Advanced Drug Delivery Reviews xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

The solubility–permeability interplay and oral drug formulation design: Two heads are better than one☆

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ARTICLE INFO

Article history:
Received 29 December 2015
Received in revised form 10 April 2016
Accepted 18 April 2016
Available online xxxx

Keywords:
Biopharmaceutics Classification System (BCS)
Drug solubility
Intestinal permeability
Solubility-enabling formulations
Solubility–permeability tradeoff

ABSTRACT

Poor aqueous solubility is a major challenge in today's biopharmaceutics. While solubility-enabling formulations can significantly increase the apparent solubility of the drug, the concomitant effect on the drug's apparent permeability has been largely overlooked. The mathematical equation to describe the membrane permeability of a drug comprises the membrane/aqueous partition coefficient, which in turn is dependent on the drug's apparent solubility in the GI milieu, suggesting that the solubility and the permeability are closely related, exhibit a certain interplay between them, and treating the one irrespectively of the other may be insufficient. In this article, an overview of this solubility–permeability interplay is provided, and the available data is analyzed in the context of the effort to maximize the overall drug exposure.

Overall, depending on the type of solubility–permeability interplay, the permeability may decrease, remain unchanged, and even increase, in a way that may critically affect the formulation capability to improve the overall absorption. Therefore, an intelligent design of solubility-enabling formulation needs to consider both the solubility afforded by the formulation and the permeability in the new luminal environment resulting from the formulation.

Contents

1. Introduction

The many factors affecting drug absorption following oral administration make this process a complex and intriguing one. The concomitant influence of physicochemical factors (e.g. pKa, solubility, lipophilicity, diffusivity, and stability), physiological parameters (e.g. GI pH, gastric emptying, small intestinal transit time, and permeation mechanisms), and element related to the dosage form (e.g. tablet, capsule, solution, suspension, and emulsion) greatly complicates the prediction of the overall performance of a given drug product, and the effort of designing an optimal delivery system that will ultimately maximize the resulted absorption [1–3].

Twenty years ago, Amidon et al. [4] developed the biopharmaceutics classification system (BCS), that pinpoints the drug solubility/dissolution in the aqueous gastrointestinal (GI) milieu, and the permeability

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Understanding the challenges of beyond-rule-of-5 compounds".

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http://dx.doi.org/10.1016/j.addr.2016.04.018
0169-409X/

of the drug through the GI membrane as the two key factors governing oral drug absorption [5–7]. Since then, the BCS has become one of the most substantial tools of modern pharmaceutics/biopharmaceutics of oral drug products, revolutionizing bioequivalence regulatory policies worldwide, and influencing numerous aspects of research and development of both generic and innovative drug products [8–11].

Whereas each of these two key parameters, the solubility and the permeability, has been extensively investigated separately, the affiliation between the two and the potential interplay between them have been largely overlooked for many years. This solubility–permeability interplay, that has great applicability and significant impact on modern oral biopharmaceutics, is the focus of this paper.

Modern drug discovery techniques (e.g. combinatorial chemistry and high-throughput screening) are resulting more and more lipophilic drug candidates, and according to some estimates, the majority of new drug candidates are lipophilic and exhibit low aqueous solubility [12–15]. This trend profoundly complicates the development of these candidates into orally administered drug products, as dissolution of the drug in the aqueous GI environment is almost always an essential step prior to permeation and absorption.

To tackle the issue of low solubility drug candidates, many solubility-enabling approaches have been developed and are routinely used. These include formulations that are based on surfactants, cyclodextrins, lipids, cosolvents, amorphous solid dispersions, and others. These techniques may allow tremendous increase in the apparent solubility of the drug, yet their success in increasing the overall oral bioavailability of the drug is much more limited and erratic; increased, unchanged, or even decreased, overall absorption may be obtained following the use of solubility-enabling formulation. Many times, the mechanistic reason(s) for the success/failure of a given solubility-enabling oral formulation to enhance the overall absorption of the drug remains unknown, and unfortunately, the process of the formulation development is mainly empirical.

As noted above, two factors were identified and highlighted as the key parameters governing the absorption process, the solubility and the permeability, and the question this paper deals with is the relationship between them. Or phrased differently: when we increase the drugs' apparent solubility with a certain solubility-enabling formulation, what is the concomitant effect on the drugs' apparent permeability?

