

Early phase drug development: Assessing, predicting and formulating with delivery in mind

An insight into the challenges of early drug development and how they can be overcome rationally.



Introduction

Development of new therapeutics demands substantial investment of time and capital, frequently with low chances of success. As a result, there is huge pressure to deliver reduced timelines and realise drug development programmes. Scientists involved in development must balance opportunities to mitigate risk, and increase efficiency whilst maintaining quality. At Almac, we understand that developing therapeutics with a focus on delivery is fundamental to achieving success both in developmental phases, and in the final product.

Early drug development challenges

Appreciating the difficulties encountered in early development is essential to provide efficient solutions. Flexible, phase appropriate, and robust approaches are necessary, to examine a drug effectively. This includes assessment of a drug's molecular properties, developability or development of a preclinical formulation for efficacy evaluation.

A common challenge in drug development is the growing prevalence of poor aqueous solubility, with up to 90% of pipeline drugs exhibiting this characteristic.¹ Neglecting this critical attribute can lead to low bioavailability, failure to achieve desired exposure profiles and increased dose utilisation. All of which add significantly to costs and development timelines.^{2,3} Not only does this affect the formulation strategies undertaken later in development, but also those undertaken for preclinical studies to demonstrate efficacy or toxicity in animals. A recent study of preclinical exposure data of over 16,000 research compounds found that poor solubility is the major factor in pharmacokinetic variability. It demonstrated that greater than 50% of studies involving poorly soluble compounds (BCS class II and IV) exhibited a two-fold increase in pharmacokinetic variability.⁴ Such variability may impact the dose-response relationship, thereby complicating interpretation of results and affecting impact of experiments. In addition, factors such as drug ionisability and the route of administration were recognised to have significant impact on pharmacokinetics. Highlighting the complexity of delivery to animal models and the complexity of delivery in early development. Practically, a major difficulty to analysis in early characterisation is the limited quantity of drug available and resource intensive nature of analysis. This can cause issues in acquiring data, and doing so in a timely manner.

As a result of these challenges, exploring drug developability and enabling formulations early in development is increasingly practised. It has now become common for specialised instrumentation and pharmaceutical scientists to be incorporated at this stage, whether by outsourcing or through inclusion within discovery teams. This helps prevent failure at clinic and enable successful progression to viable clinical and commercial therapies.⁵

Understanding drug molecules

Drug molecules exhibit unique characteristics, which together can often present challenges for delivery. Understanding the limitations of a molecule is vital, particularly in the early phases of drug development, when little is known about a chosen drug candidate. To begin comprehending the nature of a compound, a number of characteristics can often be predicted based on the structure of the molecule. We use a rational approach to understanding a drug candidate, firstly by determining the most significant parameters that affect the behaviour of the compound in vivo, as well as in a formulation. In silico methods to understand a molecule's solubility and permeability can provide a strong indication of what may be a viable approach to formulating. This has the advantage of requiring no physical use or loss of drug material.

Modern instrumentation available to scientists provide substantial advantages in determining such parameters over conventional methods. Using specialised, small-scale equipment can facilitate profiling of a molecule without consuming significant quantities of drug. This aids determination of key molecular properties such as solubility, pKa, logP and intrinsic dissolution rate. We recommend that careful examination of a drug's physicochemical profile is used to aid assessment of drug developability, determine risk and guide formulation.

Developability assessment

Most frequently the oral route of administration is favoured and thus, tools like the biopharmaceutics classification system (BCS) have been utilised to assess drug developability. The limited scope and regulatory basis of the BCS has however led to the evolution of tools specific for early development. The developability classification system (DCS) offers a framework which is better suited to predict the risks and challenges of developing an oral drug early in the developmental stages. Drawing on the concepts first described in the BCS, the DCS assesses developability and guides formulation. The concepts of dose solubility, dissolution rate and permeability are included in this model in a different manner to the BCS. For example, solubility is measured in fasted simulated intestinal fluids (FaSSIF), a biorelevant medium. Predicted permeability may be derived from lab based assays (in silico or in vitro cell based models) correlated to previous data set of measured permeability values. In addition DCS uses the concept of solubility limited absorbable dose (SLAD). This partition indicates the cut-off point where the dose administered is limited by solubility or dissolution rate, based on the theory that high permeability can compensate for low solubility.⁶

The various regions of the DCS matrix (Figure 1) indicate when a compound is likely to exhibit favourable oral bioavailability without formulation (class 1 and 3), or if formulation efforts may be necessary to obtain sufficient oral absorption (class 2a, 2b and 4).

