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White Paper

Commentary: Why Pharmaceutical Scientists in Early Drug Discovery Are Critical for Influencing the Design and Selection of Optimal Drug Candidates

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Abstract. This commentary reflects the collective view of pharmaceutical scientists from four different organizations with extensive experience in the field of drug discovery support. Herein, engaging discussion is presented on the current and future approaches for the selection of the most optimal and developable drug candidates. Over the past two decades, developability assessment programs have been implemented with the intention of improving physicochemical and metabolic properties. However, the complexity of both new drug targets and non-traditional drug candidates provides continuing challenges for developing formulations for optimal drug delivery. The need for more enabled technologies to deliver drug candidates has necessitated an even more active role for pharmaceutical scientists to influence many key molecular parameters during compound optimization and selection. This enhanced role begins at the early *in vitro* screening stages, where key learnings regarding the interplay of molecular structure and pharmaceutical property relationships can be derived. Performance of the drug candidates in formulations intended to support key *in vivo* studies provides important information on chemotype-formulation compatibility relationships. Structure modifications to support the selection of the solid form are also important to consider, and predictive *in silico* models are being rapidly developed in this area. Ultimately, the role of pharmaceutical scientists in drug discovery now extends beyond rapid solubility screening, early form assessment, and data delivery. This multidisciplinary role has evolved to include the practice of proactively taking part in the molecular design to better align solid form and formulation requirements to enhance developability potential.

KEY WORDS: drug candidate selection; preclinical formulation development; drug candidate design; pharmaceutical properties.

INTRODUCTION

More complex biological targets and modes of drug action, such as the recent focus on the benefits of allosteric modulation [1] and polypharmacology [2], have shifted molecular parameters [3] out of the traditional "rule of five" chemical space. Unsurprisingly, many drug candidates from this non-traditional space demonstrate poor physicochemical properties such as aqueous solubility [4,5]. Over the past two decades, there has been an increasing effort to bring new drug solubilization and delivery technologies earlier in the development cycle and enable successful new molecular entity (NME) progression to become viable clinical and commercial therapies [6]. Advanced delivery technologies can also be successfully applied in the early discovery space for evaluation of critical "tool" molecules such as known competitor compounds, as well as positive or negative control compounds in exploratory preclinical proof of concept or safety studies. The need for enabled drug delivery measures to support a wide variety of preclinical studies has been greatly facilitated by the inclusion of formulation and pharmaceutical scientists in drug discovery teams.

Traditionally, the pharmaceutical scientist role has supported a multitude of activities in the early space including [7]

- Evaluation of physiochemical properties
- Biopharmaceutical evaluation
- Formulation development for preclinical *in vivo* studies

In early physicochemical property evaluations, the focus is on rapid generation of solubility and stability as well as initial solid form and salt screening data (*e.g.*, crystallinity and

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hygroscopicity). These evaluations typically occur in a moderate to high throughput fashion to keep pace with the rapid generation of candidate compounds to provide timely feedback to discovery teams. In addition to collecting and interpreting a multitude of physicochemical property data, pharmaceutical scientists highlight both the development opportunities and the risks of progressing particular drug candidates. Predictive solid-state characterization technologies for computing the crystal energy landscape show promise in guiding teams towards solid forms with ideal solid-state properties for optimum drug delivery [8].

Pharmaceutical scientists generally lead solid form selection and formulation strategy as part of the biopharmaceutical evaluation of lead compounds. As information about the chemical series develops, the limiting biopharmaceutical aspects of the molecules are often mitigated through formulation. Thus, optimal exposures and desired pharmacokinetic profiles can be realized. Occasionally, the designated delivery systems fail to achieve the desired exposure profiles and/or bioavailability, which leads to a situation where an otherwise promising candidate is not advanced. However, this failure often provides important and vital information regarding the limiting physicochemical properties of the molecule and/or compatibility with the chosen formulation. The learnings associated with these failures provide the opportunity to design more robust molecular scaffolds and subsequent drug candidates that work well with the intended formulation and delivery strategy.

At the compound optimization stage, formulation development for candidate molecules occurs rapidly to keep pace with the needs of the multitude of efficacy, pharmacokinetic, and toxicological studies. Solution, suspension, and other solubility-enabling formulations are developed to evaluate candidates and tool compounds in a number of different *in vivo* models. Often, delivery of high doses is necessary for non-orally optimized molecules with challenging physical chemical properties. The time investment to solve these delivery challenges is often worthwhile, because the information gained from these studies is invaluable in exploring structure-activity or structure-safety relationships. In the course of developing formulations for these studies, feedback on the delivery risks and development hurdles for the key lead proprietary candidates can be highlighted. Once the trends in the limiting or challenging physicochemical properties of the lead compounds are determined, the series can often be optimized for delivery, particularly when use of enabled dosage forms is required.