The mathematical equation to describe the membrane permeability of a drug is the diffusion coefficient through the membrane times the drugs' membrane/aqueous partition coefficient divided by the thickness of the membrane. Conceptually, it describes the velocity of the drugs' flow into the organ: how deep can the drug penetrate perpendicularly into the intestinal wall per time unit. The presence of K_m, the GI membrane/GI aqueous milieu partition coefficient of the drug, in the permeability description suggests a close association between the solubility and the permeability, since the value of this partition coefficient depends on the drug's aqueous solubility. This relationship between the solubility and the permeability suggests that treating these two key parameters separately may miss a complexity that exists when developing a solubility-enabling formulation, which may eventually lead to a failure to increase the overall absorption.

The aim of this paper is to present and discuss the available data regarding the solubility–permeability interplay in various scenarios. The interplay is formulation dependent: different solubility-enabling formulations present with different solubility–permeability interplay trends, and hence, the overview in this paper will be presented according to the different available solubility-enabling techniques. Our overall goal is to raise the awareness for the solubility–permeability interplay, that may hopefully lead to a more intelligent and less empirical solubility-enabling formulation development process, with higher a-priori knowledge of the formulation impact on the key factors governing absorption.

2. Theory

Quasi-equilibrium analyses of the effect of increased apparent solubility on apparent membrane permeability have been described in detail previously for various solubility enabling formulations including cyclodextrins, surfactants, co-solvents and supersaturation via amorphous solid dispersions [16–19]. The fundamental equations are summarized hereinafter.

The intrinsic membrane permeability of the drug in the absence of solubilizer ($P_{m(o)}$) can be written as:

$$P_{m(o)} = \frac{D_{m(o)}K_{m(o)}}{h_{m(o)}} \quad (1)$$

where $D_{m(o)}$ is the membrane diffusion coefficient of the drug in the absence of solubilizer, $K_{m(o)}$ is the membrane/aqueous partition coefficient of drug in the absence of solubilizer, and $h_{m(o)}$ is the membrane thickness in the absence of solubilizer.

Likewise, the apparent membrane permeability of the drug in the presence of solubilizer (P_m) can be written as:

$$P_m = \frac{D_m K_m}{h_m} \quad (2)$$

where D_m is the apparent membrane diffusion coefficient of the drug in the presence of solubilizer, K_m is the apparent membrane/aqueous partition coefficient of the drug in the presence of solubilizer, and h_m is the membrane thickness in the presence of solubilizer.

Assuming that the presence of solubilizer does not affect the membrane diffusivity or thickness such that $D_{m(o)} = D_m$ and $h_{m(o)} = h_m$, Eqs. (1) and (2) can be combined to give:

$$P_m = \frac{P_{m(o)}K_m}{K_{m(o)}} \quad (3)$$

$K_{m(o)}$ and K_m can be expressed as the ratio of drug solubilities in the membrane and aqueous milieu [20]:

$$K_{m(o)} = \frac{S_{m(o)}}{S_{aq(o)}} \quad (4)$$

$$K_m = \frac{S_m}{S_{aq}} \quad (5)$$

where $S_{m(o)}$ and $S_{aq(o)}$ are the intrinsic solubilities of the drug in the membrane and aqueous milieu, respectively, in the absence of solubilizer. Similarly, S_m and S_{aq} are the apparent solubilities of the drug in the membrane and aqueous milieu, respectively, in the absence of solubilizer.

Assuming that the presence of solubilizer does not affect the drug solubility in the membrane such that $S_{m(o)} = S_m$, Eqs. (3)–(5) can be combined to give:

$$P_m = \frac{P_{m(o)}S_{aq(o)}}{S_{aq}} \quad (6)$$

For cases in which the apparent solubility is increased via complexion with cyclodextrins or surfactant micellization, $S_{aq(o)}$ represents the intrinsic aqueous solubility of the free drug in the absence of cyclodextrins or surfactant and S_{aq} represents the total aqueous solubility (free + bound drug) in the presence of cyclodextrins or surfactant. The free fraction (F) of drug is expressed as $F = S_{aq(o)}/S_{aq.}$ Thus, P_m is directly proportional to F:

$$P_m = P_{m(o)}F \quad (7)$$

Please cite this article as: A. Dahan, et al., The solubility–permeability interplay and oral drug formulation design: Two heads are better than one, Adv. Drug Deliv. Rev. (2016), http://dx.doi.org/10.1016/j.addr.2016.04.018