International Journal of Pharmaceutics xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

1 Pharmaceutical nanotechnology

Direct comparison of two albumin-based paclitaxel-loaded nanoparticle formulations: Is the crosslinked version more advantageous?

Chunlei Li [a,*], Yanhui Li [b], Yuqing Gao [b], Na Wei [b], Xi Zhao [b], Caixia Wang [b,c,d], Yongfeng Li [b,c,d], Xian Xiu [b,c,d], JingXia Cui [a,**]

[a] School of Pharmacy, Hebei Medical University, Shijiazhuang, PR China
[b] CSPC ZhongQi Pharmaceutical Technology (Shijiazhuang) Co., Ltd., Shijiazhuang, PR China
[c] Hebei Pharmaceutical Engineering & Technology Research Center, Shijiazhuang, PR China
[d] State Key Lab of Novel Pharmaceutical Preparations and Excipients, Shijiazhuang, PR China

ARTICLE INFO

Article history:
Received 16 December 2013
Received in revised form 5 March 2014
Accepted 3 April 2014
Available online xxx

Keywords:
Nanoparticles
Paclitaxel
Albumin
Stability
Pharmacokinetics
Distribution
Safety
Efficacy

ABSTRACT

Nanoparticles using albumin as particle matrix have entered the mainstream of drug delivery. It was reported that non-crosslinked albumin nanoparticles were unstable in circulation and could deliver drugs into tumor through gp60/SPARC pathway; in contrast, the delivery of drugs with stable nanoparticles was dependent on enhanced permeability and retention effect. Thus, it is questionable which kind of nanoparticles was more advantageous. Two versions of albumin-bound paclitaxel nanoparticles were prepared. In vitro, the non-crosslinked particles could rapidly disintegrate and the crosslinked was stable. The pharmacokinetics of both formulations was different especially at early time and the non-crosslinked particles were cleared rapidly. After non-crosslinked particle treatment paclitaxel had a tendency to accumulate into heart and kidney and following therapy with the crosslinked particles, paclitaxel was liable to be delivered into lung, spleen and liver. The delivery efficiency of paclitaxel into tumor following the non-crosslinked particle treatment was greater than that of the crosslinked ($p < 0.05$), thus resulting in a considerably improved antineoplastic activity. Moreover, the non-crosslinked formulation was only slightly more toxic. It was concluded that the non-crosslinked formulation was more advantageous for the delivery of paclitaxel and our conclusion might be generalized to other lipophilic drugs delivered with albumin nanoparticles.

© 2014 Published by Elsevier B.V.

1. Introduction

Paclitaxel is a mitotic inhibitor used in cancer chemotherapy and has been approved for the treatment of various solid tumors (Hájek et al., 1996). The marketed paclitaxel injection (Taxol) is a sterile non-pyrogenic solution of paclitaxel in purified Cremophor EL and dehydrated alcohol. Cremophor EL is polyethoxylated castor oil, which is used to dissolve paclitaxel due to its poor solubility in common pharmaceutical solvents (Guchelaar et al., 1994). Following the infusion of Taxol, anaphylaxis and severe hypersensitivity reactions might occur, which have been proved to be associated with the excipient used, Cremophor EL (Guchelaar et al., 1994). Therefore, the novel Cremophor-free paclitaxel formulations have been actively pursued.

Recently, novel formulations such as Abraxane (Moreno-Aspitia and Perez, 2005), in which paclitaxel is bound to albumin, and Genexol (Yoon et al., 2013), a polymeric micellar paclitaxel formulation made from monomethyoxy poly(ethylene glycol)-block-poly(D,L-lactide), have been approved by regulatory authorities of United States of America and South Korea, respectively. Liposome delivery of paclitaxel has also been extensively investigated and some formulations have entered phase II clinical trial including LEP-ETU (Insys Therapeutics) and EndoTAG-1 (MediGene) (Zhang et al., 2005; Strieth et al., 2008). Of these novel drug delivery systems, albumin-based nanoparticles attracted more attentions due to their advantages and the approval of Abraxane by regulatory authorities.

