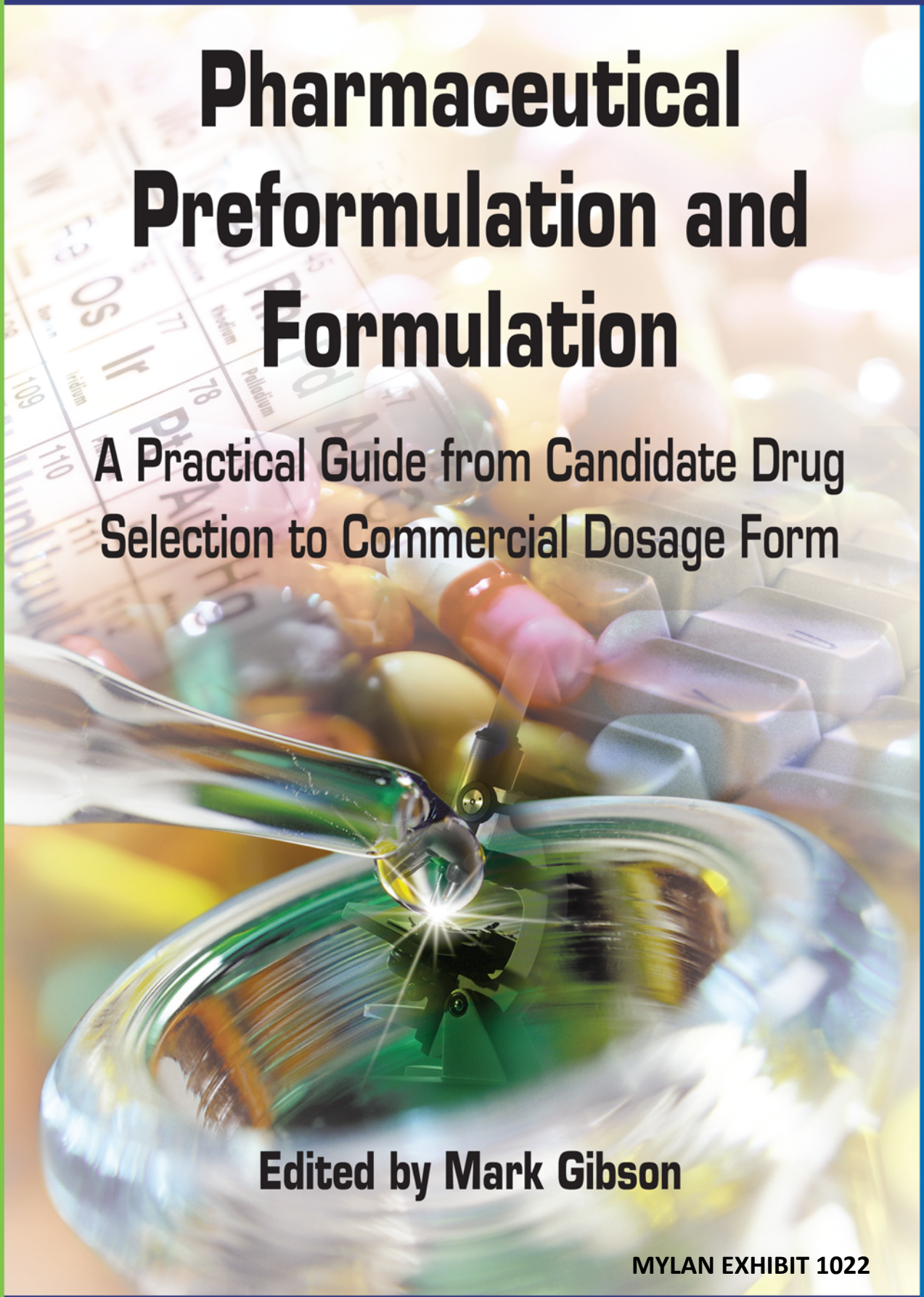
Pharmaceutical Preformulation and Formulation

A Practical Guide from Candidate Drug Selection to Commercial Dosage Form



Edited by Mark Gibson

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Biopharmaceutical Support in Candidate Drug Selection

