PHARMACEUTICAL PREFORMULATION AND FORMULATION

A Practical Guide from Candidate Drug Selection to Commercial Dosage Form

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Editor

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Biopharmaceutical Support in Formulation Development

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The pharmaceutical formulation plays an important role in the delivery of a drug to the body. The clinical benefit of a drug molecule can thereby be optimised by delivering the right amount at the right rate to the right site at the right time. For example, extended-release (ER) formulations have been used for a long time to control the rate of absorption and thereby keep drug levels within the therapeutic interval during an entire dosage interval. More examples of biopharmaceutical properties that can be provided by oral formulations are given in Table 7.1. In the future, the pharmaceutical possibilities for improving clinical utility may be extended to include site-specific drug delivery systems that reach systemic targets, such as cancer cells and the central nervous system (CNS), or gene delivery to cell nuclei. Such areas of drug delivery are, however, outside the scope for the present chapter.

In order to achieve the potential clinical benefits that can be provided by a formulation, as exemplified in Table 7.1, biopharmaceutical input is needed from the start of preformulation, through formulation development, to documentation for regulatory applications. The main objective is to obtain and verify desirable drug delivery properties for a pharmaceutical formulation. The key activities are as follows:

- Characterisation of relevant physicochemical, pharmacokinetic/dynamic prerequisites provided by the drug molecule
- Identification of the relevant biopharmaceutical targets and hurdles in formulation development

- Definition of test methods/study designs needed to obtain the biopharmaceutical targets in the formulation development and correct interpretation of the study results obtained
- Choice of suitable drug form, formulation principles and excipients

In addition, understanding of the physiological processes that may interact with the biopharmaceutical function of the dosage form is crucial.

Successful biopharmaceutical input during development can make a significant contribution to clinical efficiency and tolerability of a drug product. In certain cases, such as poorly absorbable drugs or drugs that are degraded in the gut, the biopharmaceutical aspects can make the difference between a new useful product or an aborted development programme of a potentially very useful drug compound. Additionally, appropriate use of biopharmaceutics will also contribute to a time and cost-efficient development process.

The present chapter is limited to presentations and uses of different biopharmaceutical test methods in formulation development, such as

- *in vitro* dissolution testing,
- bioavailability studies,
- *in vitro/in vivo* (IVIVC) correlation of drug dissolution,
- use of animal models in *in vivo* studies of formulations and
- *in vivo* imaging of formulations by gamma scintigraphy.

This chapter is strongly focussed on oral drug delivery. The relevant principles and methods involved in biopharmaceutical characterisation of a drug molecule, mainly applied in the preformulation phase, are described in Chapter 4, "Biopharmaceutical Support in Candidate Drug Selection".

Table 7.1
Examples of biopharmaceutical properties of oral dosage forms.

Biopharmaceutical Target	Formulation Function
Increase amount absorbed/ reduced variability of amount absorbed	Dissolution or permeability enhancement Protection from degradation in GI tract
Control rate of absorption	Extended release
	Pulsed release
Control site of delivery	Gastric retention
	Colon release
	Mucoadhesive

IN VITRO DISSOLUTION

In vitro dissolution testing of solid dosage forms is the most frequently used biopharmaceutical test method in formulation development. It is used from the start of dosage form development and in all subsequent phases. Examples of different purposes of dissolution testing in research and development are as follows:

- Investigation of drug release mechanisms, especially for ER formulations
- To obtain a predefined target release profile and robust formulation properties regarding influences of physiological factors (e.g., pH and food) on the drug release
- Generation of supportive data to bioavailability studies as an aid in interpretation of *in vivo* results
- Validation of manufacturing processes
- Investigation of effects of different storage conditions
- Batch quality control (QC)
- A surrogate for bioequivalence studies

An *in vitro* dissolution method for batch QC is always defined for a new solid dosage form product. However, this method may not be sufficient for all the different aims of dissolution testing that might arise. The choice of dissolution method and test conditions should therefore be adapted to best serve their purpose. For example, simplicity and robustness are crucial properties of a QC method; whereas physiological relevance may overrule these factors when a method is used for *in vivo* predictions.

Standard *in vitro* dissolution testing models two processes; the release of drug substance from the solid dosage form and drug dissolution. Drug release will be determined by formulation factors such as disintegration/dissolution of formulation excipients or drug diffusion through the formulation. Drug dissolution will be affected by the physicochemical substance properties (e.g., solubility, diffusivity), solid-state properties of the substance (e.g., particle surface area, polymorphism) and formulation properties (e.g., wetting, solubilisation). *In vitro* dissolution testing should thus provide predictions of both the drug release and the dissolution processes *in vivo*. Therefore, in most situations, the use of *in vitro* dissolution will be meaningless if the method used does not provide some correlation with *in vivo* data or resemblance with the physiological conditions in the gastro-intestinal (GI) tract. In order to reach this goal, the choice of dissolution apparatus and test medium should be carefully considered. Another important aspect in the development and definition of a new method is that it must be designed and operated in such a way that drug release and dissolution are not sensitive to minor variations in the operating conditions.

This chapter will provide some practical considerations for developing and using *in vitro* dissolution methods. Aspects of study design and evaluation of *in vitro* dissolution data will also be discussed. For additional information on *in vitro* dissolution testing, the "FIP Guidelines for Dissolution Testing of Solid Oral Products" (1997), *Handbook of Dissolution Testing* (Hansson 1991), pharmacopoeias and regulatory guidelines are recommended.

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