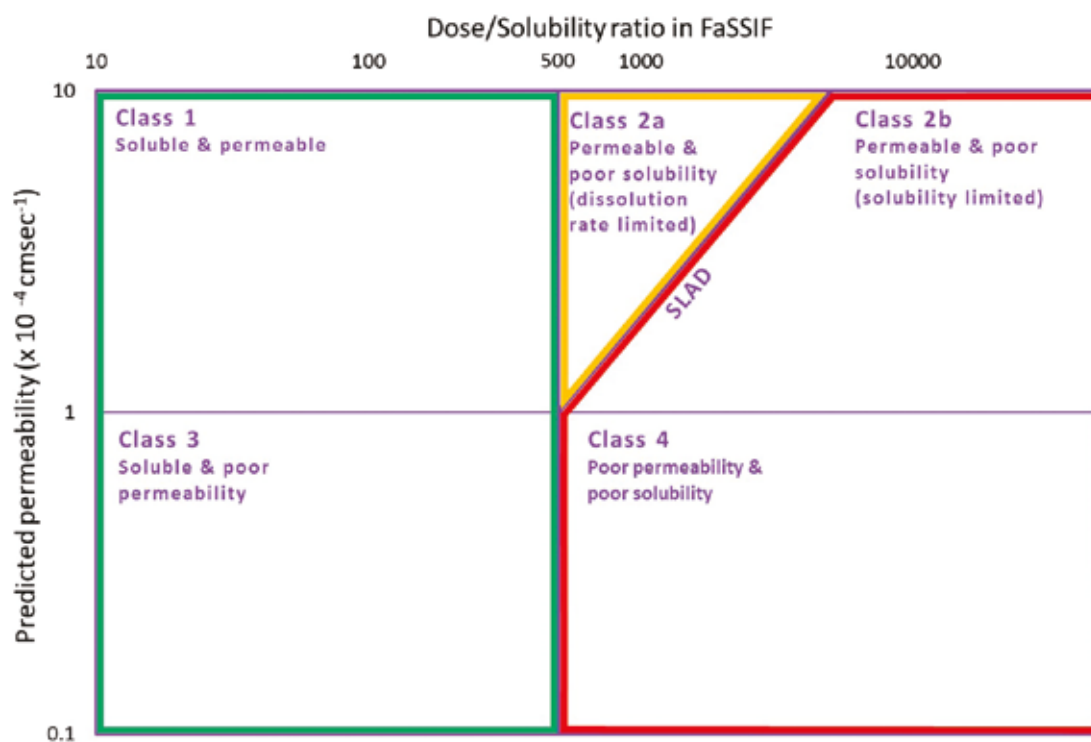


Figure 1. The developability classification system. Drugs residing in the area highlighted green are unlikely to exhibit major oral bioavailability issues, those in the yellow region may exhibit dissolution rate limited bioavailability, which can often be compensated by particle size reduction. Those situated in the red area are solubility limited and generally require pre-dissolved drug formulations such as solutions, amorphous dispersions or lipid formulations.

The recently published “refined” DCS emphasises the need for advanced characterisation of a drug. This includes experiments which examine supersaturation, as well as small-scale dissolution studies.⁷ This is particularly important for examining and mitigating risk of candidate molecules. For example weakly basic drugs which may undergo precipitation on entering the intestine from the strongly acidic environment of the stomach.

The DCS tool aids risk mitigation, guides formulation and offers a strong indication of drug developability in early phase studies. Implementation of developability assessment generates valuable information on drug candidates, supporting decision making process. In some cases assessment may be abbreviated where logical correlations and extrapolations from in vitro and early in vivo data are made. Examples include molecules which are classified as highly soluble and highly permeable or potent (low dose). The net result is reduced resource consumption and expediting of compound to the clinic.

Formulating for success

Rational design of a drug formulation is necessary to ensure maximum therapeutic performance. Accordingly, strategies may be employed to overcome limiting physicochemical properties of a molecule and enhance the therapeutic performance by exploiting the effects of suitable excipients.

