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Review

Polymeric micelles drug delivery system in oncology

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ABSTRACT

Polymeric micelles (PM) system, as an efficient drug carrier, has received growing scientific attention in recent years owing to its solubilization, selective targeting, P-glycoprotein inhibition and altered drug internalization route and subcellular localization properties. Seven PM formulations of anti-tumor drugs being evaluated in clinical trials are reviewed in this paper, in terms of formulation study, *in vitro* cytotoxicity, *in vivo* pharmacokinetics, anti-tumor efficacy and safety as well as clinical trials, to shed new light on the discovery of novel PM formulations. In these seven PM formulations, PM system was employed to overcome the issues of low water solubility, high toxicity and (or) multidrug resistance accompanied with the conventional formulation, which greatly hampered their clinical application. Those promising preclinical and clinical results combined with rapid advancement and intense multidisciplinary collaboration enable the extension of the PM system to traditional Chinese medicine, imaging agents, gene and combination agent deliveries as well as some other administration routes, which facilitate the clinical translation of the PM drug delivery system.

Contents

1. Introduction

In the past two decades, new drug exploration in terms of new chemical compounds was more and more challenging. In 2007, Somatuline Depot®, Lanreotide Acetate long-acting injection, was approved

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by the US Food and Drug Administration as a new molecular entity [1], indicating a significant role of the drug delivery system (DDS) in new drug exploration. Poor water solubility accompanied with many potential new drugs due to the required lipophilic groups for receptor recognition and membrane permeability, is rapidly becoming the principal obstacle for their clinical application [2]. Besides, many conventional chemotherapy regimens should be discontinued because of the significant adverse effects resulted from the non-selective targeting, despite their persisting effects. Polymeric micelles (PM) are composed of two separated functional segments: inner core and outer shell. The outer shell controls the *in vivo* pharmacokinetic (PK) behavior, while the inner core is responsible for drug loading capacity, stability and drug release behavior. The suitable PM size, too large for extravasation from normal vessel walls and renal excretion, and too small for extravasation from tumor blood vessels, combined with the pathophysiological characteristics of solid tumor tissues, hypervascularity, incomplete vascular architecture, secretion of vascular permeability factors and absence of effective lymphatic drainage leads to enhanced permeability and retention (EPR) effect of PM in solid tumors [3,4], which warrants the passive targeting of PM, while the passive targeting is the basis of active targeting. Apart from its solubilization, small particle size, long circulation, targeting and easy production properties, PM system can alter the drug internalization route and subcellular localization, lessen the P-glycoprotein (P-gp) efflux effect, consequently, exert a different mechanism of action from the entrapped drugs [5,6]. As well, compared with those more recent nano-DDSs, including liposomes, nanoparticles and dendrimers, PM possesses higher drug loading capacity as well as improved stability. Due to the promising characters, PM received fast-increasing scientific attention as an efficient drug carrier in recent years. In this paper, seven PM formulations of anti-tumor drugs being evaluated in clinical trials are reviewed (Table 1) to shed new light on the discovery of novel PM formulations. The future prospects of PM systems are also discussed.

2. Polymeric micelles formulations of anti-tumor drugs in clinical trials

2.1. Genexol®-PM

Paclitaxel (PTX) is an effective anti-tumor agent by promoting the assembly of microtubules from tubule dimmers and preventing them from depolarizing [27]. Because of its low solubility (0.3 μg/mL), commercially common used formulation Taxol® is formulated in a 50/50 (v/v) mixture of Cremophor EL (CrmEL)/ethanol. However, CrmEL is biologically and pharmacologically active and the amount of CrmEL required is considerably high, which results in significant side effects [28]. Because of the inherent problems associated with CrmEL, some new DDSs for PTX, which have good aqueous solubility and fewer side effects, are under current investigation including emulsion [29], liposomes [30], water-soluble prodrugs [31], nanoparticles [32], polymeric micelles [33] and nanoparticle colloidal suspension [34]. Among these DDSs, the most successful formulations which have been marketed are Genexol®-PM and Abraxane®.

