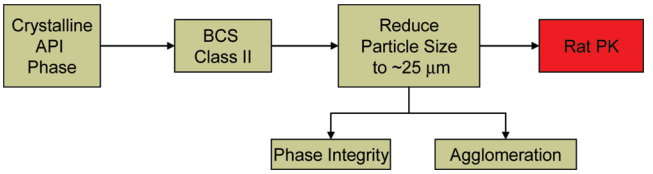


Figure 7. Workflow for micronization.

Continuum of Preclinical Formulation Options

Once a suitable API phase is identified and its fundamental solubility and intrinsic properties are understood, appropriate preclinical formulations (including toxicology) become a key area of focus. For the growing number of poorly soluble compounds, various enabling formulation options (ranging from simple to heroic) can be engaged for enhancing oral absorption.[21,22] One way we envision formulation options in relation to complexity is shown in Figure 8. Although we are not at liberty to disclose Merck's particular decision tree used for formulation selection, several excellent early formulation guidances or decision trees have been reported.[10,23] Not surprisingly, there are considerable similarities in the various decision trees reported.

When a simple suspension is adequate, micronization, as described earlier, is a relatively simple and well established means of increasing dissolution rate and reducing absorption variability. As particle size is further reduced, nanoparticles ("nanos", particle size below 1 μm) come into use for maximizing dissolution rate.[24,25] Small-scale methods for making nanoparticles such as media milling and high-pressure homogenization are becoming increasingly common in a discovery setting. Generally, the addition of a surfactant stabilizer is required to keep the nanoparticles from agglomerating. Regardless of particle size, it is worth noting that all suspension formulations should be characterized at least by light microscopy to have some understanding of what was dosed. In the case of nanoparticles, laser or photon correlation spectroscopy instrumental methods are required for characterizing the particle size distribution.[26] Although a simple solution or suspension formulation is always preferred, poor solubility or the need for increased exposure often requires us to move toward the right in Figure 8. There is a wealth of information available on the use of various enabling excipients such as surfactants,[27] cosolvents,[28] or lipid/emulsion formulations[29,30] which all can be very effective for enhancing the absorption of insoluble compounds.[31] However, one should take care when selecting the formulations used for in vivo behavioral models, where a poorly tolerated enabled formulation can confound observations from the study. Furthermore, although tremendous improvement in oral exposure can be gained through the use of enabled formulations, such measures often are less effective for challenging intrinsic API properties such as poor cell membrane permeability[32] (often observed initially via low permeability in the in vitro Caco 2 cell model). An example of the use of a small in vivo enabled formulation screen for enhancing exposure of an insoluble compound is shown in Figure 9. An observation here was that the most powerful solubilizing excipients (i.e., vitamin ETPGS) provided little increase in aqueous solubility (all <1 mg/mL) and no enhancement in oral exposure, whereas a nanoparticle was effective in driving exposure at the higher dose. Thus, implementation of a commonly used downstream drug delivery technology in discovery space was very useful in progressing this particular insoluble compound.

A well-known caveat exists with the use of concentrated solution formulations that contain significant amounts of a solubility enhancing excipient. This is the likelihood that the API will "crash" out of solution once the formulation enters the aqueous environment at some point in the GI tract. This is not always insurmountable, since the compound may precipitate as a reasonably soluble form such as an amorphous phase or nanoparticles. Regardless, the potential impact of this precipitation process can be evaluated by in vitro means, where the API formulation is sequentially diluted into simulated gastric fluid followed by a second dilution into FaSSIF as shown in Figure 10. The final concentration of the supernatant solution after removal of any precipitates allows for a series of formulations to be rank-ordered for solubility enhancement in the GI tract and gives a reasonable prediction of the formulation's in vivo performance and a rationale for the formulation selection.