Approaches in early development centre on mitigating pharmacokinetic variability, increasing drug concentration, or inhibit in vivo precipitation on administration.⁴ Ease of preparation, rapid development and minimal drug consumption through analysis are key considerations. The main formulation goals are to ensure drug stability (both physical and chemical) and optimal exposure on administration. Subsequently, preclinical formulations for efficacy, pharmacokinetic and toxicology studies often employ relatively simple formulations. This includes vehicles such as solutions and suspensions, particularly when bioavailability issues are not expected. If a compound exhibits solubility limitations, enabling formulations which enhance solubility are commonly employed. Approaches include the use of buffers or excipients such as cosolvents, surfactants and cyclodextrins to maximise drug concentration in solution and enhance bioavailability. The excipients chosen should act as a silent partner of a drug, enhancing the effect of the active, without confounding the anticipated outcome. The approach taken must carefully balance multiple factors and take into consideration the study type, animal model, indication and route of administration among other factors (Figure 2). In particular it is important to consider the effect of excipients in the development of a preclinical formulation for a multiple dose or chronic study. Consequently excipient biocompatibility is fundamental, tolerated excipient levels are often based on previously published data or by relying on institutional knowledge.

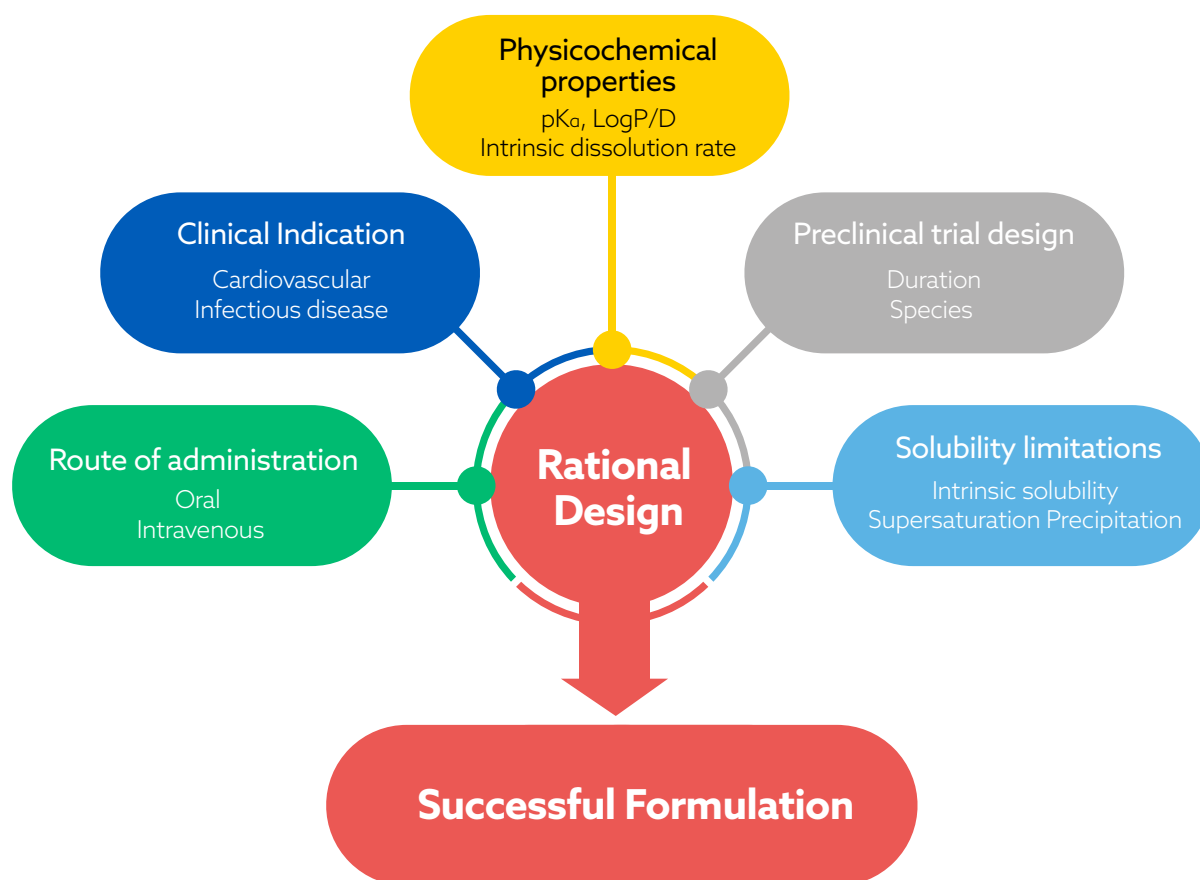


Figure 2. Factors which commonly affect preclinical formulation design.