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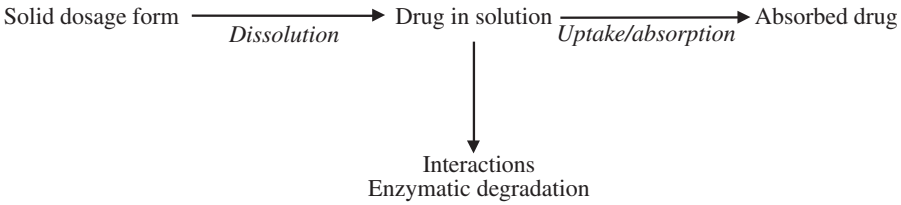
Adminstration via the oral route has been, and still is, the most popular and convenient route for patient therapeutics. However, even though it is the most convenient route, it is not the simplest route, as the barriers of the gastro-intestinal (GI) tract are in many cases difficult to circumvent. The main barriers of the GI tract to systemic delivery are the environment in the stomach and intestinal lumen, the presence of different enzymes, the physical barrier of the epithelium and the liver extraction. These barriers are of functional importance for the organism in controlling intake of water, electrolytes and food constituents and still remain a complete barrier to harmful organisms such as bacteria, viruses and toxic compounds.

Generally, drug absorption from the GI tract requires that the drug is brought into solution in the GI fluids and that it is capable of crossing the intestinal membrane into the systemic circulation. It has therefore been suggested that the drug must be in its molecular form before it can be absorbed. Therefore, the rate of dissolution of the drug in the GI lumen can be a rate-limiting step in the absorption of drugs given orally. Particles of drugs, e.g., insoluble crystalline forms or specific delivery systems such as liposomes, are generally found to be absorbed to a very small extent. The cascade of events from release of the drug from its dosage form, i.e. *dissolution* of the drug in the gut lumen, *interactions* and/or degradation within the lumen and the *uptake* of its molecular form across the intestinal membrane into the systemic circulation, is schematically shown in Figure 4.1. For rapid and effective design and development of new drug products, methods for drug absorption are required that describe the different steps involved before and during the absorption process. The need for such specific

Figure 4.1 Drawing showing the different steps in the absorption process including the dissolution of the compound from the solid dosage form, interactions with the dissolved material in the gastro-intestinal lumen and the uptake of the compound through the epithelial membrane.



methods is determined by the information on the rate-limiting step in the cascade of events (e.g., solubility, permeability or metabolic instability limited). The results from these methods act as a guide to a more efficient discovery process in which resources are given to optimising structures that lead to the selection of a good drug candidate with well-defined pharmacokinetic and physicochemical properties. A method now available is multivariate analysis for analysing large data sets. Screening and optimisation of several parameters in parallel, e.g., permeability, metabolic stability, solubility, potency, duration and toxicity, represent a growing area for rationalising drug discovery using multivariate statistical models (Eriksson et al. 1999). The importance of this is obvious: There is no point in using resources to increase the potency of an oral drug candidate if the drug is not predicted to be orally bioavailable. The consideration of biopharmaceutical properties in the selection of candidate drugs has also been shown in a recent survey, based on statistics published by the Pharmaceutical and Research Manufacturers of America (PhRMA), to be the most common reason for terminating drug development projects in the clinical phase.

The dissolution rate and/or the aqueous solubility of the drug will also affect the outcome of studies using biological methods, in very early phases of screening. If not dissolved in the test system, low solubility drugs will not appear on the receiver side/blood side of a membrane or will show incomplete absorption *in vivo*. Consequently, the drug will be considered a low permeability drug and be discarded as being of no potential use as a systemically active drug. The situation is even more complex, since there are also mechanistic membrane processes that can give the same result. Such processes include drug efflux systems that transport the drug from inside the epithelial cell to the lumen of the intestine [e.g., efflux proteins (Hunter and Hirst 1997)] or metabolism during transport and adhesion to plastics in the test system (Table 4.1). The evaluation of the reason for low transport is therefore crucial for the design of proper screening procedures.

In the drug discovery process, the selection of a suitable candidate drug is the milestone for continuing into a costly development and clinical phase. Some *optimal absorption criteria* from a biopharmaceutical point of view are shown below:

- High permeability coefficient (determined using in vitro assays such as Caco-2 cell monolayers, Ussing chambers, intestinal perfusions, etc.; see below) throughout the GI tract [Extended Release (ER) formulation]

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