The shared experiences of the authors as pharmaceutical scientists supporting drug discovery teams in different companies indicate the value and necessity of a more active and expanded role for the discipline within discovery teams. This expanded role includes assessing and providing guidance on molecular factors and elements that limit enable formulations (*e.g.*, solubility enhancement) for optimized drug delivery. This philosophy of "designing with delivery in mind," combined with the knowledge and expertise of pharmaceutical scientists on the necessary structure and molecular attributes is envisioned to enable efficient design and selection of compounds, solid forms, and delivery formulations. This in turn will aid successful clinical translation, clinical development, and commercialization efforts. A more detailed assessment of the current and future directions for pharmaceutical scientists to support the selection and development of new chemical entities from *in vitro* studies at early stage drug discovery to the use of enabling technologies for development of clinical formulations is expressed in the following section.

EARLY STAGE DRUG DISCOVERY SUPPORT INTERACTIONS

Involvement in early drug discovery provides pharmaceutical scientists the opportunity to influence structural design and ensure that clinical drug candidates have biopharmaceutically suitable or so-called "druggable" features. Thousands of compounds are screened with *in silico* tools and *in vitro* assays against predefined thresholds to yield a smaller yet still substantial subset of promising candidates for further *in vivo* pharmacodynamic and pharmacokinetic testing. Molecular knowledge gained at the early stages is broad but not deep, yielding a lot of data across several chemotypes or structurally similar compounds, but little specific data for any one compound. Emerging structure analysis tools, such as the Quantitative Estimate of Drug Likeness score (QED), are very helpful in quickly assessing a drug candidate for degree of drug-likeness and are useful for comparing large molecular data sets for clues about limiting pharmaceutical proprieties or molecular properties that are useful for efficient formulation [9]. Pharmaceutical scientists must therefore use prior experience, insight, new assessment tools, and judgment to interpret the available information and guide compound progression and selection decisions, an ability which can be as much art as science.

In Vitro Screening Support and Interpretation

In vitro assays are used to establish whether compounds possess the desired target affinity, off target toxicity liabilities, and biopharmaceutical properties such as permeability, metabolism, protein binding, and solubility [10]. These experiments are tiered to balance resource use, with the most critical and least resource intensive data collected first. As a result, greater amounts of information are collected on fewer compounds as they are successively filtered through each testing tier [11] (Fig. 1).

An unintended consequence of the initial focus on target affinity is that it often yields compounds with poor aqueous solubility [4,5]. This can be problematic for subsequent assays requiring higher concentrations. To overcome this challenge, compounds are predissolved in an organic solvent such as dimethyl sulfoxide (DMSO) prior to dilution into the aqueous assay media. This can create a thermodynamically unstable supersaturated state [12] that can lead to precipitation or container surface adsorption [13,14].

Nephelometry [15] is a turbidimetric assay commonly used to provide confidence that a negative assay readout is a true reflection of the compounds' lack of activity rather than a

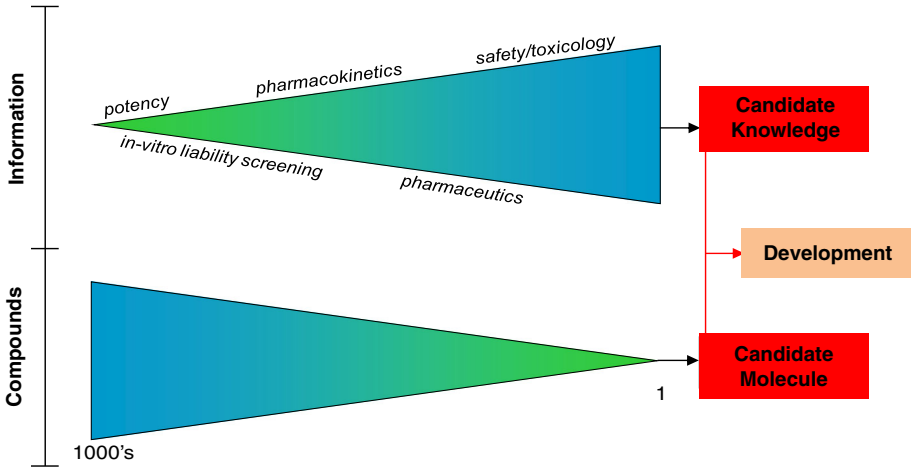

Fig. 1. Depth of knowledge gained during the drug discovery process (adapted from [11])