Genexol®-PM is a PM formulation of PTX in monomethoxy poly(ethylene glycol)-*block*-poly(D,L-lactide) (mPEG-PDLLA) which was synthesized by the ring opening polymerization procedure with mPEG molecular weight of 2000 g/mol [7]. In a similar system by Zhang [35], the optimum mPEG-PDLLA diblock copolymer was characterized by mPEG molecular weight and mPEG-PDLLA weight ratio of 2000 g/mol and 60:40, respectively, in terms of the drug loading capacity and stability. In this system, the drug loading was as high as 25% and the reconstitution solution can be stable with the size smaller than 50 nm for 2 months and 1 day at 4 °C and room temperature, respectively. Genexol®-PM was prepared by a solid dispersion technique with a drug loading of 16.7% [7,8].

Table 1
Information of polymeric micelle formulations of anti-tumor drugs in clinical trials.

Formulation	Polymer	Drug	Issues solved	Incorporation mode	Diameter	Drug loading	*In vitro* cytotoxicity (*vs.* free drug)	*In vivo* PK parameters fold change (*vs.* free drug)			MTD (mg/m^2)	Status	Company	Ref.
								$t_{1/2}$	AUC_{blood}	AUC_{tumor}				
Genexol®-PM	mPEG-PDLLA	Paclitaxel	Solubilization	Physical entrapment	<50 nm	16.7%	Comparable	0.62[a1]	0.74[a1]	1.74[a1]	390[b1]	II[c]	Samyang, Korea	[7–12]
NK105	PEG-P(Asp)[d]	Paclitaxel	Solubilization Targeting	Physical entrapment	85 nm	23.0%	Comparable	6.11[a2] 3.71[a3]	86.11[a2] 50.40[a3]	24.00[a2] 24.06[a3]	180[b2]	II	Nanocarrier/Nippon Kayaku, Japan	[13–15]
NC-6004	PEG-P(Glu)(Cisplatin)	Cisplatin	Targeting	Coordinate bonding	30 nm	39.0%	6–15 fold lower	0.19	64.77	3.59	120[b2]	I/II	Nanocarrier, Japan	[16–18]
NC-4016	PEG-P(Glu) (DACHPt)	DACHPt	Targeting	Coordinate bonding	40 nm	N/A	N/A	N/A	N/A	N/A	N/A	I	Nanocarrier, Japan	[19]
NK012	PEG-P(Glu)(SN-38)	SN-38	Solubilization Targeting	Chemical conjugation	20 nm	20.0%	Comparable or a little bit lower	16.41[e]	14.09[e]	9.53[e]	28[b3]	II	Nippon Kayaku, Japan	[20,21]
NK911	PEG-P(Asp)(DOX)	Doxorubicin	Targeting	Physical entrapment	40 nm	N/A	Comparable	2.62	28.88	3.46	67[b4]	II	Nippon Kayaku, Japan	[22,23]
SP1049C	Pluronic L61, F127	Doxorubicin	Anti-MDR	Physical entrapment	30 nm	8.2%	Improved cytotoxicity on DOX-resistant cells	1.38[f1] 1.05[f2]	2.06[f1] 1.20[f2]	1.69	70[b5]	III	Supratek, Canada	[24–26]

Abbreviation: AUC: area under curve; DACHPt: dichloro-(1, 2-diaminocyclohexane) platinum(II); DOX: doxorubicin; MDR: multidrug resistance; MTD: maximum tolerated dose; N/A: Not available; P(Asp): poly(aspartic acid); P(Glu): poly(glutamic acid); PDLLA: poly(D,L-lactide); PEG: poly(ethylene glycol); PK: pharmacokinetic; SN-38: 7-ethyl-10-hydroxy-camptothecin.
[a]Dose. [a1]150 mg/kg dose of Genexol®-PM *vs.* 20 mg/kg dose of Taxol®; [a2]50 mg/kg; [a3]100 mg/kg.
[b]Dosage regimen. [b1]3-h infusion every 3 weeks; [b2]1-h infusion every 3 weeks; [b3]30-min infusion every 3 weeks; [b4]10 mg/min every 3 weeks; [b5]4 mg/min every 3 weeks.
[c]Marketed in South Korea in 2007.
[d]P(Asp) modified with 4-phenyl-1-butanol.
[e]Polymer-unbound SN-38 from NK012 group (30 mg/kg) *vs.* SN-38 from CPT-11 group (66.7 mg/kg).
[f]Mice condition. [f1]Normal mice; [f2]Tumor bearing mice.