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Review article

BCS class IV drugs: Highly notorious candidates for formulation development

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ABSTRACT

BCS class IV drugs (*e.g.*, amphotericin B, furosemide, acetazolamide, ritonavir, paclitaxel) exhibit many characteristics that are problematic for effective oral and per oral delivery. Some of the problems associated include low aqueous solubility, poor permeability, erratic and poor absorption, inter and intra subject variability and significant positive food effect which leads to low and variable bioavailability. Also, most of the class IV drugs are substrate for P-glycoprotein (low permeability) and substrate for CYP3A4 (extensive pre systemic metabolism) which further potentiates the problem of poor therapeutic potential of these drugs. A decade back, extreme examples of class IV compounds were an exception rather than the rule, yet today many drug candidates under development pipeline fall into this category. Formulation and development of an efficacious delivery system for BCS class IV drugs are herculean tasks for any formulator. The inherent hurdles posed by these drugs hamper their translation to actual market. The importance of the formulation composition and design to successful drug development is especially illustrated by the BCS class IV case. To be clinically effective these drugs require the development of a proper delivery system for both oral and per oral delivery. Ideal oral dosage forms should produce both a reasonably high bioavailability and low inter and intra subject variability in absorption. Also, ideal systems for BCS class IV should produce a therapeutic concentration of the drug at reasonable dose volumes for intravenous administration. This article highlights the various techniques and upcoming strategies which can be employed for the development of highly notorious BCS class IV drugs. Some of the techniques employed are lipid based delivery systems, polymer based nanocarriers, crystal engineering (nanocrystals and co-crystals), liquisolid technology, self-emulsifying solid dispersions and miscellaneous techniques addressing the P-gp efflux problem. The review also focuses on the roadblocks in the clinical development of the aforementioned strategies such as problems in scale up, manufacturing under cGMP guidelines, appropriate quality control tests, validation of various processes and variable therein *etc.* It also brings to forefront the current lack of regulatory guidelines which poses difficulties during preclinical and clinical testing for submission of NDA and subsequent marketing. Today, the pharmaceutical industry has as its disposal a series of reliable and scalable formulation strategies for BCS Class IV drugs. However, due to lack of understanding of the basic physical chemistry behind these strategies formulation development is still driven by trial and error.

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1. Introduction

The rate and extent of drug absorption from the gastrointestinal (GI) tract are very intricate and affected by many factors. These include physicochemical factors, physiological factors, and factors related to the dosage form [1,2]. Despite this complexity, the Biopharmaceutics Classification System (BCS) developed by Amidon et al. [3] revealed that the essential key parameters controlling oral drug absorption are the solubility/dissolution of the drug dose in the GI milieu and the permeability of the drug through the GI membrane. These important parameters are characterized in the BCS as one of the most significant tools in modern pharmaceutics and biopharmaceutics of oral drug products. The progress made in combinatorial chemistry and innovative high-throughput screening has led to the production of a vast number of potential drug candidates. However, at the same time these techniques have introduced more poorly water-soluble drugs in the pharmaceutical pipeline. It is estimated that >40% of marketed drugs are poorly water-soluble [4,5]. Lipinski et al. pointed out that leads obtained through high-throughput screening (HTS) tend to have higher molecular weights and greater lipophilicity than leads in the pre-HTS era [4]. Dissolution of the drug in the aqueous milieu of the GI is almost always a prerequisite for oral absorption, and hence, inadequate aqueous solubility often causes limited or poor oral bioavailability. Furthermore the problems associated with poor stability and membrane permeability adds on to the dilemma of low bioavailability [4,6]. All these problems are plaguing the lead molecules or drug candidates in the pipeline of most major pharmaceutical companies. Low/variable bioavailability of a drug is one of the major hurdles for formulation scientists, because it can lead to compromised product performance and the drug is unlikely to reach its molecular target. Such drugs require a high dose but have low systemic exposure, result in adverse effects because of the high dose and may vary in their effect in individual patients [7].

Based on the BCS, drugs are classified into four categories according to their solubility and permeability properties as follows; high solubility–high permeability (class I); low solubility–high permeability (class II); high solubility–low permeability (class III); and low solubility–low permeability (class IV) [3]. The drugs exhibiting low solubility but reasonable membrane permeability such as phenytoin, glibenclamide, carbamazepine, ibuprofen *etc.* are categorised as BCS class II. The rate-limiting process of absorption for class II drugs is the dissolution step. Formulation plays a major role in determining the rate and extent of absorption of such drugs from the gastrointestinal tract. A number of formulation strategies have been developed to improve the delivery of BCS class II drugs like complexation, micronization, crystal modification *etc.* They are based on techniques either to increase the drug dissolution rate or to achieve sustained solubilization of the drugs. The poorly water-soluble drugs with poor membrane permeability (Table 1) belong to BCS class IV such as amphotericin B (AmB), furosemide (FUR), acetazolamide, ritonavir (RTV) *etc.* Usually techniques used for BCS class II drugs do little to improve the absorption of class IV drugs due to the limited membrane permeability. As a result, the best solution to improve the bioavailability of class IV drugs is to go back to the lead optimisation phase of drug discovery and modify their structures to obtain the appropriate physicochemical properties. However, discovering a novel therapeutic agent, itself is a challenging, time-consuming and costly process. It takes US $800–1200 million and 10–15 years to develop a new chemical entity. Also, very few of the millions of compounds after being tested reach the market. Hence, sending a drug molecule back to the lead optimisation phase is not a feasible option because of the constraints associated with time, cost, labour and resources. As a

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