solubility limitation. Essential structure-property relationship data can be collected for these poorly soluble compounds by incorporating an adsorption/precipitation inhibiting excipient into the assay media, albeit one which does not interfere with the assay readout [16]. Counterintuitively, false negative results due to precipitation or surface adsorption can also be beneficial for pharmaceutical scientists since compounds with poor physicochemical properties tend to be removed early from further consideration as drug candidates.

While solubility is a critical biopharmaceutical property impacting all areas of drug discovery, measuring equilibrium solubility values across large compound sets is not practical. Nephelometry and direct supernatant concentration measurements provide an early assessment of solubility. Unfortunately, these kinetic solubility values tend to overpredict equilibrium solubility, sometimes by orders of magnitude [15]. Despite this, the data can provide some insights. For instance, tracking kinetic solubility progression over time both across and between chemotypes provides an early warning of potential solubility risks for the ultimately selected drug candidates.

In Vivo Study Support and Interpretation

Promising drug candidates meeting the *in vitro* assay screening criteria are scaled up for further preclinical pharmacodynamic and pharmacokinetic profiling studies. At this stage, both the physicochemical nature of the compounds and the formulation strategy play crucial and sometimes underappreciated roles.

Material scale-up can result in a more thermodynamically stable polymorphic form, especially if the synthetic route or purification procedure has been further optimized. Such form changes may lower solubility, both in gastrointestinal fluids and in formulation vehicles. Early discovery formulations must overcome solubility limitations and satisfy several additional criteria:

- *Universality*—effective delivery across a wide range of compounds
- *Capacity*—effective delivery across a large range of doses
- *Throughput*—efficient and consistent preparation across multiple dosing groups
- *Tolerability*—safe to test animals and non-interfering with the assay readouts

Compatibility between the chemotype and the formulation is established early using a small subset of representative compounds, but the formulation may require modification as the chemotype progresses. The particular formulation strategy employed can also influence chemotype evolution, for example:

- Emulsions favor more lipophilic compounds
- Cyclodextrin solutions favor compounds with better complexing efficiency
- Suspensions favor compounds with better dissolution and/or solubility characteristics
- Supersaturated formulations favor compounds with greater inherent supersaturation tendency

The need for throughput also precludes the use of more advanced formulations such as amorphous solid dispersions. These early compounds may not be optimized for oral delivery and may be susceptible to high first-pass metabolism [17], necessitating delivery by parenteral routes such as intraperitoneal, subcutaneous, or intravenous administration in order to collect critical structure activity relationship information. In general, oral dosing is the ultimate and preferred route of administration and the metabolic liabilities are designed out of the molecule during further optimization iterations.

The potential for increased oral absorption from a supersaturated formulation can also be an important point of differentiation during compound optimization, especially for a poorly soluble compound [18]. Supersaturation is achieved by transferring a compound from a higher energy environment to a lower energy environment [19], such as

- A higher energy solid form (amorphous, salt, or cocrystal)

- Fast intestinal dilution of a cosolvent-containing vehicle
- The gastric-to-intestinal pH shift for weakly basic compounds

The supersaturation advantage may be negated by rapid precipitation, and gastrointestinal differences in pH and bile content [20,21] between test animals can lead to different precipitation profiles and oral exposure variability. Precipitation inhibiting formulations and excipients is employed to reduce this variability, but care must be taken that the chemical potential driving force for intestinal increased absorption is not unintentionally lowered through oversolubilization that exceeds supersaturation limits [22].

It is also valuable for pharmaceutical scientists to look beyond standard pharmacokinetic readouts [C_{max}, T_{max}, and area under the curve (AUC)] and examine individual plasma profiles to observe the source of variability [23] (Fig. 2). In cases where alternative or enabling formulations do not improve exposure, physiological factors may be responsible. Codosing with an efflux inhibitor such as elacridar [24] can diagnose whether compounds and perhaps chemotype moieties are efflux substrates. Portal and jugular vein cannulated pharmacokinetic studies are useful in distinguishing poor intestinal absorption from hepatic first-pass effects [25,26], respectively. An improved formulation may overcome the former but not the latter.

