EDITED BY **ELIZABETH KWONG**

ORAL FORMULATION ROADMAP FROM EARLY DRUG DISCOVERY TO DEVELOPMENT

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Contents

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Preface

The discovery and development of new drugs is a very complex machine. Despite increasing investments in research and development, the number of new drug approvals has not increased, while the attrition rate of new drug candidates has increased. Many of these challenges are due to failure to properly identify formulations that are translatable from preclinical to the clinic due to lack of effective predictions of therapeutic and toxicological responses in the preclinical stages. Moreover, efforts spent to integrate the formulation scientists in the early discovery that leads to the lead candidate selection had been disappointing. Most of the time, the lack of understanding of the interplay of the physiological system to the formulation contributed to the failure to integrate the right expertise at the right time, which leads to poor clinical successes. The lack of collaboration and proper integration between the formulation and discovery scientists is the root cause of most of the failure in the clinic. Lastly, the understanding of regulatory requirements for formulations also can add to the burden of the timeline and cost of bringing a drug candidate forward.

This book describes and explains key factors that will help determine the types of formulation needed at the different stages of discovery. The considerations of limited amount of API in early stages to the use of the formulation to determine key efficacious or toxicological end point that will not interfere with readouts will be discussed. The formulation selection stage-dependent approach will be detailed up to the planning for the regulatory filing. The interplay of drug metabolism, absorption, and physicochemical properties of the active will be laid out to help understand when a formulation can be improved and when a different lead candidate should be selected. Current formulation approaches based on the biopharmaceutics classification system (BCS) of the lead will be explained. The book will also focus on the relationships between various disciplines like physical chemistry, analytical chemistry, biology, DMPK, toxicology, and medicinal chemistry in determining the appropriate formulation to deliver the candidate in different forms. API sparing approaches including *in vitro* and fit-for-purpose formulation to support first-in-human

study will also be covered in the book. Partnership considerations with contract manufacturing organization (CMO) will also be described and shared to increase the probability of meeting tight timelines and to ensure the proper selection of formulation to support an early stage development and how this can impact the late stage development of the drug candidate. Introduction of current formulation approaches including enabling formulations such as solid dispersions used in the industry will widen partnership with emerging innovators and sponsors, making it possible for the otherwise difficult drug candidate to be studied in the clinic.

This book will be the first in detailing the formulation approaches by stage of discovery to early development to help scientists of different disciplines. Practical challenges and solutions will be discussed. The content of the book will guide the proper use of resources to lead scientists to generate the proper database that can help in quick decision-making. The target audience for the book will be drug discovery scientists including medicinal chemists, leaders in pharmaceutical industry (big pharma or start-up companies), and academics who are interested in bringing a potential drug candidate to the clinic. The book will provide real case studies of challenging candidates that allows readers to understand the importance of formulation to their cases. My numerous years (>23 years) working in big pharmaceutical companies, especially the intimate involvement with discovery in the last 15 years of my career and my recent interaction with small- and medium-sized pharmaceutical companies, allowed me to identify collaborators for this book to address the real problems and solutions in drug discovery related to all types of formulations.

The editor wishes to thank all the authors for their expertise in their respective sections and their patience during the revision procedures that were necessary to arrive at this juncture of delivering a well-outlined roadmap.

July 2016 *Elizabeth Kwong*

1

Introduction

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1.1 Overcoming Challenges in Big Pharma and Evolution of Start-Up Companies

The discovery and development of new drugs is a very complex process. No matter how you implement Lean Six Sigma Black Belt or in-depth data mining into the process, cost and success rate of commercializing drugs had not improved. It was estimated that it takes at least 10 years for a drug to make the journey from discovery to consumer at an average cost of $5 billion (Herper, 2013). Another study conducted by BIO and BioMedTracker (Hay *et al*., 2011), which collects data on drugs in development, had reviewed more than 4000 drugs from small and large companies that indicated that overall success rate for drugs moving from early stage phase I clinical trials to FDA approval is about 1 in 10, down from 1 in 6 seen in reports earlier. Despite increasing investments in research and development, the number of new drug approvals has not increased, while the attrition rate of new drug candidates has increased.