No discussion of enabled formulations is complete without commenting on the use of amorphous API phases for enhancing

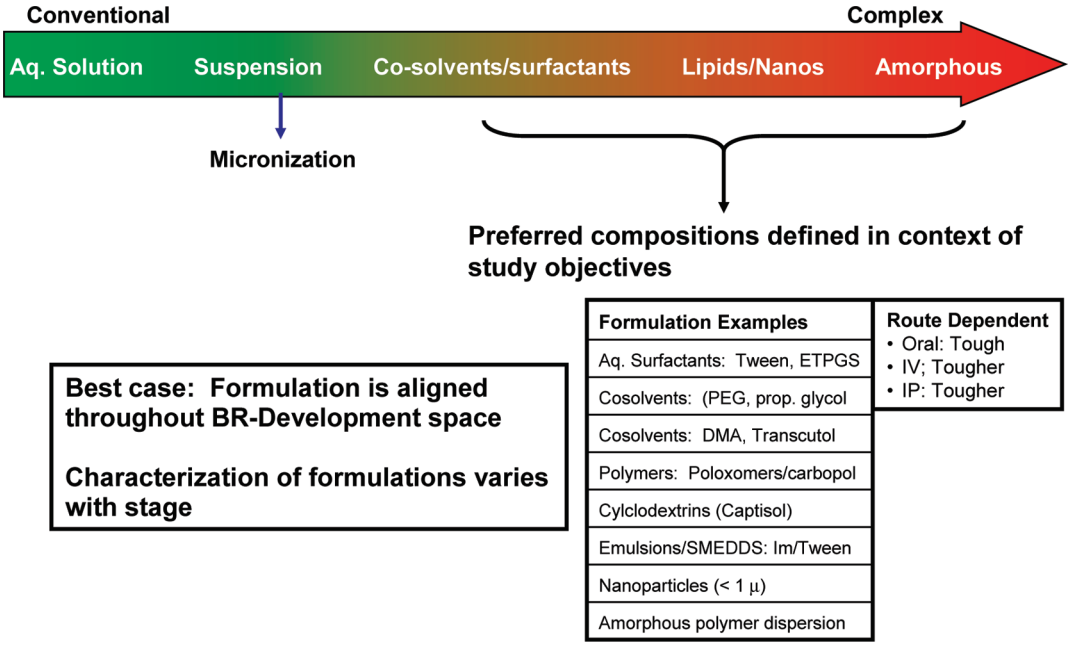


Figure 8. Some preclinical formulation options in relation to complexity (PEG, polyethylene glycol; PG, propylene glycol; iv, intravenous; ETPGS, vitamin E−PEG−succinate conjugate). Reprinted with permission from *American Pharmaceutical Review*.[5] Copyright 2009 Russell Publishing.

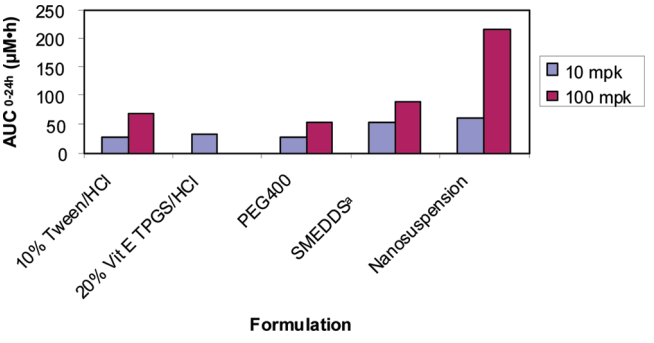


Figure 9. Oral exposure of an insoluble compound using various enabled formulations (male Wistar rats, 10 and 100 mg/kg (MPK); SMEDDS, self-emulsifying drug delivery system).

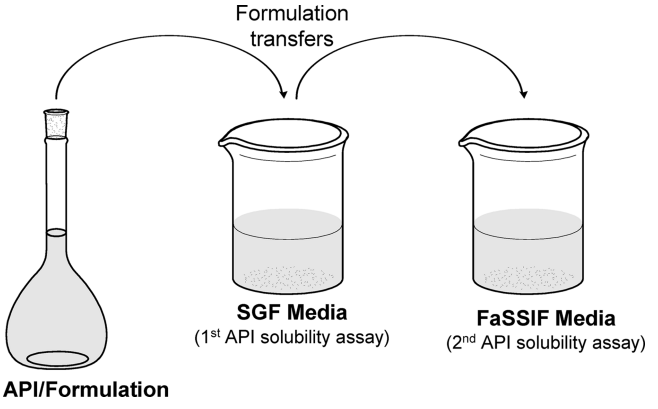


Figure 10. Simple GI dispersion experiment for predicting API precipitation from an enabled formulation.