SOLID FORM ASPECTS

The crystallinity of solid forms and their stability are closely linked to the physicochemical and biopharmaceutical properties of new chemical entities. Many drug candidates can exist in more than one solid crystalline form, or polymorph. These forms are characterized by their unique X-ray powder diffraction, unit cell dimensions, and melting point. Changes in the crystalline structure such as defects and imperfections in the crystal lattice can change the apparent solubility and affect dissolution rates [27]. For example, amorphous solids lack crystallinity and are often more soluble than their crystalline counterparts. However, amorphous solids are thermodynamically unstable and pose a developability risk compared to the more physically and chemically stable crystalline solids. Thus, evaluating the potential for multiple solid forms of a drug candidate is an important aspect of the developability assessment as it may affect solubilization, compaction, and flow and impact manufacturability of dosage forms.

Forming salts or cocrystals represents alternative solid phases of a compound that can improve dissolution, solubility, hygroscopicity, and stability. Salts are formed by complete proton transfer to create ion pairs, whereas cocrystals are formed from an incomplete proton transfer or proton sharing. More specifically, cocrystals are defined as "crystalline structures made up of two or more components in a definite stoichiometric ratio where the arrangement is not based on ionic bonds" [28]. Cocrystal formation is mostly applicable to compounds with weakly ionizable groups that cannot form true salts.

Salts, cocrystals, and amorphous forms are also used in early development to improve dissolution which in turn can maximize exposure in preclinical pharmacokinetic and toxicology experiments. For developability assessments of these forms, the effect of temperature, humidity, compression, and grinding should be tested to determine if there are any solid form changes. Such form changes can, in turn, affect storage, stability, excipient compatibility, and manufacturing processes. Additionally, when salts and cocrystals are in solution or suspension, the physical instability of these forms due to disproportionation should be considered [29].

Understanding the relationship between the different solid forms and the most stable thermodynamic form is essential for ensuring a reproducible manufacturing process for both drug substance and drug product. Screening for possible crystalline

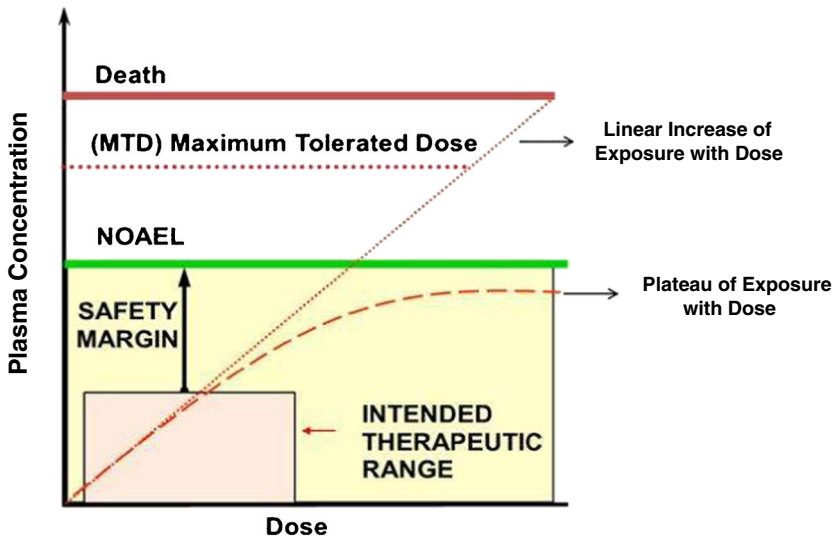

Fig. 2. Plasma concentration *versus* dose relationship in toxicology testing (reproduced with permission from [54])

forms of a drug candidate can be accomplished through either manual or moderate to high throughput procedures to assess for different potential polymorphs, salts, and/or cocrystals. Both methods typically involve a number of techniques to crystallize the drug candidate: use of various solvents, fast or slow evaporation, addition of anti-solvents, and possibly by mechanical stress [26]. Early development often involves testing a subset of these conditions to minimize material consumption when supplies are limited. More extensive screening can be pursued as more material becomes available. These screens are designed to maximize success rates in selecting a thermodynamically stable solid from that can be scaled up and reproduced successfully.

Yang et al. have recently shown the most stable polymorphs for benzene, a small, simple, symmetrical, and rigid organic molecule, can be predicted. However, predicting the most stable polymorphic forms of more complex and flexible small molecule drugs has remained elusive [30].