Formulations for preclinical studies commonly require rapid turnaround. This can be difficult to achieve within time and drug material constraints, particularly if the formulation requires a tailored approach. The development of fast, material sparing screening techniques, as well as an in depth understanding of drug-formulation interplay is therefore essential. At Almac the formufast™ platform allows rapid, tailored screening of small quantities of API against a range of excipients. This is possible by taking advantage of miniaturised and semi-automated systems and rapid determination of drug physicochemical properties. As a result multiple excipients, combinations and formulations may be screened rapidly, providing tailored formulations in a time and material efficient manner.

Alternatively the use of “off-the-shelf formulations” derived from in-house knowledge and experience may be employed to accelerate development even further. This approach offers a rapid formulation turnaround based on the type of formulation required (IV, oral, suspension), rather than screening large numbers of excipients individually. Such formulations often contain high levels of excipients and are therefore most useful when studies are single dose administration, such as a pharmacokinetic study. We suggest that investing time to overcome delivery challenges in early development is worthwhile. The information gained may be invaluable in the course of developing formulations for future studies, as well as designing an end product. Identifying and communicating the delivery risks and development hurdles not only aids formulation later in development. In addition it also underlines the challenging properties of lead compounds in discovery and potentially aid optimisation of a compound series.

Assessing formulations

Conventional preclinical formulations evaluation is conducted by several simple tests. These include visual assessment, solubility evaluation, precipitation assessment and stability studies. This is sufficient to demonstrate the likely effects in vivo and mitigate risk of failure. However, more can be done prior to use in clinic to further reduce risk and increase the chances of success.

In particular, with advanced instrumentation, it is becoming possible to characterise formulations beyond traditional testing using assays such as small-scale dissolution studies. This is particularly useful to investigate the supersaturation and precipitation of ionisable compounds which may occur due to pH variations in the gastrointestinal tract, causing a reduction in, or variable bioavailability. Evaluation using pH-shift dissolution assays which mimic the transit of a dosage form between the stomach and small intestine can be used to achieve more information-rich assessments.⁸ This is used to determine the degree and duration of supersaturation, elucidate formulation performance differences and assess potential in vivo behaviour.

The effect of formulation of a weakly basic drug in a pH-shift assay is demonstrated in Figure 3. In this example we demonstrate the crystalline solid demonstrates precipitation on shift to intestinal media from gastric pH. Alternative delivery approaches using a suspension formulation and a hydroxypropyl β -cyclodextrin (HP β CD) solution formulation show improved dissolution properties. In particular, the HP β CD formulation exhibited the greatest apparent solubility and prevented precipitation and therefore, is likely to enhance bioavailability. These analyses afford advantages over traditional dissolution methods, which can over, or under estimate the dissolution properties and subsequent bioavailability.

