Journal of Drug Delivery Science and Technology 30 (2015) 342–351

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

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

Strategies for formulating and delivering poorly water-soluble drugs

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ARTICLE INFO

Article history:
Received 19 March 2015
Received in revised form
12 May 2015
Accepted 12 May 2015
Available online 14 May 2015

Keywords:
Insoluble drugs
Formulation
Delivery
pH
Pharmaceutical strategies
Alternative administration route

ABSTRACT

Water solubility is a key parameter in drug formulation since it highly influences drug pharmacokinetics and pharmacodynamics. In the past decades, the challenge with poorly water soluble drugs has been growing continuously. As a matter of fact, poorly soluble compounds represent 40% of the top 200 oral drugs marketed in the US, 33% of drugs listed in the US Pharmacopeia, 75% of compounds under development and 90% of new chemical entities. The present article presents and discusses the pharmaceutical strategies available to overcome poor water solubility in light of final drug product examples. First, chemical modifications based on the adjustment of the pH and the design of prodrugs are presented and discussed. Physical modifications based on modified solid states of the drug, small drug particles, cosolvents, surfactants, lipids and cyclodextrins are discussed in a second part. Finally, the option of modifying the route of administration is briefly presented.

1. Introduction

The water solubility of drugs strongly influences their pharmacokinetics and pharmacodynamics and is a key parameter for formulators. Drug solubilization is based on the breaking of some drug–drug and water–water interactions for the creation of new drug–water interactions. The strength of such interactions determines the solubility of a drug in water. Water solubility is one of the main parameters of the biopharmaceutical classification system (BCS) of drugs, as illustrated in Fig. 1A [1]. Moreover, "Lipinski's rule of 5" considers the solubility of drug candidates in view of the rejection of inappropriate candidates at early stages of the drug discovery process [2].

In the past decades, the challenges linked to poor water solubility have been continuously growing. The surge of combinatorial chemistry and high throughput miniaturized screening methods for drug discovery have resulted in an increase in molecular weight and lipophilicity of drug candidates [3–5]. In addition, the push towards increasing the potency of drugs often resulted in an increase in their lipophilicity (leading to stronger interactions with their receptors). Currently, poorly soluble compounds represent approximately 40% of the top 200 oral drugs marketed in the US and Europe, as shown in Fig. 1B [6]. In addition, they represent 90% of new chemical entities, 75% of compounds under development and 33% of drugs listed in the US Pharmacopeia [2,3,6–11].

Interestingly, a variety of pharmaceutical strategies have been designed to address the formulation and delivery challenges presented by poorly soluble drugs, these are reviewed and discussed in the present article.

2. Strategies for formulating and delivering poorly water-soluble drugs

The pharmaceutical strategies to address the poor water solubility of a drug can be organized into three categories according to the nature of the modification involved: the chemical, physical and administration strategies, as illustrated in Fig. 2. These approaches can of course be used separately or combined.

Over the past decades, many efforts have been made to improve the formulation and delivery of poorly water-soluble immunosuppressants, prostaglandins and antineoplastic agents, which will often be used as examples in the following sections.

It is worth mentioning that colloidal systems represent a more recent option for the formulation of poorly water soluble drugs that can involve chemical or physical modifications [12]. Thus, colloidal systems can be found in the sections describing prodrug design, small drug particles and surfactant-lipid-based formulations. The prodrug design can include drug-polymer nanoparticles and drug covalent link to inorganic nanoparticles. The use of small drug particles can involve nanocrystals and the use of nanoparticles for

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http://dx.doi.org/10.1016/j.jddst.2015.05.009
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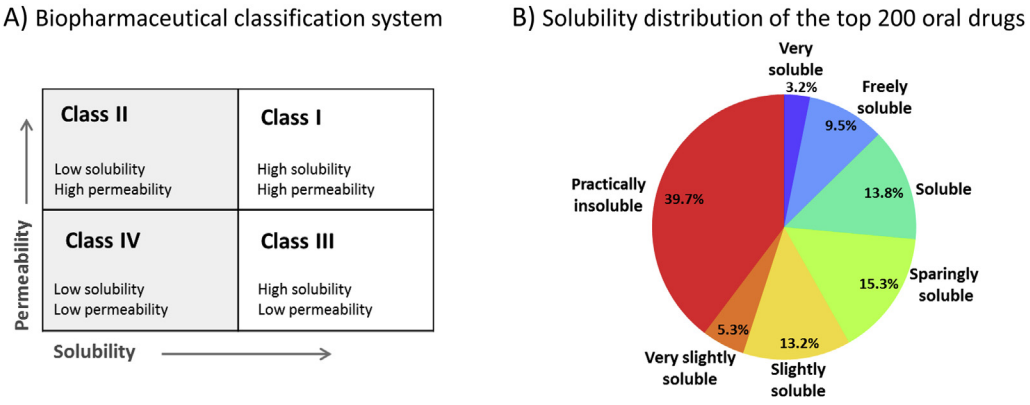

Fig. 1. A) The biopharmaceutical classification system (BCS) and B) the solubility of the top 200 marketed oral drugs in the US and Europe (adapted from [6]).

drug loading or adsorption. Finally, the surfactant and lipid formulations could include nanoemulsions, micelles, liposomes or solid lipid nanoparticles.