drug solubility.[33] Toward this end, it is generally preferred to disperse the amorphous drug into an amorphous polymer (i.e., a "solid solution or dispersion" in polyvinyl pyrrolidine or a cellulosic polymer) in order to prevent crystallization. The practical methods of choice for the preparation of amorphous drug−polymer dispersions are hot melt extrusion[34] or spray drying.[35] Although it is fairly common in academic and development settings, the routine use of amorphous drug polymer dispersions in a discovery setting is less mature, partly because of the relatively large quantities of drug required to make the dispersion. As the preparative methods increase in efficiency (and decrease to milligram scale), amorphous solid dispersions are becoming an effective method for obtaining in vivo exposure for poorly soluble drug candidates when other formulations are not adequate.

Again, it should be recognized that the intended route of administration directly impacts the choice of formulation excipients,[36] and while there is significant overlap with some excipients, (i.e., PEG is useful for oral, iv, and ip routes), care must be taken to select formulation excipients that will be tolerated when administered by a given route.[37,38]

API Stability in Formulations. Once a suitable API phase and a functional preclinical formulation are identified, the chemical and physical stability of the API in the formulation must be well understood and carefully monitored. Although the API chemical stability requirement is obvious, phase changes often are more subtle but can be just as deleterious to the formulation's performance. This is exemplified in Figure 11, where XRPD of API solids isolated from a suspension formulation revealed that after several hours, the initial phase of the API was converted to a new polymorph. Naturally, this was not visible to the naked eye. As is often the case, the new phase was less soluble (more stable) than the starting phase. As expected, this resulted in lower and more variable exposures.

Ultimately, this scenario supports the strategy of performing at least some initial polymorph screening before any significant preclinical safety studies start, in order to build confidence that the most stable API phase is in hand and adequate exposure can be maintained.

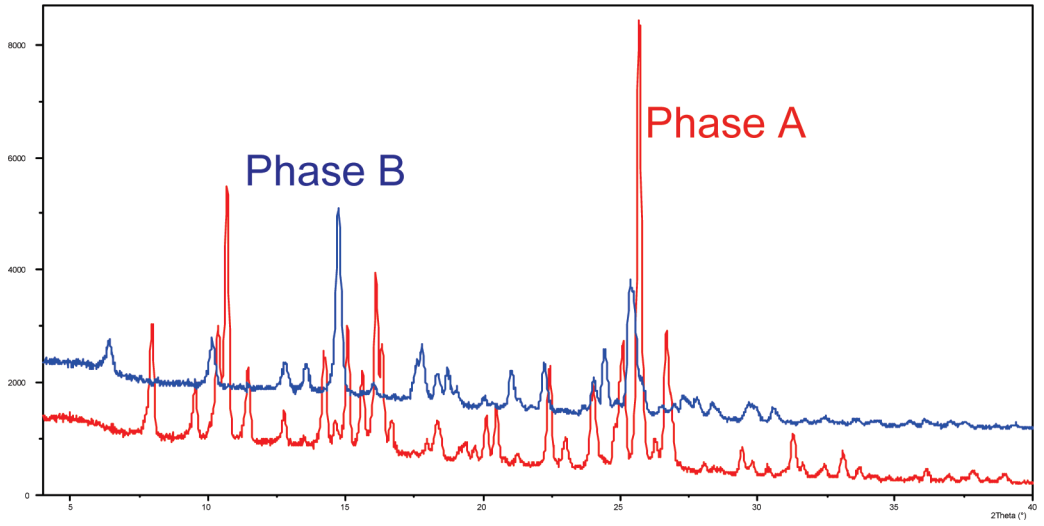


Figure 11. XRPD patterns showing the formation of a new polymorph isolated from a suspension formulation (conversion from phase A to phase B).