Recent publication in Fortune entitled "Big Pharma Innovation in Small Places" (Alsever, 2016) quoted several big pharma executives as to the current nature of big pharmaceutical companies where the focus of R&D is diminished to sorting out changes in the company and reprioritizing programs. Furthermore, with investor money flooding in and shift of drug pipelines from internal R&D to start-ups licensing opportunities, big pharma is acquiring

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small companies at faster pace than before. Small start-ups are now becoming the "new" innovative machines, which offer the high risk–high reward paradigm. According to surveys, last year, 64% of the approved phase I studies originated at a smaller start-ups.

1.2 Overview of Activities Involved in Current Drug Discovery and Development

There had been many surveys that revealed the cause of attrition of molecule in clinical development through the years. The major factors for discontinuation of clinical candidates are lack of efficacy (~30%) and toxicity (~30%). Kola & Landis (2004) further revealed that a 10% drop in attrition in 2000 was partly due to advancement in formulation technologies. Furthermore with increase in molecular obesity in drug candidates in recent years, majority of new drug development is poorly water soluble (Hann, 2011). About 40% of drugs with market approval and nearly 70–90% of molecule in discovery are poorly water soluble, which can lead to low bioavailability with conventional formulations (Kalepu & Nekkanti, 2015). With the introduction of various drug delivery technologies, numerous drugs associated with poor solubility and low bioavailability have been formulated into successful drug products. In fact, recently an increase in NDA file under 505(b)(2) is gaining more importance. New dosage forms with improved solubility and enhanced bioavailability such as prodrugs/active metabolite of drug and reformulation of poorly absorbed drugs using new technologies are turning into lucrative business. According to the Q&A with Ken Phelps, president of Camargo Pharmaceutical Services, which provides services for drug development for 505(b)(2) applications, approximately 20% of new drug approved in 2006 is through 505(b)(2) process. By 2008 more than half of new drug approval was based on 505(b)(2) process (Phelps, 2013).

Poor solubility of development candidates can limit drug concentration at the biological target site, which can lead to loss of therapeutic effect. Increasing the dose can overcome this lack of therapeutic effect but can lead to high variability in absorption, which can be detrimental to the safety and efficacy profile. For these reasons, solubility-enhancement technologies are being used increasingly in the pharmaceutical field. A formulation scientist's approach to solubility enhancement of a poorly water-soluble drug can vary. Often, physicochemical characterization, solid-state modifications, nonconventional formulation technologies, and enabling formulations are often utilized. There are numerous literature resources available to provide guidance toward formulation development from discovery to development of development candidates; however, a single reference where formulation approaches are described in each stage is lacking. This book describes and explains key factors

that will help determine the types of formulation needed at the different stages of discovery. The considerations of limited amount of API in early stages to the use of the formulation to determine key efficacious or toxicological end point that will not interfere with readouts will be discussed. The formulation selection stage-dependent approach will be detailed up to the planning for the regulatory filing. The interplay of drug metabolism, absorption, and physicochemical properties of the active will be laid out to help understand when a formulation can be improved and when a different lead candidate should be selected. Current formulation approaches based on the biopharmaceutics classification system (BCS) of the lead will be explained. The book will also focus on the relationships between various disciplines like physical chemistry, analytical chemistry, biology, DMPK, toxicology, and medicinal chemistry in determining the appropriate formulation to deliver the candidate in different forms. API sparing approaches including fit for purpose formulation to get candidates into development will also be covered in the book. Each stage of formulation (see Table 1.1) development has its goals, degree of complexity, and increasing availability of information, which ultimately leads to candidate that will have properties that can be administered in humans.

1.3 Value of the Right Formulation at the Right Time

Many of the discovery challenges are due to failure to properly identify formulations that are translatable from preclinical to clinical due to lack of effective predictions of therapeutic and toxicological responses in the preclinical stages. Moreover, efforts spent to integrate the formulation scientists in the early discovery that leads to the lead candidate selection had been disappointing. Most of the time, the lack of understanding of the interplay of the physiological system and physicochemical properties of the molecule to the drug delivery system contributed to the failure to integrate the right expertise at the right time, which leads to poor clinical successes. The lack of collaboration and proper integration between the formulation and discovery scientists is the root cause of most of the failure in the clinic. Lastly, the understanding of regulatory requirements for formulations also can add to the burden of the timeline and cost of bringing a drug candidate forward.

Although discovery starts off with the structure-based drug design, a better design of drug should be an understanding of how the biological effect is influenced by physicochemical properties, PK of the drug, and pharmaceutical delivery system. Optimization of the API via salt formation or co-crystal and physical changes such as particle size reduction through milling or formation of amorphous dispersions are often employed to improve oral bioavailability of insoluble compounds. These approaches can be applied even at the lead

Table 1.1 Activity definition from discovery to preclinical development.