ABSORPTION MODELING TO FACILITATE DELIVERY AND FORMULATION AND DESIGN EFFORTS

Absorption modeling of orally administered compounds is the pivotal component that connects the solid (or physical) form of the compound, the delivery system, the intended pharmacokinetic and toxicokinetic profiles, and the desired therapeutic outcome. A number of tools of varying levels of sophistication are available for this purpose and, when used appropriately, can provide valuable information with multi-faceted applications. Absorption modeling can be used to guide formulation selection for pharmacology and toxicology studies, establish particle size parameters for clinical dosage forms, and enable formulation development and solid form (salt and cocrystal) selection for clinical formulations. In the hands of an experienced pharmaceutical scientist, the use of these tools can minimize the number of *in vivo* studies that would otherwise be necessary to drive these important project decisions.

The most basic modeling tools use the measured solubility, intestinal permeability, and particle size as inputs into simple tools to estimate the maximum absorbable dose as a function of particle size [31]. These tools generally provide reasonable guidance and are very convenient to use, especially for early assessments where there is limited knowledge of compound properties. However, for compounds with a significant pH-dependent solubility or a high supersaturation propensity, measured equilibrium solubility at neutral pH may not adequately model dissolved drug concentration throughout the entire absorption window. In these cases, the use of biorelevant dissolution tools along with more sophisticated absorption modeling tools such as MiMBa®, GastroPlus®, STELLA®, or Simcyp® might be better suited [32–36]. The solid form from either undissolved or precipitated material should also be assessed as a change in polymorphic form can affect solubility and dissolution [37]. A number of excellent reports discuss the comparative features and applications of the wide variety of biorelevant dissolution technologies available [38,39].

Figure 3 illustrates an absorption modeling flow scheme, incorporating the *in vitro* absorption parameters, the available non-clinical pharmacokinetic data, and an *in silico* absorption model to derive clinical absorption parameters in the context of the planned clinical dose range. The final outcome is an estimate of the amount absorbed as a function of administered dose for a specified particle size. Alternatively, plots can be generated to predict the relationship between amount absorbed and particle size at a specified dose.

Absorption may also be influenced by gastric pH and feeding state leading to oral exposure variability, depending on the pH-dependent solubility profile and dissolution properties of the drug candidate. These factors should be characterized and appropriately applied in designing formulations as well as clinical studies. For Biopharmaceutics Classification System (BCS) Classes 2 and 4 compounds, particle size reduction alone may not provide adequate

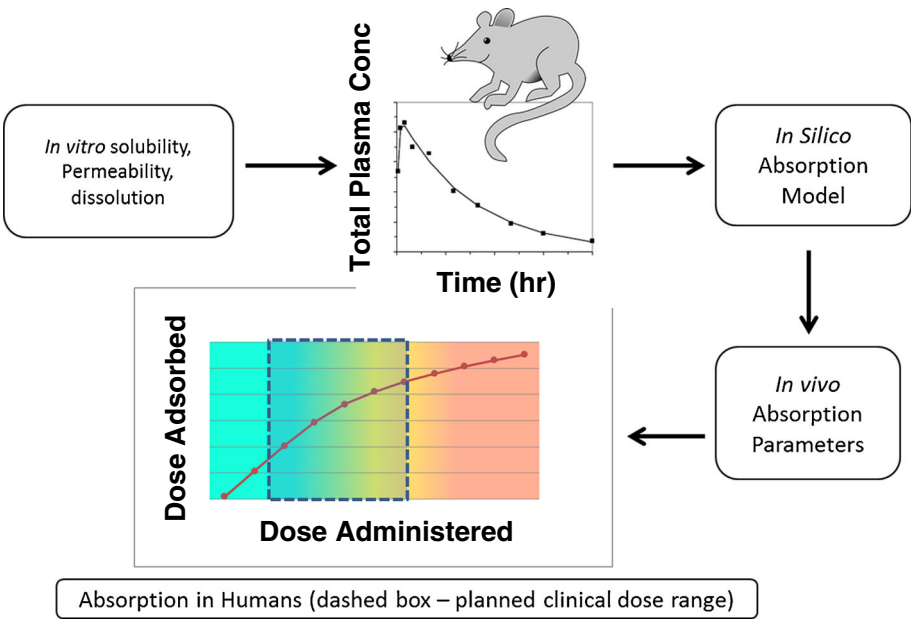

Fig. 3. Illustration of the absorption modeling flow scheme

absorption over the desired clinical dose range. It may therefore be necessary to develop alternate options such as salts, cocrystals, amorphous solid dispersions, lipid-based, or nanocrystalline formulations to provide the desired exposure profile.