Abraxane is an albumin-bound form of paclitaxel with a mean particle size of about 130 nanometers, which has been approved

* Corresponding author at: CSPC ZhongQi Pharmaceutical Technology (Shijiazhuang) Co., Ltd., No. 226, Huanghe Road, Shijiazhuang City, Hebei Province 050035, PR China. Tel.: +86 0311 67808800; fax: +86 0311 67808777.
** Corresponding author at: School of Pharmacy, Hebei Medical University, No. 361, ZhongShan East Road, Shijiazhuang City, Hebei Province, 050017, PR China.
E-mail addresses: lcllib@hotmail.com (C. Li), cjxlib@hotmail.com (J. Cui).

http://dx.doi.org/10.1016/j.ijpharm.2014.04.010
0378-5173/© 2014 Published by Elsevier B.V.

for the treatment of metastatic breast cancer, non-small cell lung cancer and adenocarcinoma of the pancreas in combination with gemcitabine (Ma and Mumper, 2013; Kratz, 2008; Fu et al., 2009). Based on previous studies, Abraxane was not stable in circulation. After intravenous injection of Abraxane, the nanoparticles could rapidly disintegrate in blood, resulting in the rapid transfer and binding of paclitaxel to endogenous (native) albumin (Fanciullino et al., 2013; Ma and Mumper, 2013; Yardley, 2013; Kratz, 2008). The resulting paclitaxel-bound albumin complexes could utilize albumin receptor (gp60, the 60 kDa glycoprotein)-mediated transcytosis through microvessel endothelial cells in angiogenic tumor vasculature and target to the albumin-binding protein SPARC (secreted protein, acidic and rich in cysteine) (Fanciullino et al., 2013; Ma and Mumper, 2013; Yardley, 2013; Kratz, 2008). The superior antitumor activity of Abraxane was proved to be due to increased transendothelial gp60-mediated transport and increased intratumoral accumulation as a result of the SPARC-albumin interaction (Fanciullino et al., 2013; Ma and Mumper, 2013; Yardley, 2013; Kratz, 2008). Accordingly, the mechanism underlying the enhanced delivery of paclitaxel into tumors following Abraxane therapy was different from enhanced permeability and retention effect (EPR), based on which stable nanoparticles (typically smaller than 200 nm) could be selectively delivered to the malignant zones with leaky blood vessels and lack of functional lymphatics.

The studies on stable albumin-based nanoparticles were also extensively reported (Langer et al., 2003). Typically, the nanoparticles were prepared by coacervation, emulsification or thermal gelation technology, followed by a crosslinking step to increase the stability of the resulting nanoparticles (von Storp et al., 2012; Langer et al., 2003, 2008; Rhaese et al., 2003; Elzoghby et al., 2012). However, no direct comparison of both kinds of albumin-based nanoparticles (crosslinked and not) was performed and thus it is hard to predict which kind of nanoparticles is more advantageous.

In the study, two versions of albumin-bound paclitaxel-containing nanoparticles were prepared. First, a non-crosslinked version similar to Abraxane was prepared using an emulsion-based method, which involved the formation of crude emulsion, homogenization to reduce the particle size and evaporation to remove the residual solvents (Elzoghby et al., 2012). And then one part of the resulting nanoparticles was crosslinked with glutaraldehyde to achieve the crosslinked version. The in vitro stability, pharmacokinetics, biodistribution and efficacy of both versions of nanoparticles were compared in a systemic manner to investigate whether the crosslinked version was more advantageous. It was the first study on the influence of the crosslinking on the formulation properties and biological activity of albumin-bound nanoparticles.

2. Materials and methods

2.1. Materials

Paclitaxel was provided by Yunnan Hande biotechnology Co., Ltd. (Yunnan, China). Human serum albumin was obtained from Guangxi Shuanglin Pharmaceuticals (Guangxi, China). All other chemicals used in this study were analytical or high-performance liquid chromatography (HPLC) grade.