Early discovery (lead ID/target validation)	Lead optimization/candidate nomination	Preclinical development to phase I

• Un-optimized phase of the molecules
• Limited compound supplies
• HTS-short timeline and high number of leads being screened
• Pharmacology studies (target engagement, efficacy studies)
• *In silico* tox screen
• *In vitro* metabolism
	• More API available
	• Chronic efficacy/biomarker studies
	• Initiate physicochemical characterization
	• Assess developability of the candidate
	  • Synthetic scale-up (~1–10 g)
	  • Potential dose
	  • Dose range finding (DRF) studies
	  • ADME
		• GLP tox study
		• Polymorph/salt screen
		• Scale-up of API

• Standardized solutions for *in vitro* HTS and *in vivo* PK screen
• No vehicle screen
• Usually contains DMSO or other standardized cosolvent vehicle (such as PEG/EtOH), low dose PK with IV/oral for %F
	• Dose range finding to identify exposure multiples
	• Resort to vehicle screen decision tree[a,b,c,d]
	• Goal of formulation selection are:
	  ○ Vehicles do not have any biological adverse effect
	  ○ Achieve exposure at the highest toxicological dose
	  ○ Can reach up to 2 g/kg
	  ○ Key is to identify adverse effects
		• Vehicle identified and dose range identified for GLP tox
		  ○ Repeat preparation of vehicle using optimized API
		  ○ Characterize physical properties of API in vehicle
		  ○ Meet GLP requirements

Pharmacology studies—needed a sustained plasma level use of Alzet Osmotic pumps[e]	PK–PD studies—use solution at low dose and suspension at high dose to assess relationship	CTM development—based on physical properties, such as flow, stability, particle size, and BCS, bioavailability

[a] Higgins *et al.* (2012). [b] Maas *et al.* (2007). [c] Li & Zhao (2007). [d] Palucki *et al.* (2010).
[e] Neervannan (2006).

identification if a candidate is deemed to show some potential. Various available formulations are discussed for early discovery in Chapter 2. This chapter will explain which formulation will be suitable at what stage and what features of the drug might suggest one technology over another. Chapters 3 and 4 deal with the different toxicology studies in relations to what formulation will be suitable. Following the development of suitable formulation to deliver required exposure in the early stage of discovery, this will then provide adequate safety assessment and risk of the candidate before proceeding to the more expensive

clinical trials. Following this stage, Chapter 7 will cover the formulation technologies that will be scalable to support the first clinical trial study.

Selecting a suitable formulation for your drug candidate can be complicated. Publications on formulation options for poorly soluble drugs are widespread. Each publication would have its approaches with decision trees and had shown proof of success that suits the specific pharmaceutical support system. In other words, taking this approach to another company with a different support function may not work. In my years of experience, to properly select the "right" formulation for a specific compound will still need input from a formulation scientist. This will be someone who poses the breadth of knowledge that can span from understanding of the physiological environment, pharmacology, and physicochemical properties of the molecule that will be intended for development. First to note here is the dose that will be required to be formulated, since solubilization techniques will have their limitation if the doses needed will be high. For example, at the lead optimization stage where safety of the candidate will need to be assessed, high doses are usually expected, and no means of solubilization can be possible that uses excipients that are inert unless your candidate is truly water soluble, which is very rare. It is also worth noting that the term "solubilization" is for the candidate to be soluble in the vehicle or mixture, and this does not include the fact that once this formulation is dosed, solubilization in the physiological environment may pose another hurdle that still can limit the absorption of the drug. This then leads to the question of what is the solubility of this molecule in the physiological milieu? One has to consider the micro-environment that may not be visible and static as we would envision during an *in vitro* test. For example, size reduction technology, which is also one of the solubilization techniques, is used to improve bioavailability. This technology is easy to achieve but may not be applicable to a large proportion of poorly soluble compounds. Evaluation of agglomeration potential of the molecule, understanding of the interplay of the excipients with the physical environment, and stability of the particle, molecule, and crystalline form are required. Another tool is the use of lipid technologies, which uses lipids as primary ingredient to deliver the water insoluble molecule. Lipid formulations are more complex and can produce micelles and microemulsions and will need a formulator to understand how each component of the mixture can ensure the target performance of the molecule from the *in vitro* to the *in vivo* environment. Most of the ingredient may be limited by the amount that can be administered in a preclinical study. At the same time, getting the number of additives together can result in a very viscous vehicle that may itself produce some challenge in a multiple day dosing during a toxicology study. Furthermore, use of such formulation for clinical supplies poses other challenges including use of soft gelatin capsule that can be in an appropriate size for dosing in patients and can be costly.