2.1. Chemical modifications

2.1.1. pH adjustment

The pH can influence the solubility of a drug by affecting its degree of ionization as a function of its pKa. In its ionized form, a drug has a higher solubility than at its neutral form. However, drugs are generally neutral at physiological pH. Thus, the pH of the formulation can be adjusted with buffering excipients to ensure the presence of the most soluble form of the poorly water-soluble drug.

For solid dosage forms, the buffering excipients control the pH of the microenvironment surrounding drug particles during *in vivo* dissolution [13]. Kranz and coworkers achieved a constant pH-independent release of the immunosuppressant, ZK811752, by adding organic acids to the final composition of the tablets [14].

The pH adjustment is a simple approach and represents a first-line strategy for the formulation of insoluble drugs. It is frequently combined with other solubilizing approaches such as surfactants, cyclodextrins or cosolvents. The pH of the final formulation is selected not only according to drug solubility, but also considering its tolerance, bioavailability, efficacy and stability, which can strongly depend on the pH. In addition, the potential risk of drug precipitation after administration needs to be considered.

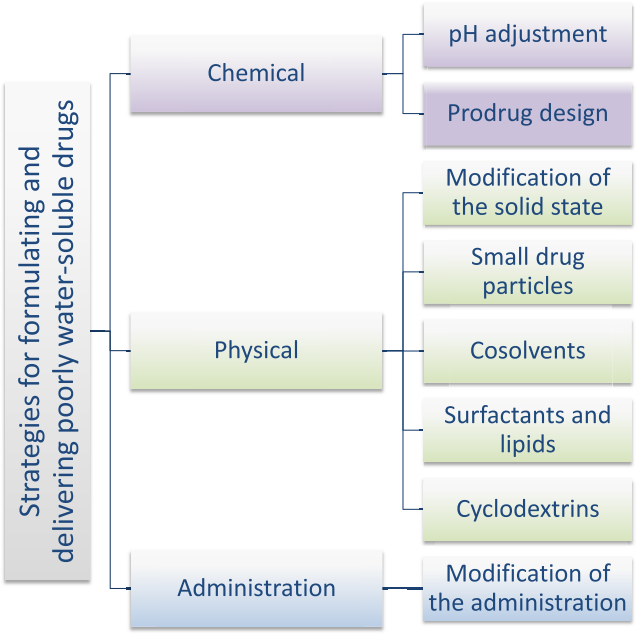

Fig. 2. A schematic representation of the different strategies for formulating and delivering poorly water-soluble drugs.

2.1.2. Prodrug design

A prodrug can be defined as an inactive, chemically modified version of a parent drug displaying improved physico-chemical properties and being able to generate the active parent drug through a rapid biotransformation. Two main prodrug design categories can be identified: i) carrier-linked prodrugs where the parent drug backbone is covalently linked to a prodrug moiety and ii) bioprecursor prodrugs which are modified parent drugs with functional groups requiring hydration or redox reactions, as illustrated in Fig. 3A. In addition, pre-prodrugs or double prodrugs combine two prodrug design approaches in their design (carrier-linked and/or bioprecursor), one example being illustrated in Fig. 3B.

The prodrug strategy has been gaining interest in the past years and today its usefulness in drug formulation is unquestionable. Prodrugs represent 10% of worldwide marketed drugs and were 33% of the small active molecules approved in 2008 [15,16]. Prodrug design represents a versatile and powerful approach that can solve a large variety of issues related to drug solubility, absorption, distribution, metabolism, toxicity or stability, among others [17,18].

The prodrug bioconversion is of major importance and needs to be carefully evaluated and optimized. Ideally, the prodrug should have an *in vitro* half-life one million times higher than its *in vivo* half-life. Such a difference is only possible with enzyme-based biotransformations [19].

For Anderson and Conradi, the prodrug of a poorly water soluble drug should not be limited to the covalent link of a promoiety to the parent drug, but should represent a new and optimized drug delivery system of its own [19]. In this sense, the use of prodrugs to address the challenges with poor water-solubility will be discussed through a number of examples, covering both the carrier and bioprecursor approaches.

For **carrier-linked prodrugs**, the first type of prodrug design, four main carrier moieties can be used: i) hydrophilic groups, ii) hydrophobic groups, iii) amino acids and iv) macromolecules, as illustrated in Fig. 3A. Carrier-linked prodrugs are frequently used to simultaneously address the question of poor water-solubility of a drug and achieve its targeted delivery.

The covalent linking of ***hydrophilic structures*** often confers a higher solubility to the parent drug. Phosphate ester prodrugs are