Strategies for improving the payload of small molecular drugs in polymeric micelles

CrossMark

Yu Zhang [a,b,*], Tianyang Ren [a], Jingxin Gou [a], Ling Zhang [c], Xiaoguang Tao [a], Bin Tian [a], Pengqian Tian [a], Dandan Yu [a], Jianbo Song [a], Xiaolin Liu [a], Yanhui Chao [a], Wei Xiao [b], Xing Tang [a,*]

[a] Department of Pharmaceutics Science, Shenyang Pharmaceutical University, Shenyang 110016, China
[b] Jiangsu Kanion Pharmaceutical Co., Ltd., Lianyungang 222047, China
[c] Department of Biotherapy, Cancer Research Institute, The First Affiliated Hospital of China Medical University, Shenyang 110001, China

ARTICLE INFO

ABSTRACT

In the past few years, substantial efforts have been made in the design and preparation of polymeric micelles as novel drug delivery vehicles. Typically, polymeric micelles possess a spherical core–shell structure, with a hydrophobic core and a hydrophilic shell. Consequently, poorly water-soluble drugs can be effectively solubilized within the hydrophobic core, which can significantly boost their drug loading in aqueous media. This leads to new opportunities for some bioactive compounds that have previously been abandoned due to their low aqueous solubility. Even so, the payload of small molecular drugs is still not often satisfactory due to low drug loading and premature release, which makes it difficult to meet the requirements of *in vivo* studies. This problem has been a major focus in recent years. Following an analysis of the published literature in this field, several strategies towards achieving polymeric micelles with high drug loading and stability are presented in this review, in order to ensure adequate drug levels reach target sites.

© 2017 Elsevier B.V. All rights reserved.

1. Introduction

With the development of high-throughput screening technique (HTS), new candidate compounds or new chemical entities are continually being discovered and developed [1,2]. However, HTS prioritizes perfect matching between candidates and the exact geometry of the target receptor, and therefore the obtained candidates tend to be of relatively higher molecular weight and log *P*, leading to very low water solubility [3,4]. Additionally, the more water-soluble candidates are already effectively formulated due to the relative ease in achieving this aim, leaving the poorly water-soluble drugs still in need of effective formulation strategies [5,6].

Therefore, the development of suitable formulations for the administration of these hydrophobic candidates is a challenging and exciting task for pharmacists. Traditionally, a variety of surfactants, such as Cremophor EL and Tween 80, have been used for the solubilization of poorly water-soluble drugs. However, these face restrictions in their use due to their potential toxicity and/or limited solubilizing ability [7–11]. In the past decade, with the rapid development of polymer

material science, many polymer-based materials have now been applied for the purpose of delivering hydrophobic drugs.

Undoubtedly, polymeric micelles are one of the promising candidates in this field. Polymeric micelles are usually formed by the self-assembly of amphiphilic copolymers in aqueous media, when the polymer concentration is above the critical micelle concentration (CMC) [12]. Generally, micelles are comprised of a spherical core–shell structure, with a hydrophobic inner core and hydrophilic outer shell [13]. Thus, the hydrophobic core can be used to solubilize or entrap hydrophobic drugs, while the outer water-soluble shell can protect the drugs from the surrounding aqueous environment and additionally provide the particles with steric stability [14,15]. Based on this, hydrophobic drugs can be effectively solubilized in aqueous environments. In addition to this, polymeric micelles also have other advantages as drug nanocarriers: (a) the hydrophilic shell, such as polyethylene glycol (PEG) or polyoxyethylene (PEO), endows the micelles with a 'stealth' property, which reduces non-specific interactions between micelles and endogenous substances, and helps micelles escape recognition by the RES, contributing to prolonged blood circulation; (b) a suitable size (typically 20– 200 nm) with a small polydispersity index (PDI) to not only avoid rapid renal excretion and achieve a high accumulation at target sites through the enhanced permeation and retention (EPR) effect, but also to facilitate cellular uptake *via* endocytotic internalization pathways, which helps to reduce multidrug-resistance (MDR) caused by drug efflux; (c) the addition of a targeting moiety on the surface of the micelles can aid in delivering drugs precisely to target tissues, thereby avoiding any non-specific organ toxicity; (d) polymeric materials used for the formation of micelles can be tailor-made to meet all necessary requirements. Moreover, these materials can provide excellent biocompatibility as they can be degraded *in vivo* into non-toxic components, which can be absorbed or excreted *in vivo* [7,16–20].

