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REVIEW

Core-crosslinked polymeric micelles: Principles, preparation, biomedical applications and clinical translation

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Summary Polymeric micelles (PM) are extensively used to improve the delivery of hydrophobic drugs. Many different PM have been designed and evaluated over the years, and some of them have steadily progressed through clinical trials. Increasing evidence suggests, however, that for prolonged circulation times and for efficient EPR-mediated drug targeting to tumors and to sites of inflammation, PM need to be stabilized, to prevent premature disintegration. Core-crosslinking is among the most popular methods to improve the *in vivo* stability of PM, and a number of core-crosslinked polymeric micelles (CCPM) have demonstrated promising efficacy in animal models. The latter is particularly true for CCPM in which (pro-) drugs are covalently entrapped. This ensures proper drug retention in the micelles during systemic circulation, efficient drug delivery to pathological sites *via* EPR, and tailorable drug release kinetics

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at the target site. We here summarize recent advances in the CCPM field, addressing the chemistry involved in preparing them, their *in vitro* and *in vivo* performance, potential biomedical applications, and guidelines for efficient clinical translation.

Introduction

In the last 2—3 decades, nanomedicines have started to attract significant attention. Both at the academic and at the industrial level, an ever-increasing number of scientists are working on the development of 1—100(0) nm-sized drug delivery systems. This increasing interest in nanomedicine research is on the one hand based on the continuing progress made in the fields of nanotechnology, polymer chemistry and chemical engineering, giving rise to an ever increasing number of nanomaterials that can — in principle — be used for drug delivery purposes [1—5]. On the other hand, in spite of many years of drug delivery research, there still are many drug molecules (in particular highly hydrophobic compounds, proteins and nucleic acids) and diseases (in particular cancer) which require further improvements in delivery, to really improve therapeutic outcome and the quality of life of patients [6—9].

Chemotherapeutic drugs are an excellent example to demonstrate the need for improved delivery. *In vitro*, *i.e.* in cell culture, chemotherapeutic agents are often highly potent, killing the vast majority of cancer cells at pico- to micromolar concentrations. In animal models and in patients, on the other hand, they generally fail to provide sufficient therapeutic efficacy. This failure is likely mostly due to inefficient accumulation and insufficient retention at the target site, resulting in suboptimal therapeutic responses. At the same time, significant amounts of intravenously (i.v.) administered chemotherapeutic drugs accumulate in healthy tissues, causing serious side effects and therefore lowering the quality of life of patients. These deleterious pharmacokinetic and biodistributional properties result from a number of chemical, anatomical, biological and physiological barriers [10—12]. Among the most important (physico-) chemical barriers are the low molecular weight, low solubility, low stability and high hydrophobicity of anticancer agents. These parameters generally lead to short circulation times upon i.v. injection, with only a small percentage of the i.v. injected dose (%ID) eventually reaching the target site. In addition, they result in a relatively large volume of distribution, causing chemotherapeutic drugs to accumulate in several different healthy organs.

By entrapping chemotherapeutic drugs in liposomes or micelles, or by conjugating them to water-soluble polymers or proteins, the apparent molecular weight of the agents increases, and their volume of distribution decreases. The latter attenuates their accumulation in healthy tissues, while the former increases their circulation times, and by means of the Enhanced Permeability and Retention (EPR) effect, enables them to accumulate in tumors more efficiently. The EPR effect has been described by Maeda and colleagues ~30 years ago, and it is based on the notion that cancerous (and inflamed) tissues possess leaky blood vessels, allowing for the extravasation of nanomaterials with sizes of up to several hundreds of nanometers, while at the same time promoting their retention at the pathological site because of defective lymphatic drainage [13,14].

Many different nanomedicines have been designed and evaluated over the years [2—9,12,15—19]. The (pre-) clinically most relevant formulations are depicted in Fig. 1, and virtually all of them are designed to take advantage of the EPR effect. This implies that the key characteristics of nanomedicines are (I) ensuring efficient, stable and reversible drug loading and (II) enabling prolonged circulation times (as a prolonged circulation time constitutes the basis for efficient EPR). Of particular importance in this regard is the development of systems that improve the administration and target site accumulation of highly hydrophobic drugs. In the case of cancer, for instance, taxane-based chemotherapeutics such as paclitaxel and docetaxel are known to be among the most potent drugs, and they are extensively employed in the clinic. However, because of their high hydrophobicity, their i.v. administration is problematic, requiring drop-wise infusion for multiple hours in relatively toxic (immunogenic) solubilization enhancers, such as Cremophor. Thus, the co-administration of corticosteroids and anti-histaminics, to suppress infusion-related inflammatory and hypersensitivity reactions, is mandatory.

Nanomedicines hold significant potential for improving this situation, *i.e.* to substantially enhance the bioavailability of highly hydrophobic anticancer agents. This can be best exemplified by looking at Abraxane [20,21]: by co-condensing paclitaxel with albumin, a 130 nm-sized nanoparticulate-formulation is obtained, which is administered to patients without the need for corticosteroid and anti-histaminic co-administration. Because of the increased tolerability profile, this albumin-based paclitaxel formulation enables the administration of higher doses (175 mg/m^2 for Taxol (*i.e.* paclitaxel in Cremophor) *vs.* 225 mg/m^2 for Abraxane), which likely explains the improved patients responses observed in phase III clinical trials [22]. However, it has to be kept in mind in this regard that although Abraxane is a nanomedicine formulation, it disintegrates almost immediately upon i.v. injection, as demonstrated by an equal pharmacokinetic profile as compared to Taxol, with paclitaxel being transferred to endogenous albumin (as in the case of Taxol). Consequently, Abraxane does not provide improved circulation times as compared to Taxol, and therefore does not exploit the EPR effect to result in higher tumor concentrations [23,24].

Because of their physicochemical nature, consisting of a hydrophobic core and a hydrophilic shell, polymeric micelles (PM) are highly suited for enabling EPR-mediated passive drug targeting of hydrophobic compounds [25—32]. PM are based on amphiphilic block-copolymers, which can self-assemble into well-defined core—shell-structures at