An important strategy to consider for your formulation selection is simplicity. Try to understand the criticality of solubilization to permeability/metabolism.

In some cases where the molecule is poorly soluble, the oral absorption is still acceptable when given a suspension where the only solubilization was the use of a low concentration of surfactant as a wetting agent aid. This approach can provide a PK profile that will have less C_{max} to C_{trough} ratio and can mitigate some of the adverse effects related to high plasma levels. At the same time this may provide sustain release if solubilization of the molecule is slow and the absorption window is wide. To manage the reproducibility of the PK profile, it will be important to properly characterize the suspension including the form and particle size of the compound in suspension. Such formulation approach in preclinical can also translate into a simple blend in a capsule that can be used in clinical formulation. On the other hand, if the molecule is being metabolized or transported at specific dose or species, formulation may not provide the solution even with the help of permeability enhancers. This is part of the reason why optimal drug-like properties are significant in drug discovery to minimize the complexity of downstream activities.

This book will be the first in detailing the formulation approaches by stage of discovery to early development to help scientists of different disciplines. Practical challenges and solutions will be discussed. The content of the book will guide the proper use of resources to lead scientists to generate the proper database that can help in quick decision making. The target audience for the book will be drug discovery scientists including medicinal chemists, leaders in pharmaceutical industry (big pharma or start-up companies), and academics who are interested in bringing a potential drug candidate to the clinic.

Partnership considerations with contract manufacturing organization (CMO) will also be described and shared to increase the probability of meeting tight timelines and to ensure the proper selection of formulation to support an early stage development and how this can impact the late stage development of the drug candidate. Introduction of current formulation approaches including enabling formulations such as solid dispersions used in the industry will widen partnership with emerging innovators and sponsors, making it possible for the otherwise difficult drug candidate to be studied in the clinic.

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2

Lead Identification/Optimization

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2.1 Introduction

Over the last two decades, the introduction of high-throughput screening (HTS) and combinatorial chemistry has changed the drug discovery process by enabling the rapid evaluation of large number of compounds against targets of interest (Bajorath, 2002; Hefti, 2008; Hughes *et al.*, 2011). In the past, selection of compounds for progression (lead identification) focused mainly on affinity and selectivity. However, it has since been recognized that the physicochemical properties (such as solubility and lipophilicity) of a compound play a significant role in whether the compound progresses to be a successful drug candidate. To ensure that leads selected for progression have the right absorption, distribution, metabolism, and excretion (ADME) properties, rule-based systems such as the "rule of five" have been used to predict the drug-likeness of a

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compound and guide the selection of compounds for progression (Lipinski *et al.*, 1997).The "rule of five" was developed based on a review of compounds that have successfully progressed into clinical studies and stipulates that for an orally active compound to be successful; it should not violate more than one of the following criteria:

- No more than five hydrogen bond donors (the total number of nitrogen–hydrogen and oxygen–hydrogen bonds)
- No more than 10 hydrogen bond acceptors (all nitrogen or oxygen atoms)
- Molecular weight of less than 500
- Octanol–water partition coefficient (log*P*) not greater than five

Despite the implementation of "rule of five" type filters to lead selection, a relatively high proportion of drugs entering clinical studies fail to reach the market (Hann, 2011). As a result, alternative methods such as "quantitative estimate of drug-likeness" (QED) have been introduced (Bickerton *et al.*, 2012). QED measured drug-likeness based on the concept of desirability and enabled values for multiple molecular properties to be combined into a single measure of compound quality using a desirability function.

Once the leads are selected, the optimization process starts whereby the weaknesses of the compound are improved, while maintaining the favorable properties of the compound (Hughes *et al.*, 2011) such that the compound entering clinical studies has a good balance of *in vitro* properties and ADME properties.