In spite of these advantages, until now, only one micelle-based formulation (Genexol-PM®, South Korea) has been used in clinical applications [18,21]. What are the major obstacles in developing an effective polymeric micelle system for the transport and delivery of therapeutic drugs? In our opinion, the low drug loading capacity and poor *in vivo* stability typically displayed by polymeric micelles are two major obstacles. It can be seen after reviewing the literature that most micelle systems suffer from a low drug loading capacity [7,22,23]. To our knowledge, the majority of hydrophobic drugs loaded in micellar formulations are cytotoxic anticancer agents, and the efficacy of these particular drugs is positively correlated with the dose, meaning that the higher the dose that can be given, the better the efficacy will be. Therefore, the clinically recommended dose of these drugs is very high, *e.g.* 75– 100 mg/m^2 for docetaxel (DTX) and 135– 175 mg/m^2 for paclitaxel (PTX). This means that polymeric micelles with low drug loading would require a larger volume and potentially more excipients to be administered, which could result in undesirable toxic effects. Another consideration is that the drug-loaded polymeric micelles will be diluted >25 times by the circulating blood following intravenous administration [13,24]. This dilution poses a threat to the *in vivo* stability of the micelles, by breaking them down into their single polymer chains [21,25,26]. If the final concentration of the polymer in the blood circulation is less than CMC, the micelles are likely to disassemble into single polymer chains, resulting in premature leakage of the encapsulated drug into the blood stream before they can arrive at the target sites. Furthermore, the poorly water-soluble drugs would be likely to precipitate inside blood vessels, which leads to negative side effects [13].

Taking all these factors into consideration, the main purpose of this review is to shed light on the strategies for increasing the drug loading capacity of polymeric micelles and prevent drug leakage during blood circulation, or, in other words, how to improve the payload of small molecule drugs in polymeric micelles to ensure adequate drug levels at the target sites. Previously employed strategies will be systematically presented using specific examples, and any additional challenges will also be considered.

2. The selection/modification of drug and polymer

2.1. Improving the compatibility between drug and polymer

The compatibility between drug and polymer refers to the miscibility, [27] which is closely associated with the drug loading capacity and stability of polymeric micelles [28,29]. The Flory–Huggins interaction parameter (χ) is usually used to indicate the drug–polymer compatibility. Generally, the lower the $\chi_{\text{drug-polymer}}$ value, the higher the compatibility between the drug and polymer unit – in the case of micelles, the hydrophobic polymer core [30]. $\chi_{\text{drug-polymer}}$ is calculated by the following equation [31]:

$$\chi_{\text{drug-polymer}} = \frac{V_{\text{drug}}}{RT}\left(\delta_{\text{drug}} - \delta_{\text{polymer}}\right)^2$$

where V_{drug}, T, R, δ_{drug} and δ_{polymer} represent the molar volume of the drug, temperature in Kelvin, the ideal gas constant and the Hansen solubility parameter (HSP) of the drug and the polymer repeating unit, respectively. The HSP can be obtained by dispersion (δ_{d}), polar (δ_{p}) and hydrogen bonding interactions (δ_{h}), which can be calculated according to the additive group contribution method.

$$\delta^2 = \delta_{\text{d}}^2 + \delta_{\text{p}}^2 + \delta_{\text{h}}^2$$

$$\delta_{\text{d}} = \sum \frac{F_{\text{di}}}{V}$$

$$\delta_{\text{p}} = \frac{\sqrt{\sum F_{\text{pi}}^2}}{V}$$

$$\delta_{\text{h}} = \sqrt{\sum \frac{E_{\text{hi}}}{V}}$$

Herein F_{di}, F_{pi} and E_{hi} are the dispersion attraction constant, polar attraction constant and hydrogen bonding energy, respectively. The values of these parameters for common groups are summarized in Table 1.

According to the compatibility theory, it is essential to select both suitable polymers and drugs for the construction of stable micelles with high drug loading. Mao et al. [34] used chitosan as the hydrophilic section and selected glycerol monostearate, glyceryl monolaurate and glycerol monooleate as the hydrophobic sections for the synthesis of three different copolymers. The $\chi_{\text{drug-polymer}}$ values between the three copolymers and the drug 10-hydroxycamptothecin (HCPT) were calculated by the group contributions, which showed that compatibility was in the order of chitosan-g-glyceryl monolaurate (CS-g-ML) < chitosan-g-glyceryl monostearate (CS-g-MS) < chitosan-g-glyceryl monooleate (CS-g-MO). The resultant CS-g-MO/HCPT micelles were fairly spherical in shape, and no HCPT crystallization was observed after 6 days of storage. The drug loading content of CS-g-MO/HCPT micelles was close to 30 wt% and the drug loading efficiency was as high as 91.8 wt%. However, for the CS-g-MS/HCPT micelles, the miscibility of HCPT with CS-g-MS was so poor that the drug molecules separated from the micelles and recrystallized, while the CS-g-ML/HCPT micelles formed large aggregates which could not be redispersed by shaking. Maysinger and Kakkar et al. [35] successfully constructed mitochondria-targeting micelles for the delivery of coenzyme Q10 (CoQ10) from ABC miktoarm polymers (A: PEG, B: PCL, and C: triphenylphosphonium bromide). A good linear relationship was observed between the CoQ10/polymer weight ratio and the drug loading when the weight ratio was varied from 5% to 150%. Therefore, an extremely high loading of CoQ10 (60 wt%) was achieved at a weight ratio of 150%, which was significantly higher than other reported nanoparticles. Moreover, there was no observed drug precipitation during the storage of the micelles at room temperature for several weeks. This extremely high CoQ10 loading was