The *in vivo* dissolution behavior of crystalline solids can be relatively well characterized with standard biorelevant *in vitro* dissolution tools. However, the dissolution, supersaturation, and precipitation of enabled solids are more complex and the assessment tools are still evolving [40]. Consequently, judicious application of orthogonal dissolution screens and careful analysis and modeling of data can provide reasonably predictive results [41,42].

While the importance of modeling clinical absorption to inform drug product development and clinical research cannot be overstated, the same tools can be used to inform non-clinical *in vivo* studies in pharmacology and toxicology [43]. When appropriately applied, these tools can vastly influence compound progression in discovery lead optimization, increase the technical success of the studies, and minimize wasteful synthesis of material that might go unabsorbed despite the best enablement technologies.

FORMULATION AND DELIVERY ASPECTS

In the course of a drug discovery program, many different compounds are evaluated during early stage formulation development. Typically, predicted and/or measured physicochemical properties are utilized to guide the initial formulation selection process. More recently, there is a high prevalence for utilizing enabled formulations early, when the biopharmaceutical properties of the chemical matter are unoptimized and often high doses as well as larger dose ranges are needed to fully explore efficacy and safety end points.

During the formulation screening and development process, "structure-formulation performance relationships" can be constructed with the understanding that these are subtle at such an early stage. Careful observations on which formulation approaches succeed or fail may be correlated to possible/probable specific structural attributes. Working hypotheses for structure-formulation performance relationships should also be developed for key lead series. From these relationships, the formulation scientist can recommend areas of the molecule to be optimized to increase the performance of the enabled formulation, thereby enabling a more robust drug delivery.

General descriptions of molecular properties that guide enabled formulation selection are outlined in Table I. This information includes the typical physicochemical space and preferred solid form of the drug candidate for each formulation approach. If a formulation platform appears promising for a certain series, the formulation scientist can guide the drug design teams to remain within a designated chemical space and incorporate any molecular changes determined from the structure-formulation performance observations which will improve or enhance the drug's performance in that formulation.

Non-aqueous pharmaceutical solvent solubilization (polyethylene glycols, propylene glycol, etc) is an early formulation approach that can be utilized for both oral and parenteral dosing [44]. This type of formulation platform can be translated into liquid filled capsules for drug product production to support clinical and commercial drug delivery. In most cases, non-ionized acidic or basic as well as neutral molecules are best to achieve optimal solubilization; however, salt forms of bases ameliorate potential oxidative chemical stability risks. General molecular and physical chemical property considerations for efficient formulation include a moderate lipophilicity (Log *P*, between1 and 3), the presence of several hydrogen bond acceptors, and a moderate melting point, T_m (*i.e.*, T_m <200 °C) [45]. Relative to dose, the drug candidate should have sufficient solubility and long-term physical stability in these solvent systems.

An additional factor to consider is the high precipitation potential which solvent systems pose upon introduction to aqueous environments. This phenomenon is a major concern for bioperformance, and the risk increases with increasing dose. Precipitation inhibiting excipients is typically screened and utilized in these formulations. Screening for lipophilicity, crystallinity (melting point), solubility, and precipitation potential as well as chemical and physical stability in these solvent systems are key factors in guiding candidate selection. These factors should be considered early and throughout the design process. Alternatively, compounds may precipitate as an amorphous form through either liquid-liquid phase separation (LLPS) or liquid-solid phase separation (LSPS) [46,47]. In these cases, the supersaturation advantage is not completely lost as the amorphous form tends to be more soluble and faster dissolving than the original crystalline material.

Self-emulsifying formulations (SEDDs) of the lipophilic type, such as Type I, II, and IIIA [48], are often considered for hydrophobic compounds with moderate to high Log *P* (>3) and compounds with melting points less than 225 °C and preferably less than 150 °C. Formulation development factors include the solubility of the drug in the lipoid excipient components, the chemical and physical stability of the drug in the formulation, and the amphiphilicity of the drug, which can correspond to the degree of association and solubility of the drug in the surfactant excipients. Lipids can form peroxides over time and drug candidates with strongly basic sites (conjugate acid p*K*a >6) may be prone to oxidation. Consequently, recommendations to design teams may involve the decreasing of the basicity of free amine sites. Crystallization of the drug substance from the formed emulsion (*i.e.*, after dispersal in water and/or following lipid digestion) is often a concern and molecular design factors which can decrease melting point, such as removal of hydrogen bond donors and acceptors, can alleviate emulsion crystallization problems.