Preclinical Toxicology Formulation

Definition of a robust vehicle that provides the uniquely high exposures required to support a toxicology program often is the most challenging part of the preclinical formulation search. Success requires a close collaboration between pharmaceutical sciences, PK, and toxicology departments. Naturally, there are fewer formulation options for toxicology studies compared to efficacy or DMPK studies because of the concern that the presence of some excipients may confound a drug's toxicity profile. In this regard, there are several useful reports on the specific excipients that are widely accepted for use in toxicology studies and the associated dose limitations.[39]

Summary and Future Direction

In this article, we have highlighted our perspective on how early attention to the API solid state phase and preclinical formulation can benefit drug research programs in both the discovery and development stages. The strategies discussed represent one of many different approaches that can be applied to move from identification of a preclinical drug candidate through phase and formulation optimization as a final prelude to human clinical trials. However, early identification of an optimal phase and formulation comes at a cost, since time and resources from several areas spanning the discovery−development continuum must be engaged in order to quickly execute studies that historically were reserved for later stages when time and drug supplies are more abundant. One rationale we described for such investment relies on the significant benefits of maximizing physicochemical properties such as solubility in order to drive exposure in the toxicology program. Many have opined that contemporary biological targets often require highly lipophilic compounds in order to achieve the requisite pharmacological potencies. In order to also meet in vivo exposure targets, a strong interdisciplinary collaboration between medicinal chemists and colleagues with expertise in solid state phase evaluation and enabled formulation methods also is needed. This is now commonplace in the pharmaceutical industry.

Looking forward, it can be anticipated that lines will continue to blur at the traditional discovery−development interface. Given the long-standing challenge of API phase identification and evaluation, there continues to be a need for development of predictive modeling approaches that can be used to understand the relative solid state stability of various phases, including neat or stabilized amorphous phases relative to crystalline phases. Future needs also include further miniaturization of automated solid state phase discovery techniques and improvements in screening procedures that give confidence that these automated screening approaches are providing wide access to the potential of phase diversity. Likewise, development of new formulations and formulation screening approaches is needed in order to drive absorption of compounds with suboptimal physicochemical properties. Finally, as standard methods for preparation of amorphous dispersions such as spray drying and hot melt extrusion are further miniaturized and new synthetic solubilizing agents such as dendrimers[40] gain momentum, we can expect the arsenal of toxicology formulations to continue to grow.

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Biographies

Michael Palucki is currently a Senior Investigator in the Process Research and the Basic Pharmaceutical Sciences Department. He received his B.S. degree in Chemistry at the California State University of Fullerton in 1990. He then completed his Ph.D. in 1995 at Harvard University under the guidance of Professor Eric N. Jacobsen, focusing on asymmetric catalytic oxidations. He subsequently worked in the laboratory of Professor Stephen L. Buchwald at Massachusetts Institute of Technology as a NIH Postdoctoral Fellow developing Pd-catalyzed coupling reactions. Since 1997, he has worked in the Merck Research Laboratories wherein his current role is the West Point scientific leader of the chemistry group in the Basic Pharmaceutical Sciences.

John D. Higgins is currently Director of Basic Pharmaceutical Sciences at Merck Research Laboratories in West Point, PA. He received a B.S. in Biochemistry from Albright College and his Ph.D. in Synthetic Organic Chemistry from Brown University. After completing a Postdoctoral Fellowship at the Sloan-Kettering Cancer Institute, he has worked in a broad range of research areas in the pharmaceutical industry, spanning both drug discovery

(medicinal chemistry) and development. He is co-inventor on 12 U.S. patents and author of numerous publications and book chapter in the fields of organic, solid state, and medicinal chemistry and drug discovery.

Elizabeth Kwong is a Global Senior Scientific Director at Merck & Co., Basic Pharmaceutical Sciences at Merck Research Labs in Rahway, NJ. In addition, Dr. Kwong is currently appointed adjunct professor in the Department of Pharmaceutics at the University of Montreal, Canada, and Department of Chemistry at Concordia University, Canada. She received her B.S. in Pharmacy (1980) and Ph.D. degree (Pharmaceutical Chemistry, 1984) from University of British Columbia, Canada. She completed a postdoctoral fellowship in Pharmaceutics at the School of Pharmacy, University of Washington in Seattle (1984−1986).

Allen C. Templeton is currently a Senior Director and leads a group of about 80 staff dedicated to performing pharmaceutical science and process chemistry research in collaboration with discovery sciences at Merck's four discovery research sites. Dr. Templeton received his B.S. in Chemistry at Texas A&M at Commerce and his Ph.D. in Chemistry at the University of North Carolina at Chapel Hill. His personal areas of research interest include photochemistry, pharmaceutical product photostability, and solid-state pharmaceutical science.

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