RM-1 prostate tumor cell line was originally purchased from Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences (Shanghai, China). BDF1 mice (8–10 weeks old) were obtained from Beijing Vital River Experimental Animal Co., Ltd.

2.2. Preparation of albumin-bound paclitaxel nanoparticles

300 mg paclitaxel was dissolved in 2.7 mL chloroform and 0.3 mL ethanol. The solution was added to 270 mL of human serum albumin solution (1% w/v). The mixture was homogenized for 5 min at a low rpm (BioHomogenizer, Biospec Products, Inc., USA) to form a crude emulsion, and then transferred into a high pressure homogenizer (M-110EH Microfluidizer Processor, Microfluidics, USA). The emulsification was performed at 20,000 psi while recycling the emulsion for at least 6 cycles. The resulting system was transferred into a rotary evaporator, and the chloroform was rapidly removed at 40 °C at reduced pressure (~30 mm Hg) for 15–30 min. The resulting dispersion was translucent, and the typical diameter of the resulting paclitaxel-containing particles was 140–160 nm (zeta average, Malvern Zetasizer).

The nanoparticles were stabilized by the addition of an aqueous 8% glutaraldehyde solution (1.175 μL/mg HSA) (Langer et al., 2003, 2008). The crosslinking process was performed under stirring of the suspension over 24 h at 25 °C. The resulting nanoparticles were purified by dialysis against purified water using a Millipore Labscale TFF system (with 10,000 nominal molecular weight limit polysulfone filters) in order to eliminate glutaraldehyde. As determined by dynamic light scattering technology, the crosslinking step had no influence on the particle size and the distribution of the size.

In both cases, the dispersions were filtered through a 220 nm filter (Sartorius, sartobran 300), without any significant change in turbidity, or particle size. The sterile dispersion was aseptically filled into sterile glass vials and lyophilized without adding any cryoprotectant. The resulting cake could be easily reconstituted to the original dispersion by addition of sterile water or saline. The particle size after reconstitution was the same as before lyophilization.

2.3. Particle size

The zeta average size of nanoparticles was analyzed using quasi-elastic light scattering (Zetasizer Nano ZS; Malvern Instruments, UK). Before analysis, the samples were diluted in 0.9% NaCl to a paclitaxel concentration of 1 mg/mL (albumin: ~9 mg/mL). DTS 4.0 software was used to collect the data that were analyzed using "multi-narrow modes".

2.4. Determination of paclitaxel and albumin levels

A Shimadzu HPLC system controlled by LC solution software was used for chromatographic analysis, which was composed of DGU-20A5 degasser, LC-20AT liquid chromatograph, SIL-20A autosampler, SPD-M20A diode array detector and CTO-20A column oven. The column compartment was maintained at 25 °C. The HPLC separations were achieved using an Agilent SB C_{18} column (250 mm × 4.6 mm i.d., 5 μm particle size). The isocratic mobile phase was a mixture of water and acetonitrile (11:9) running at a flow rate of 1.5 mL/min. Detection was accomplished at 228 nm (Sharma and Straubinger, 1994). The retention time for paclitaxel was ~10.2 min, and the standard curve was linear over the range of 5–500 μg/mL with an *r*-value of 0.9999.

Before the determination of paclitaxel levels, the suspensions of nanoparticles was diluted to a paclitaxel concentration of ~0.1 mg/mL with purified water and the resulting dispersion was further diluted with acetonitrile in a volume ratio of 1:5. Ultrasonator was used to facilitate the dissolution of paclitaxel in acetonitrile/water mixture and the samples were stored at 4 °C for at least 30 min before the injection into HPLC.

The same HPLC system was used to detect the content of albumin, but the separation was carried out on a Tosohaas TSK G3000 column (30 cm × 7.8 mm i.d., 5 μm particle size) at 25 °C at a flow rate of 0.7 mL/min. The $NH_4H_2PO_4$ buffer (0.1 mol/L, pH 7.0) was used as mobile phase and the detection was accomplished at

Download English Version:

https://daneshyari.com/en/article/5819806

Download Persian Version:

https://daneshyari.com/article/5819806

Daneshyari.com