Advanced Drug Delivery Reviews xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

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

Drug delivery design for intravenous route with integrated physicochemistry, pharmacokinetics and pharmacodynamics: Illustration with the case of taxane therapeutics ☆

L. Harivardhan Reddy *, Didier Bazile

Drug Delivery Technologies and Innovation, Pharmaceutical Sciences Department, Sanofi Research and Development, 13 Quai Jules-Guesde, 94403 Vitry-sur-Seine, France

ARTICLE INFO

Article history:
Accepted 24 October 2013
Available online xxxx

Keywords:
Drug delivery systems design
Physicochemistry
Biopharmacy
Pharmacokinetics
Pharmacodynamics
Efficacy
Safety
Taxanes
Classification
Paclitaxel
Docetaxel
Cabazitaxel
Nanoparticles

ABSTRACT

This review is aimed at combining the published data on taxane formulations into a generalized Drug Delivery approach, starting from the physicochemistry and assessing its relationships with the pharmacokinetics, the biodistribution and the pharmacodynamics. Owing to the number and variety of taxane formulation designs, we considered this class of cytotoxic anticancer agents of particular interest to illustrate the concepts attached to this approach. According to the history of taxane development, we propose a classification as (i) "surfactant-based formulations" first generation, (ii) "surfactant-free formulations" second generation and (iii) "modulated pharmacokinetics drug delivery systems" third generation. Since our objective was to make the link between (i) the physicochemistry of the drug and carrier and (ii) the efficacy and safety of the drug in preclinical animal models and (iii) in human, we focused on the drug delivery technologies that were tested in clinic.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Editor's Choice 2014".

* Corresponding author.
E-mail address: harivardhan-reddy.lakkireddy@sanofi.com (L.H. Reddy).

0169-409X/$ – see front matter © 2013 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.addr.2013.10.007

1. Introduction

As the Drug Delivery concepts are becoming more and more widespread as ways to enhance the therapeutic performance of pharmaceutical products, the consideration of the impact of the formulation on the pharmacokinetics and, consequently on the efficacy and safety profiles of a drug, are growing [1–3]. In fact, as far as the intravenous route is concerned, the administration of a drug as a true solution (i.e. when a drug molecule is only interacting with water molecules) is the only situation where Drug Delivery can be considered both theoretically and practically independent of the influence of the formulation. Nevertheless, this situation is more and more rare owing to the poor aqueous solubility of most of the new chemical entities [4,5]. At the same time, when a chemical series has exhibited promising results in a pharmacological model, the design of an enabling formulation aimed at overcoming the poor aqueous solubility of the compounds is the only way forward when the efforts to synthesize soluble derivatives were unsuccessful.

Starting from the basic affinity principle, the pharmacological activity and/or efficacy of a drug is related to its binding constant and its local concentration in the vicinity of the pharmacological target. Thus, a drug exhibiting a lower binding constant but delivered at a significantly higher local concentration is prone to exhibit the same or even higher efficacy than a drug exhibiting a higher affinity but reaching the target at a lower local concentration, due to the dilution process. Since the drug metabolism and elimination are prone to have a significant impact on its distribution (i.e. on the local concentration at the target), these parameters are included in the drug candidate selection criteria, early in the Discovery process, as Absorption, Distribution, Metabolism and Elimination (ADME) package [6]. The impact of other phenomenon, such as the efflux of the drug from the target cell, driven by the Multidrug Drug Resistance (MDR) complex, has led to the addition of this parameter to the drug design.

The general assumption of the Drug Discovery paradigm is that other parameters such as the association of the drug to the components of the enabling formulation has only a minor impact on its biopharmacy and is not significantly different from one drug to another. It is worth mentioning that this assumption is most of the time valid since the drug and the formulation components are quickly dissociated upon dilution in the bloodstream. Nevertheless, in some instances, a particular attention has to be paid to this drug/excipient(s) association to interpret the pharmacokinetic profiles.

The development of the nanotechnologies has shed a new light on the understanding of the physicochemical principles of Drug Delivery and on their impact on the fate of the drug in the body [1]. The notions, of drug/nano-carrier association/dissociation, of interaction of the nano-carriers with the blood components impacting its pharmacokinetics and elimination, and of exchange between the nano-carrier and the natural carriers such as plasma proteins and lipoproteins, are now taken into account on a regular basis by the pharmaceutical scientists for the design of the nano-objects aimed at improving the delivery of the drugs.

