Polymeric micelles: a promising tool for tamoxifen delivery in cancer?

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With the recent progress in polymer science, polymeric micelles (PMs) as drug carrier have gained an increasing interest in cancer therapy. PMs comprise amphiphilic graft/block copolymers that form self-assembled nanostructured core-shell architectures in an aqueous milieu at or above a concentration called critical micelle concentration (CMC). These self-assembled core-shell architectures are known as PMs. The hydrophobic core of PMs can accommodate a large variety of hydrophobic drugs at higher concentrations, while the hydrophilic corona protects the payloads from the surrounding environment to decide their biological fate [1]. Being small in size, PMs can easily permeate through the leaky vasculature and are subsequently retained there for longer periods of time, thus delivering the payload selectively at the target site, the so-called enhanced permeability and retention effect. The efficiency of the micellar carriers can be further improved by active targeting. Active targeting is accomplished by attaching a specific ligand to the surface of drug-loaded PMs [2]. In addition, the properties of PMs such as drug loading, release rate and tumor targeting can be readily adjusted by precisely engineering the constituent block/graft copolymers. The successful entry of NK105 (paclitaxel-loaded PMs) and NC-6004 (epirubicin-loaded PMs) into Phase III clinical studies [3], further corroborates the use of PMs in cancer chemotherapy.

Polymeric micelles of tamoxifen: a way to negate endometrial cancer

ICI Pharmaceuticals (now known as AstraZeneca, Hamilton, OH, USA) introduced tamoxifen (TMX) to the UK market for breast cancer treatment in 1973 and as an inducer of ovulation in 1975. Even today also it is considered as the gold standard for the endocrine treatment of all stages of estrogen-receptor-positive breast cancer. Chemically TMX, 2-[4-[(Z)-1,2-diphenylbut-1-enyl]phenoxy]-N,N-dimethylethanamine, represents a category of poorly soluble drug with an aqueous solubility $0.04 \mu\text{g} \cdot \text{mL}^{-1}$ at 37°C [4]. Nevertheless, long-term treatment of TMX leads to a modest increase in blood clots and endometrial cancer in postmenopausal women [5]. Moreover, metabolic activation of TMX to electrophilic intermediates by CYP P450 isoenzymes in the liver results in the overproduction of reactive oxygen species, responsible for oxidative liver damage and hepatocarcinoma in rats [6]. Hence, there is a need to develop novel/targeted drug delivery systems for TMX to circumvent potential side/adverse effects.

PMs offer promising advantages over other nanoformulations and hence have been tried as pharmaceutical carriers for TMX to enhance the solubility, bioavailability and tumor accumulation, thus reducing the administered dose and long-term side effects. For instance, micelles from poly(ethylene glycol) (PEG) with MW equivalent to 5000 Da modified with distearoyl-phosphatidylethanolamine

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(PEG₅₀₀₀-PE) has been proposed by Gao *et al.* to endow enhanced tumor accumulation of TMX. These micelles can accommodate as much as 20 wt% of the TMX with particle size and CMC of 10–40 nm and 6.2×10^{-6} M, respectively and demonstrated much higher accumulation in C57BL/6J mice tumors when injected via the tail vein [7–9]. Further, Cavallaro *et al.* have reported TMX-loaded graft copolymeric micelles formed by α,β -poly(*N*-2-hydroxyethyl)-D,L-aspartamide (PHEA) modified PEG chain and/or hydrophobic hexadecylalkyl groups (C₁₆) (PHEA-PEG_{2000/5000}-C₁₆). Micelles prepared from PHEA-PEG₅₀₀₀-C₁₆ can accommodate as high as 4.1 wt % TMX as compared with PHEA-PEG₂₀₀₀-C₁₆ which accommodate less than 2 wt % of TMX. Collectively, these approaches enable greater control over the particle size approximately 10–30 nm, enhancing micelle stability in human plasma while releasing the payload at target site slowly as a function of time [10]. Exploiting the chemical reactivity of PEG for PEGylation, Yadav *et al.* have recently developed TMX-loaded PMs, using poly(lactic-co-glycolic acid)-PEG diblock copolymers to endow enhanced bioavailability and tumor accumulation via topical delivery. The bioavailability of TMX in epidermis was enhanced approximately 3.5-times when compared with plain TMX gel [11]. However, it is difficult to predict the *in vivo* performance of drug on the basis of *in vitro* studies only. Nevertheless, the immunogenicity and *in vivo* degradability of low MW PEG cannot be overlooked in formulations for long-term treatments [12]. Recently, we exploited α -tocopherol succinate (TS) and low MW carboxymethyl chitosan (Cmc) (MW ~22 kDa) to synthesize amphiphilic graft copolymer Cmc-TS that self-assemble into TMX-loaded nanostructured core-shell architecture in an aqueous milieu for breast cancer targeting via oral route. This polymer (Cmc-TS) possesses inherent biodegradability and no immunogenicity and hence may be substituted for synthetic polymers as a means to evade toxicity associated with synthetic polymers. These PMs possess particle size and CMC equivalent to 141.53 ± 2.59 nm and 1.58×10^{-6} g/ml, respectively and can accommodate as high as 8.08 ± 0.98 wt % of TMX. The defining features of these micelles is their stability in the harsh conditions of the GI tract and their ability to permeate the epithelial barrier via the

paracellular route without causing any intestinal damage [13]. Furthermore, at equivalent dose of TMX, TMX-loaded PMs were more effective in suppressing breast cancer in *N*-methyl-*N*-nitrosourea-induced mammary carcinogenesis rat model with the least amount of side effects [AT SANGAMWAR *ET AL.* UNPUBLISHED DATA]. Collectively, these approaches enable a 1.9-fold increase in oral bioavailability, enhancing anticancer efficacy while minimizing hepatotoxicity associated with TMX.

Future perspective

Tamoxifen citrate is selectively used in the treatment of breast cancer in pre- and post-menopausal women. However, endometrial carcinoma, liver cancer, venous thrombosis, pulmonary emboli, retinopathy and corneal opacities limit the long-term use of TMX in therapeutic use. It is observed that most of the side effects associated with TMX are dose and concentration dependent. Hence, several nanoscaled drug-delivery approaches are suitable for TMX that deliver a lower dose over a prolonged period. PMs demonstrate several advantages, such as controlled drug release, tissue-penetrating ability and reduced toxicity in comparison with other nanocarrier systems. Other important features of PMs, such as small particle size, gastrointestinal stability, drug-loading capacity and improved release kinetics further improved the efficacy of drug in its therapeutic dose. Additionally, PMs offer translational ability, which has been proven in several preclinical and clinical studies.

The reported Cmc-TS graft copolymer-based PMs proved the efficiency of TMX at the laboratory scale, while integrating it to the physiologically based pharmacokinetic model, which will provide an idea to go into preclinical study and also its translation into a commercial product.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

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