2.2 Early Characterization of Compounds

During this stage, preformulation data generated on the leads are used to identify developability risks and guide molecular structure modifications. The key challenge for the formulation scientist at this stage is the limited information available on the compound and limited bulk (if any) available of experimentation. Therefore, during the early stages of lead identification and lead optimization, computational modeling and HTS play a crucial role in assessing the physicochemical and pharmaceutical properties of the compound. As the compound progresses through to the later stages of lead optimization and larger quantities of material are available, focused experimentation can be used to answer specific questions about the compound as well as improve the quality of the data generated.

2.2.1 Preformulation

High oral bioavailability is often an important goal for drug development. Therefore, it is important to gain sufficient understanding of the properties that can limit oral bioavailability. In order to obtain an accurate assessment of

the biopharmaceutical properties of a compound, the key physicochemical parameters determined during the preformulation stage are solubility, lipophilicity, pK_a, and permeability.

2.2.1.1 Solubility

For orally absorbed drugs, the compound must be dissolved and in solution for absorption to occur. With the increasing number of compounds with poor solubility, solubility-limited absorption has become one of the main reasons for poor bioavailability in the clinic (Di *et al.*, 2012). Solubility-limited absorption is even more of a problem during the preclinical stage for assessment of safety issues, especially where high doses are required. As a result, the importance of conducting solubility studies during the drug discovery stage is well recognized.

During the early stages of lead identification where solubility experimentation is not feasible due to the large numbers of compounds being screened and lack of material, computational models may be used for solubility prediction. These computational models range from simple models using semiempirical equations based on physicochemical properties such as log$P$ and pK_a to more complex models based on molecular properties such as molecular weight, polar surface area (PSA), and hydrogen-bonding capacity. Although solubility predictions are useful, the accuracy of these models is variable and highly dependent on the training sets used.

Once material is available, experimentation can be conducted to more accurately determine the solubility of a compound. A range of different solubility assays can be conducted depending on the development stage of the compound, amount of material available for experimentation, and the purpose of the data generated. For example, high-throughput (HT) kinetic solubility screens can be used to help compound selection, while equilibrium solubility experiments can be used to help biopharmaceutical predictions and guide formulation development.

2.2.1.1.1 Kinetic Solubility

Kinetic solubility assays are typically conducted during lead identification as the assays use stock solutions (e.g., DMSO stock solution), which are readily available at this stage. In addition, the assay uses minimal material, and the format of the assay readily lends itself to automation and integration into the HTS process (Lipinski *et al.*, 2001).

A typical kinetic solubility study would involve the addition of small volumes of stock solution to media to form a supersaturated solution. The solution is then incubated for a short period of time to allow precipitation of the compound. The amount of compound remaining in solution is then analyzed by UV or nephelometry (Avdeef and Testa, 2002; Kerns *et al.*, 2008).

While kinetic solubility is an indicator as to whether a compound may have solubility issues, studies have shown that kinetic solubility tends to overestimate

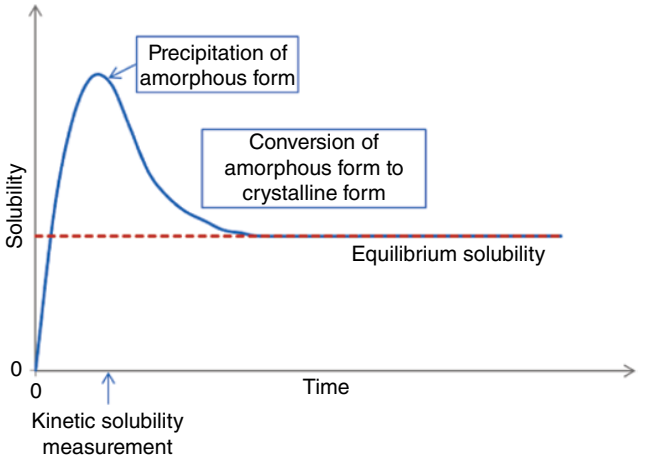

Figure 2.1 Precipitation of amorphous form resulting in over prediction of solubility.

the actual solubility of a compound (Saal and Petereit, 2012; Sugano *et al.*, 2006). This difference could be a result of several factors including the short incubation time and precipitation of an amorphous or metastable solid form (Figure 2.1).

2.2.1.1.2 Equilibrium/Thermodynamic Solubility

Equilibrium or thermodynamic solubility of a compound is defined as the maximum concentration of a compound, which, at a defined temperature and pressure in a given solvent, is thermodynamically valid as long the solid phase exists in equilibrium with the solution phase (Murdande *et al.*, 2011). While equilibrium solubility is considered the "gold standard" for determining the solubility of a compound, it is less commonly used in early lead identification due to the higher bulk and resource requirements as well as longer turnaround times.