In this context, the formulations of taxanes are of particular interest since the biopharmacy of these anti-cancer drugs is closely linked to the formulation. Therefore, the purpose of this article is to review the literature on taxanes formulations in an attempt to outline the relationships between physicochemistry and biopharmacy and to foresee further improvements that could be expected from drug design and drug delivery system design. In order to propose a link between the physicochemistry of the drug carrier and its biopharmaceutical behavior both in preclinic animal models and in human, this article focuses on the drug delivery technologies for which clinical data is available.

1.1. Taxanes

Taxanes form an important class of anticancer agents due to their unique mechanism of action and their wide applications in cancer therapy. Three taxanes i.e., paclitaxel, docetaxel, and cabazitaxel have been approved for human use and commercialized to date for intravenous injection to human.

1.1.1. Paclitaxel

Paclitaxel (Fig. 1a) is a cytotoxic agent that is chemically a complex diterpene having a taxane ring with a four-membered oxetane ring and an ester side chain at position C-13 [7–9]. Paclitaxel binds to β-subunit of tubulin, enhances the polymerization of tubulin to stable microtubules, and also interacts directly with microtubules, stabilizing them against depolymerization by calcium ions [9], thereby leading to the inhibition of the interphase, the mitotic cellular functions, and apoptosis [10,11]. The fact that paclitaxel binds to microtubules macromolecules in the cells in a specific, reversible, and saturable manner, makes this drug unique among chemotherapeutic agents [12]. Paclitaxel has demonstrated activity against ovarian, breast, lung, Kaposi's sarcoma, bladder, prostate, esophageal, head and neck, cervical, and endometrial cancers [13–15].

Paclitaxel was approved by the FDA in 1992 and was commercialized under the trade name Taxol®, a non-aqueous concentrate, designed to be diluted in a suitable parenteral aqueous infusion solution prior to intravenous administration. The composition includes 6 mg paclitaxel dissolved into 527 mg of purified Cremophor® EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol/mL of concentrate (Bristol-Myers Squibb's package insert for Taxol (paclitaxel) injection, http://packageinserts.bms.com/pi/pi_taxol.pdf). The clinically recommended doses of Taxol® are 135–175 mg/m^2 intravenously administered over a 3 h infusion every 3 weeks. This dose includes also the injection of ~22–29 g Cremphor® EL and ~21–27 mL of alcohol to the patient (see Table 1).

1.1.2. Docetaxel

The pioneering work of Pierre Potier's team using a semi-synthetic pathway based on chemical modification of the 10-deacetylbaccatin III extracted from the needles of the European yew *Taxus baccata* has led to the discovery of docetaxel (Fig. 1b) [16]. Like paclitaxel, docetaxel causes the blockade of G2/M phase of cell cycle of the treated cells [17,18], preventing microtubules depolymerization resulting in an arrest of cell division [19,20]. Docetaxel showed a 1.9-fold higher affinity than paclitaxel for the binding site and, accordingly, induced tubulin polymerization at a 2.1-fold lower critical tubulin concentration [21]. Docetaxel has demonstrated a significant cytotoxic activity in vitro, and a broad spectrum of antitumor activity in preclinical animal models [19,22]. Although docetaxel has shown antitumor activity in paclitaxel-resistant carcinoma in both preclinic [23] and clinical studies [24,25], its potential limitation, as observed for paclitaxel, stands in its resistance observed in preclinical studies [26–29] explained by different mechanisms [30–32], and in clinic [33].

Docetaxel has been commercialized by Sanofi under the brand name Taxotere®, a non-aqueous concentrate, designed to be diluted prior to intravenous infusion with a supplied diluent containing 13% w/w ethanol in water for injection. In this two-vial product, the concentrate

Please cite this article as: L.H. Reddy, D. Bazile, Drug delivery design for intravenous route with integrated physicochemistry, pharmacokinetics and pharmacodynamics: Illustration..., Adv. Drug Deliv. Rev. (2013), http://dx.doi.org/10.1016/j.addr.2013.10.007