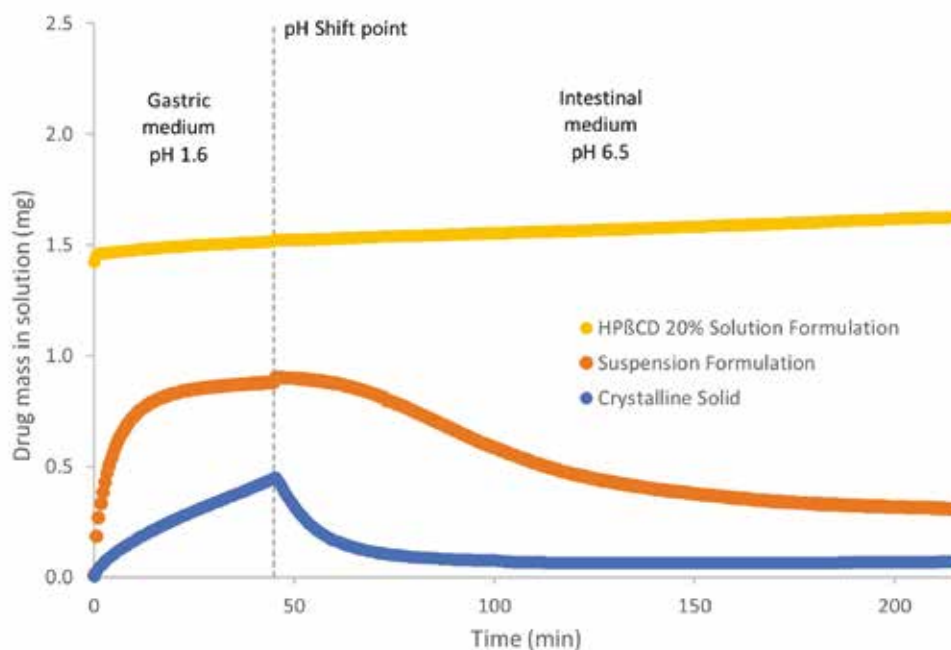


Figure 3. Behaviour of a weakly basic drug in different formulations. Test conducted in a small-scale, pH-shift dissolution test. Each formulation using approximately 10 – 20 mg of drug in 40 ml of dissolution media.

Summary

Early drug profiling and assessment are key to modern drug development programmes. Using efficient analysis in early development it is possible to derive a wealth of information regarding a molecule and the type of formulation strategy required with low material consumption. At Almac we use our in-house formufast™ platform to understand drug molecules and develop strategies to overcome their unique challenges. With improved understanding of a drug molecule's physicochemical profile, the feasibility of various formulation approaches can be quickly assessed. This includes assessing risk, predicting performance and provide guidance. We believe that tailored analyses and approaches in can ensure a successful and cost-effective progression of drug candidates into clinic. This not only serves to reduce the attrition rate during clinical development, but also reduces development costs and timelines for a drug candidate.

Glossary

Early phase drug development – development spanning from the discovery of a drug compound to first in human clinical trials

Physicochemical properties – the properties of a molecule that can be affected by the environment such as melting point, solubility, physical form, pK_a and logP

pK_a – the dissociation constant on a logarithmic scale, denoting the pH value at which a compound is equally ionised and unionised in solution

LogP – the partition coefficient, a measure of drug affinity for oil or aqueous phases in the unionised state

Intrinsic dissolution rate – the rate at which a pure drug dissolves when other important factors such as surface area, medium and temperature are controlled

Bioavailability – the proportion of a drug or other substance which enters the blood after administration

Pharmacokinetics - drug uptake, distribution, metabolism and elimination of a drug in the body which affects the bioavailability

Permeability – the ability of a drug to permeate across tissues, such as the intestinal membrane, before absorption into the blood stream

References

- ¹Thayer AM. Finding solutions, Chemical & Engineering News Archive. (2010); 88 (22), p13-18.
- ²Leeson PD. Molecular inflation, attrition and the rule of five, Advanced Drug Delivery Reviews. (2016); 101, p22-33.
- ³Hann MM, Keseru GM. Finding the sweet spot: the role of nature and nurture in medicinal chemistry, Nature Reviews Drug Discovery. (2012); 11, p355-365.
- ⁴Daublain P, Feng K, McGregor C et al. Analyzing the Potential Root Causes of Variability of Pharmacokinetics in Preclinical Species, Molecular Pharmaceutics. (2017); 14 (5), p1634-1645.
- ⁵Landis MS, Bhattachar S et al. Commentary: Why Pharmaceutical Scientists in Early Drug Discovery Are Critical for Influencing the Design and Selection of Optimal Drug Candidates, AAPS PharmSciTech. (2018); 19 (1), p1-10.
- ⁶Butler JM, Dressman JB. The developability classification system: application of biopharmaceutics concepts to formulation development, Journal of pharmaceutical sciences. (2010); 99 (12), p4940-4954.
- ⁷Rosenberger J, Butler JM, Dressman JB. A refined Developability Classification System, Journal of Pharmaceutical Sciences (2018); 107, p2020-2032.

Contact Details:

Dr Timothy Brannigan
Senior Chemist – Preformulation
Physical Sciences, Almac Group
timothy.brannigan@almcagroup.com
T: +44 (0)28 3833 2200



Get in touch

UK

Almac Group
(Global Headquarters)
20 Seagoe Industrial Estate
Craigavon
BT63 5QD
United Kingdom

almacanalytical@almacgroup.com
+44 28 3833 2200

Europe

Almac Group
IDA Technology and Business Park
Garrycastle, Athlone
Co. Westmeath
N37 X061
Ireland

almacanalytical@almacgroup.com
+353 90 646 0200

US

Almac Group
(US Headquarters)
25 Fretz Road
Souderton, PA 18964
United States of America

almacanalytical@almacgroup.com
+1 215 660 8500