Spray dried dispersions (SDD) to stabilize the amorphous form of a drug candidate in cellulosic polymers are a common enabled solid form alternative for insoluble crystalline materials. Key parameters that dictate successful SDD formulation include Log *P*, crystalline melting point (T_m), and the amorphous glass transition temperature for the drug substance. Molecules with moderate Log *P* values [2–4] and fewer hydrogen bond donating or accepting heteroatoms are generally preferred. The amorphous materials should have relatively high T_g values (*i.e.*, >40 °C) for optimal physical stability to reduce the likelihood of crystallization. Molecular

Table I. Enabling Formulation Selection Criteria and Preferred Solid Form Recommendation

Enabled formulation approach	Typical physical chemical space	Preferred solid form
Non-aqueous pharmaceutical solvents (polyethylene glycols, propylene glycol, etc)	• Moderate lipophilicity (Log *P*), generally 1–3 • Utility increases with decreasing melting point (T_m)	Salt[a] of base or free form of acidic or neutral molecules
Lipophilic self-emulsifying drug delivery systems (SEDDs): Type I, II, and IIIA [48]	• Log *P* >4.0 • T_m <225 °C, • High solubility in triglycerides oils and lipid components	Free form (no salt forms)
Spray dried dispersions in cellulosic polymers (SDD)	• Methanol, acetone, ethyl acetate, or THF solubility >5 mg/mL • T_m/T_g (K) <1.4 • T_m <250 °C, • Log *P* 1–7 • Chemically stable between pH 3–5 (for acid-containing polymers)	Free form (no salts)
Wet-milled nanosuspension	• Aqueous solubility <150 μg/mL, prefer in μg/mL range • Log *P* 0–8 • Melting point 100–350 °C • Crystalline • Mechanical properties of brittleness	Salt or free form
Cyclodextrin-containing solutions	• Compatible aryl substitution and geometry required for complexation	Salt or free form

[a] Some "hard" acid salts such as hydrochloric, sulfate, and phosphate may be less soluble in pharmaceutical solvents than the free form

features that affect the glass transition temperature of small molecules include the molecular shape and volume, as well as the type and degree of shielding of hydrogen-bonding capable functional groups [49].

Wet-milled nanosuspension (nanocrystal) formulations perform best when the drug candidates are crystalline and have a low aqueous solubility (*i.e.*, <150 μg/mL) to prevent ripening and crystal regrowth. The bulk drugs should have high brittleness properties and low ductility and elasticity properties [50] to enable efficient size reduction through attrition milling. This deliver option applies to a broad range of drug molecules, with melting points generally 100–350 °C and Log *P* values of 0–5.

Aqueous cyclodextrin formulations are common for parenteral dosing of poorly soluble drugs. Solubility is improved *via* molecular complexation of the drug molecule within the more hydrophobic interior oligosaccharide "cage" of the cyclodextrin [51]. Generally, molecules demonstrate more efficient cyclodextrin complexation when they contain (i) monocyclic aromatic groups with little substitution or few ionizable centers at or near these aromatic rings, (ii) lipophilic groups, or (iii) low steric hindrance [52]. This information and the ability to predict cyclodextrin binding from a chemical structure can be utilized, but the pharmaceutical formulator to provide important guidance to medicinal chemists on what structural features will be beneficial for incorporation into the molecular framework.

Overall, there is a range of molecular features that pharmaceutical scientists can recommend to improve the performance of drugs candidates with enabled formulations. A critical understanding of the molecular features of lead compounds that affect formulation performance is gained through comprehensive early formulation screening and careful, thoughtful experimental observation.

TOXICOLOGY STUDY SUPPORT

Discovery and design efforts often extend into Phase 1 and Phase 2 clinical evaluation, with timely feedback informing optimization of backup candidates. This feedback may include the need for improved pharmacokinetic properties, physical or chemical stability, efficacy, safety, and selectivity.

The goal of the toxicology delivery strategy for any compound is to develop a safe formulation that provides sufficient *in vivo* exposures necessary to investigate the toxicology profile of the compound and establish a clear margin of safety. Determining the *maximum tolerated dose* (MTD) to demonstrate target organ or dose-limiting toxicity is a general expectation of regulatory authorities in support of clinical testing (Fig. 2). Ideally, the formulation provides a linear increase in exposure with dose. In practice, at least some dose-escalating exposure increase is often reasonable to achieve the desired exposure end points. Solubility limited molecules may exhibit some plateauing of exposure with dose, but ensuring that the formulation provides dose separation is critical to establishing safety margins.

