In defense of a rational approach to formulation design and development for oral solid dosage forms.

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ABSTRACT

There have been quite dramatic changes in new drug development over the past 40 years, e.g., the number of poorly water-soluble drug molecules has increased, and new drug development is no longer the preserve of established pharmaceutical companies. Along with these changes, there have also been the increase in contracting organizations and venture capital funding. There is pressure to shorten development times, particularly in early stage development for Phase I clinical (first-in-human) studies. There is now increased interest in very simple formulations to reduce the time to the initiation of the Phase I studies. This need for speed has to be balanced by a sufficient understanding of the biopharmaceutical properties of the new drug molecule in order to determine whether or not a simple drug in a capsule approach will be appropriate. Without this understanding, much effort will be wasted and potentially useful new drugs may be discarded.

KEY WORDS: New drug development, biopharmaceutics, powder in a capsule, excipients

INTRODUCTION

The focus of this paper will be immediate release oral solid dosage forms.

Drugs, that is, the active pharmaceutical ingredients (APIs) are formulated for a variety of reasons:

- Convenience: it may be possible to give a patient a bag of acetaminophen powder where the dose is high, but not digoxin where the dose is very small. It is easier to carry tablets and capsules in everyday life than a bag of powder.
- Accuracy of dosing: tablet and capsule machines are very fast, accurate volumetric sampling devices; far faster and more accurate than the patient. However, accuracy of fill weight depends on the uniformity of the apparent density of the powder stream or bed.
- Improved absorption: some drugs are not well absorbed unless formulated.
- Improved palatability: many drugs have poor taste properties, often very bitter. Formulation can help mask poor taste and allow unpalatable drugs to be taken orally with minimum discomfort to the patient.
- Reduction of side-effects: some drugs are absorbed so rapidly that the blood levels exceed the threshold

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for side effects. Formulation can be used to reduce the rate of absorption and thus avoid the higher blood level peaks where side effects would be expected.

- Improved therapeutic benefit: in controlled release we are looking to modify the rate of release and the rate of drug absorption to optimize the therapeutic benefits for the patient.

There are thus three main components of a pharmaceutical product formulation, i.e., the API(s), the excipients and the process(es) (shown in Figure 1).

If any of these components are removed, the correct product cannot be obtained. However, there is one additional, often overlooked component, which must be considered, and that is the packaging. All drug products are presented to the patient or caregiver in a sealed package. Even with solid oral dosage forms, packaging is necessary to maintain the integrity of the product.

The objective for any pharmaceutical formulation project, especially for potential commercial use, is a robust medicinal product which will deliver the drug to the patient:

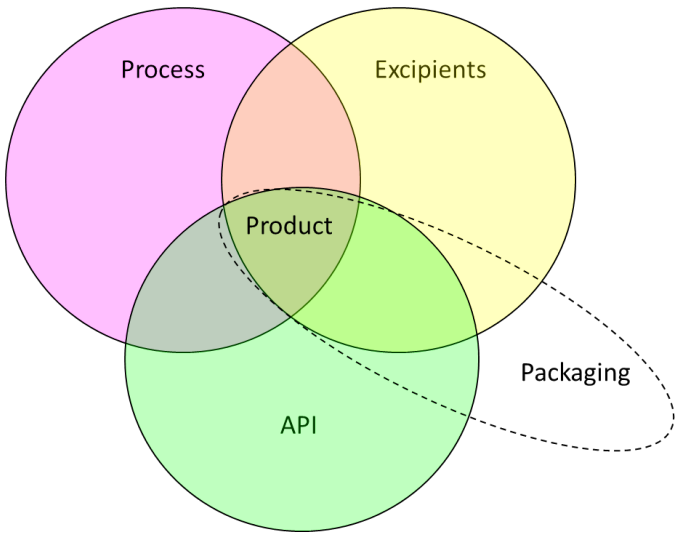

Figure 1 Components of a finished pharmaceutical product.

- In the required amount (content and assay).
- At the desired rate (*in vivo* dissolution and absorption).
- Consistently
- Within lots (blend uniformity for all components).
- Between lots validated and continuously verified manufacturing process.
- For the shelf-life of the product (stability).
- Capable of being manufactured at full production scale and production speeds.

So how should robustness be defined for pharmaceutical finished products? ICH Q8(R2) provides a definition of process robustness (1):

"Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality."

Thus, robustness is the toleration of variability in the materials and processes. Taking this ICH definition and extending it to pharmaceutical formulations, a robust formulation can be defined as follows:

A robust formulation of a medicinal product is able to accommodate the typical variability seen in:

- API
- Excipients
- Processes

Without compromising the manufacture, stability, performance or any other attribute of the product critical to the patient's care or well-being.

There are, thus, several sets of information the formulation scientist needs to understand in order to achieve their objective of a robust, stable pharmaceutical finished product:

- The properties of the API and any potential issues (from the preformulation studies), including a provisional Biopharmaceutics Classification

System (BCS) (2) classification based on the pH solubility profile over the pH range 1-7 and Caco-2 cell layer permeability.

- Excipient understanding (including their composition, uses and limitations)
- Process understanding (including its benefits and limitations)
- Understanding the interactions and potential interactions between the API, excipients and processing, and any issues or potential issues which could impact drug product quality or performance.

The formulation scientist must assess all these components and determine how the product will be manufactured, what types of excipients will be needed, and choose the specific excipients. The latter will be based on excipient compatibility studies. Excipient compatibility studies will only indicate which excipients to avoid. A 'clean' result in the excipient compatibility study for a particular excipient does not mean that the formulation will not run into problems. This is because excipient compatibility studies are typically carried out using binary mixtures of drug and excipient. The final formulation, particularly for oral solid dosage forms, will contain more than one excipient and there is the potential for more complex interactions that may not be seen using binary mixtures.