Equilibrium solubility measurements are conducted by adding excess solid material to the buffer and shaking the resulting suspension for a predetermined temperature for a defined time (typically between 24 and 48 h). The remaining solid at the end of the experiment is removed, and the amount in solution is analyzed to obtain the equilibrium solubility value of the compound. As the solid form (crystallinity and polymorphic form) of the material may change during the experiment, characterization of the remaining solid is important when reviewing solubility data.

In addition to aqueous buffers, equilibrium solubility studies are frequently conducted using simulated gastric and intestinal fluid (SGF, FaSSIF, and FeSSIF). Solubility results from these studies are used as inputs into *in silico* models such as GastroPlus™ and Simcyp® to help predict *in vivo* performance of the compound.

2.2.1.1.3 Pseudo-Kinetic Solubility

To bridge the gap between the kinetic and equilibrium solubility assays, scientists at Pfizer developed the "pseudo-kinetic solubility" screen. Like the kinetic screen, the pseudo-kinetic screen starts with pre-dissolved compound and can be easily automated. However, the pseudo-kinetic screen has a longer incubation time (20 h), and the screen plate was modified to enable information on the solid form to be obtained using polarized light microscopy (PLM) (Sugano *et al.*, 2006).

Figure 2.2 compares the correlation between the solubility values obtained from the kinetic screen and pseudo-kinetic screen against values obtained via equilibrium solubility studies.

2.2.1.2 pK_a

The acid–base dissociation constant (pK_a) of a compound is used to understand the ionization state of a compound in solution at a particular pH. The pK_a is important as it can influence the solubility, lipophilicity, and permeability of a molecule, especially when ionized at physiologically relevant pH of 2–8 (Manallack, 2007). A molecule in its charged state will show higher solubility than in its uncharged state but, conversely, will have lower permeability. In other words, the permeability and/or solubility of a compound can be altered by the introduction or modification of ionizable groups.

In early lead identification, software packages such as ACD/Labs can be used to predict pK_a values of a compound. pK_a values can also be determined experimentally using either titration (potentiometric or UV spectral detection) or capillary electrophoresis (CE) (Wan *et al.*, 2003).

2.2.1.3 Lipophilicity

The lipophilicity of a compound represents the affinity of the compound for oils, fats, and nonpolar solvents and is determined by either partition coefficient (log*P*) or distribution coefficient (log*D*) measurements using two nonmiscible solvents, typically *n*-octanol and water. Log*P* values are the ratio of concentrations of unionized drug in the octanol–water system, while log*D* values are the ratio of concentrations of both unionized and ionized drug in the octanol–water system and are affected by the pH of the system. Log*P*/*D* measurements are usually conducted by adding dissolved compound into a flask containing both octanol and water and shaking the flask until equilibrium is achieved. The concentration of compound in each solvent is then quantified using an appropriate technique such as UV.

The marketed 96-well format octanol–water shake flask method by Analiza, Inc (www.analiza.com) provides log*D* ranges of –3 to 4. Another common approach is the use of HPLC retention times in relation to a set of standards with known log*D* to predict an approximate log*D* for the compound of interest (Yamagami *et al.*, 2002).