In the absence of an MTD, other equally appropriate dose-limiting criteria may be considered, if met. For instance, establishing and characterizing either a *maximum feasible dose* (MFD) or an exposure-limiting dose (*i.e.*, 1000 or 2000 mg/kg) which provides an acceptable exposure margin

or a 50-fold exposure multiple relative to the clinical dose [53]. Several excellent publications on this topic describe the underlying principles of toxicology studies and formulation development in detail [54–57].

In general, conventional aqueous suspensions or pH-adjusted solutions are preferred as they are fairly benign and can accommodate a broad dose range. These formulations are the safest and simplest of all options. However, when absorption is limited by low solubility and/or incomplete dissolution, alternate options are required to provide sufficient exposures and meet the needs of the toxicology studies. The various approaches described in Table I may be applied for developing these alternate formulations, with due consideration being given to the large doses that need to be delivered, the therapeutic targets under investigation, and the safety/acceptability of the vehicles for the durations of the studies.

Cosolvent and lipid-based vehicles offer simple alternatives to aqueous-based formulations; however, they may not be acceptable for long-term studies. Nanocrystalline suspensions and amorphous solid dispersions are often employed to support toxicology studies when conventional aqueous-based options are insufficient [58]. For compounds with the pH-dependent solubility, it is important to ensure that gastric pH variability does not impact the dissolution profile and thus the oral absorption of the compounds, especially in dogs [59].

The design and development of these enabling formulations are not an isolated activity. An integrated approach is necessary, incorporating a comprehensive understanding of the physicochemical and biopharmaceutical properties of the compound, the intended therapeutic target and dose, the desired safety margins, and the physiological aspects of the non-clinical species in which the studies will be conducted. It is also important to balance the benefits of the formulation options with the cost, potential risks, and technical complexities associated with their manufacture and handling.

EARLY CLINICAL FORMULATION DEVELOPMENT

Clinical formulations for Phase 1 and Phase 2a studies are generally designed to be as simple and inexpensive as possible to rapidly meet the clinical testing needs. The formulations should also offer flexibility for testing large dosing ranges, since doses are subject to change as additional information on non-clinical safety margins, clinical pharmacologic, and pharmacokinetic response are collected [60]. In developing the clinical formulations, it is extremely important for pharmaceutical scientists to have a comprehensive understanding of the planned clinical dose range, the dosing protocol (including in-clinic *vs.* take-home dosing and feeding state), the absorption parameters of the compound, the desired pharmacokinetic profile, and any disease/physiological parameters that might impact absorption in the clinical subjects. It is also important to ensure that the physical and chemical stability profile of the compound in question is well understood and will not impact delivery and bioavailability of the dose. Lastly, to the extent it is possible, clinical formulations should be developed with an appropriate line of sight to commercial development.

For immediate release oral delivery, the simplest clinical formulations would include solution or suspension formulations for the so-called "drug in bottle" (DIB) administration. Alternatively, neat drug candidate or simple dry blends can be supplied in a capsule or compounded into tablets for compression in a clinical pharmacy. Controlled release formulations can also be extemporaneously prepared in the clinical setting where necessary and can significantly speed up early clinical development [61].

CONCLUSION

Pharmaceutical scientists face a number of challenges and opportunities during the discovery and development of new medicines. In the discovery environment, they must adapt their functional expertise to the ever-changing needs of drug discovery teams. This requires employing specialized physicochemical, biopharmaceutical, and delivery strategy knowledge, as well as maintaining a general understanding of the efficacy, pharmacokinetic, and toxicological requirements of each particular program.

Based on the authors' collective experience, pharmaceutical scientists can and should influence structure property relationships by "designing in" appropriate molecular features at the earliest stages of drug discovery. This can be done by ensuring compatibility with anticipated delivery strategies, such as solvent solubilization, lipidic emulsions, amorphous solid dispersion, particle size reduction, and salt or cocrystal formation. These strategies must maintain a "line of sight" to first in human (FIH) and later clinical studies and, ultimately, commercial formulation. This process, in turn, requires ensuring there are reasonable paths forward for both drug substance solid form, as well as the anticipated formulation and delivery strategies. Despite the complexities and challenges, the pharmaceutical scientists' involvement during drug discovery and molecular design stages is crucial for the development of successful clinical candidates and ultimately new medicines for patients.

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