Formulation process design and development

The solubility of drug molecules generally has changed over the last 40 years. In the 1970's and 1980's, the number of poorly water-soluble drug molecules were few, possibly <10%. Today, that has changed and it is estimated that, for small molecules, poorly water-soluble drug molecules now comprise 70-80% of new drug molecules. There are valid reasons for this shift that are outside the scope of this paper. This shift to less water-soluble new drug molecules means that a further question must be answered:

"What needs to be done with this molecule in order to get it into a form which allows it to be absorbed sufficiently from the gastrointestinal tract?"

This begs the question of how poorly water-soluble is defined. In the BCS system, for an immediate release (IR) product:

"*A drug substance is considered highly soluble when the highest strength is soluble in 250 mL or less of aqueous media over the pH range of 1-6.8*." (3)

For very early formulation purposes, the BCS classification is impractical since the dose probably would not have been defined. A more useful solubility classification is given in Table 1. This classification is based on the author's many years of experience working with many different drug molecules.

Table 1 Solubility classification for early development candidates

SOLUBILITY CLASSIFICATION	SOLUBILITY*
Soluble	>10 mg/mL
Borderline solubility	1<x<10 mg/mL
Poorly soluble	<1 mg/mL**

* Aqueous solubility over the pH range 1-6.8
** Some authorities suggest 0.3 mg/mL

The pH range referenced in Table 1 reflects the pH range relevant to the *in vivo* dissolution and absorption in the gastrointestinal tract (stomach, duodenum and jejunum). For soluble drugs (>10 mg/mL), a conventional IR oral solid dosage form (tablet or capsule) manufactured by conventional processing (direct compression, dry granulation or wet granulation) should suffice. For poorly soluble drugs (<1 mg/mL), almost certainly a dissolution enhancement technology will be necessary, such as an amorphous dispersion in a polymer, nanoparticles, or self-emulsifying drug delivery system (SEDDS). For those drugs having borderline solubility, the approach needed will depend on the final dose required. However, particle size reduction (e.g. micronization) or an alternative salt form may suffice.

First-in-human studies: "the need for speed"

There has been another shift in drug innovation in

recent years. 40 years ago, most new drug research was undertaken by medium to large pharmaceutical companies. There were a few drugs which came out of e.g. academia, and usually they were licensed to the established pharmaceutical companies. There were also very few contract research, development and/or manufacturing organizations. Today, the situation is quite different. There are many start-up companies looking to develop new drug molecules, and there are numerous companies in the contract sector covering all aspects of drug development. There has also been a rise in venture capitalist funding to finance drug development.

Unfortunately, medicinal chemists and venture capitalists do not understand the nuances of the biopharmaceutics of drug delivery, nor the challenges of getting a poorly water-soluble drug absorbed from the gastrointestinal tract. This lack of understanding can mean that mistakes are made and that potentially useful new drugs are abandoned because of poor results that could have been predicted and remedied with adequate preparation as is discussed below.

The old adage 'time is money' has now assumed a greater significance in new drug development. There is pressure to get into first-in-human studies (clinical Phase IA/B) as fast as possible to show that the new drug candidate has potential and can progress to clinical Phase II studies (proof of efficacy).

Traditional formulation development, where a pre-formulation screen (including excipient compatibility) is undertaken and then a conventional formulation developed, is considered too slow and there is much interest in quicker approaches.

One of these is powder-in-a-capsule. Literally, neat bulk drug is filled into a capsule which is administered to human volunteers in a Phase IA (single ascending dose) study. For a soluble drug, this approach is viable and can speed up the time to Phase IA results considerably. However, for poorly water-soluble drugs the powder-in-a-capsule approach is likely to fail because the drug will not be in a form which allows it to be absorbed.
An example from the author's own experience illustrates the pitfalls for powder-in-a-capsule for a poorly water-soluble drug. The drug was very poorly water soluble over the pH range 1-6.5. The solubility over this pH range was ca. 7μg/mL. Before this author was engaged in the project, the company undertook a Phase IA study using powder-in-a-capsule. The one saving grace was that they ran a fed *vs.* fasted comparison. The result was that the bioavailability in the fasted state was probably about 3-5%. The bioavailability in the fed state was about 12-fold higher. They next developed a conventional IR tablet formulation and obtained even worse bioavailability in the fasted state. They then asked the author for advice. Using an amorphous spray dried dispersion, it was possible to overcome the food effect entirely and continue with the clinical development program. However, there had been a delay of more than 18 months from the first poor bioavailability result and the successful bioavailability result for the amorphous dispersion.

This project was unusual in that the financial backer agreed to fund the further work. How many small pharmaceutical start-ups companies would be able to sustain such a delay? How many potentially beneficial drugs have been discarded because of poor understanding of the inherent limitations of the powder-in-a-capsule approach?

The need for speed has to be balanced against an understanding of the biopharmaceutical properties and the limitations of the drug molecule. Simple API powder-in-a-capsule is not appropriate for all drugs. With very little effort and time, by undertaking a pH solubility profile and a Caco-2 permeability study, the chances of success can be greatly improved. The results of such studies will indicate whether or not the API powder-in-a-capsule approach is appropriate, or if there is a need to adopt a more sophisticated approach.

CONCLUSIONS

The pharmaceutical industry has changed over the years and there is a push to reduce the time for pharmaceutical development. However, this reduction, particularly the time to first-in-human studies, is not straightforward. With the increasing number of poorly

water-soluble drugs coming into development, there has to be a rational approach to formulation, even for powder-in-a-capsule, if we want to maintain the progress in new drug development without abandoning promising drug candidates unnecessarily due to a lack of understanding of basic biopharmaceutical principles, and thus wasting time, effort and money.

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