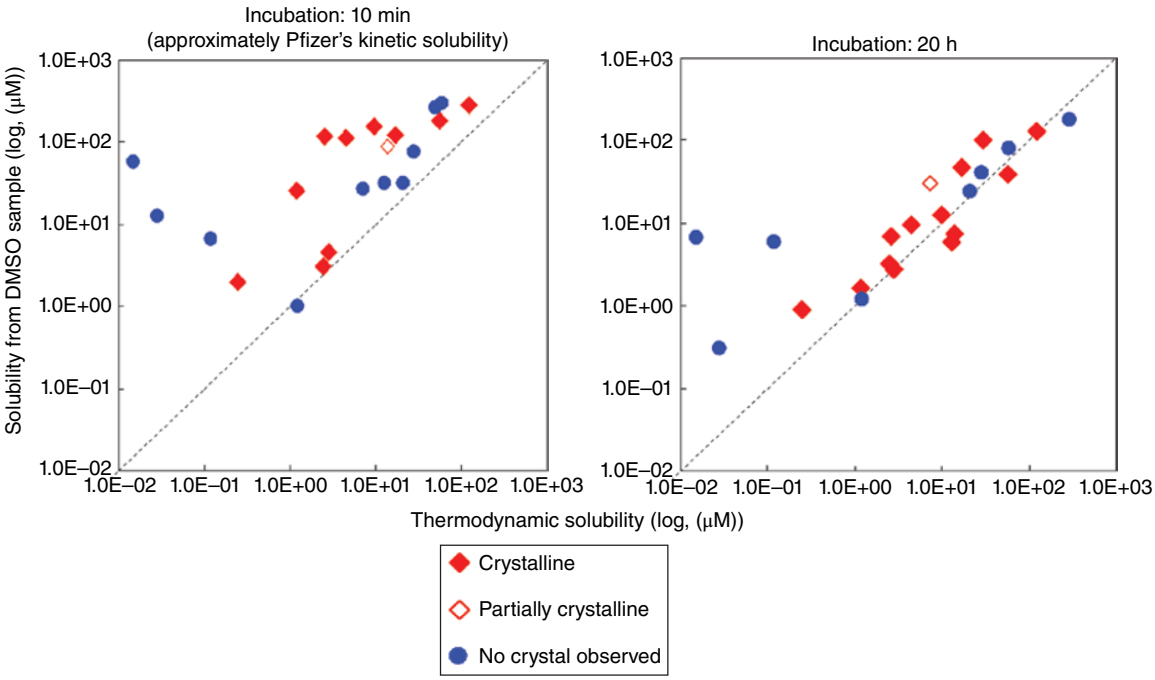

Figure 2.2 Comparison of solubility values obtained from kinetic and pseudo-kinetic solubility screens.

Furthermore, the lipophilicity of the compound influences the permeability of the compound and transport across the gastrointestinal tract (GIT) and blood–brain barrier (see Section 2.2.1.4). In addition, it can also be used during formulation development to help with selection of solubilizing formulations (e.g., use of self-emulsifying drug delivery systems for compound with high log$P$/D).

2.2.1.4 Permeability

Following oral administration, compounds dissolved in gastrointestinal (GI) fluids have the potential to be absorbed via a variety of mechanisms that involves either passive diffusion or active transport (Figure 2.3). For the majority of drug compounds, the main route of absorption occurs via passive diffusion through the transcellular pathway. The transcellular diffusion rate is mainly determined by the rate of transport across the apical cell membrane and is controlled by the lipophilicity and ionization state of the compound.

This interrelationship of pK_a, log$D$/P, and pH of the absorption site in the GIT forms the basis of the pH-partition theory (Shore *et al.*, 1957). The theory states that transcellular diffusion of a drug molecule through the lipid bilayer of the intestinal membrane can only occur if the molecule is in its unionized state. Therefore, absorption of weakly basic drugs is favored in the small intestine where the pH is higher, and therefore, a larger proportion of unionized drug will be available for absorption. Conversely, absorption of weak acids will be favored in the stomach where pH is lower. However, in reality, the small

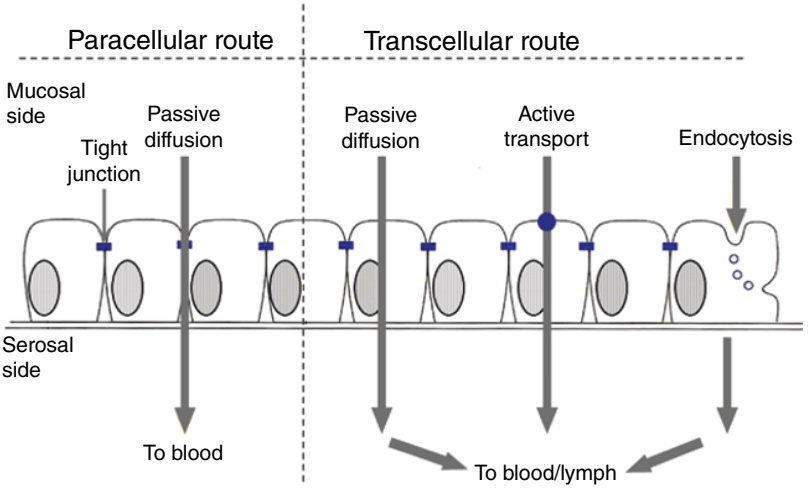

Figure 2.3 Schematic showing absorption routes for a compound.