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Preparation of stable and monodisperse paclitaxel-loaded bovine serum albumin nanoparticles via intermolecular disulfide crosslinking

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ABSTRACT

Paclitaxel (PTX) is one of the most used anti-cancer drugs worldwide. Due to its insolubility in water, the clinically available liquid formulation of PTX contains Cremophor EL that is responsible for severe hypersensitivity. Albumin-based nanoparticles have emerged as a promising carrier for anti-cancer drugs because albumin nanoparticles have high capacity to not only load lipophilic drugs without solubilizer but also accumulate in tumor by both passive and active mechanisms. In this study, we attempted to prepare solvent-free formulation of PTX-loaded bovine serum albumin (BSA) nanoparticles with high stability, and the *in vitro* stability in serum were comparatively assessed between our PTX-loaded BSA nanoparticles and clinically used nanoparticulate albumin-bound PTX (Abraxane®). PTX-loaded BSA nanoparticles were prepared by intermolecular disulfide crosslinking. When BSA molecules were used without denaturation by guanidinium, the obtained BSA nanoparticles showed broad size distribution. On the other hand, the nanoparticles composed of denatured BSA by guanidinium had a uniform size around 100 nm. The PTX encapsulation efficiency of BSA nanoparticles were approximately 30–40 %. In addition, *in vitro* gel filtration analysis and dialysis study demonstrated that PTX-loaded BSA nanoparticles had higher colloidal stability and sustained PTX release property than Abraxane® in serum. These results suggest that BSA nanoparticles is a promising drug carrier for improving therapeutic efficacy of PTX and reducing its adverse effects.

1. Introduction

Paclitaxel (PTX) is a microtubule stabilizing agent, which induces G2/M cell cycle arrest and subsequent cell death.[1,2] PTX has a broad spectrum of activity against many types of cancer including ovarian, breast, and lung cancer, and therefore is one of the most used anti-cancer agents worldwide. Due to the insolubility of PTX in water, its commercially available liquid formulation (Taxol®) contains a 1:1 mixture of Cremophor EL and dehydrated ethanol as a vehicle. However, Cremophor® EL causes severe hypersensitivity and peripheral neuropathy in some patients, being one of the reasons for limiting or even discontinuing cancer treatments.[3]

To overcome such an obstacle, albumin is used as a valuable solubilizer for lipophilic drugs due to its high water solubility and binding capacity for hydrophilic drugs as well as its biodegradability, biocompatibility and non-immunogenicity.[4,5] solvent-free formulation of nanoparticulate albumin-bound PTX (Abraxane®) has been already developed and clinically used worldwide.[6,7] Since Abraxane® is formulated without Cremophor® EL, a higher dose can be administered with a shorter infusion time, compared with Taxol®. In addition, it is known that albumin binds to gp60 expressed on the vascular endothelial cells,[8,9] which induces the transcytosis of albumin from blood vessel to tumor tissue. Moreover, albumin has the capacity to interact with secreted protein, acidic and rich in cysteine (SPARC) in tumor, resulting in the increased accumulation of albumin in tumor tissue.[10] Therefore, Abraxane® is inferred to efficiently deliver PTX into tumor interstitium.

On the other hand, although Abraxane® is a nanoparticulate formulation with a diameter of approximately 130 nm, Abraxane® undergoes the rapid dissociation of its spherical structure into two components, albumin and PTX, immediately after intravenous injection,[11,12] leading to a higher plasma clearance and larger distribution volume of PTX than that for Taxol®.[13] Moreover, this characteristic of Abraxane® is not suitable for passive targeting to tumor tissue via

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enhanced permeability and retention (EPR) effect because the ideal particle size for passive tumor targeting is considered to be between 10 and 100 nm[14] Taking these backgrounds into consideration, the colloidal stability in the blood circulation is also an important factor for the more favorable pharmacokinetic and tumor targeting properties of albumin nanoparticles.

For improving the stability of albumin-based nanoparticles, several studies prepared PTX-loaded albumin nanoparticles with crosslinking agents. Zhao et al. used glutaraldehyde,[15] and other groups used reducing agents, such as glutathione and ʟ-cysteine, for the formation of disulfide bonds.[16,17] These intermolecular crosslinked albumin nanoparticles should be more stable than the non-crosslinked albumin nanoparticles prepared by using a high-pressure homogenizer which is a similar method to prepare Abraxane®.[18,19] However, direct comparison of the colloidal stability and PTX release property between intermolecular crosslinked albumin nanoparticles and Abraxane® has not yet been carried out.

In this study, we attempted to prepare stable and monodisperse bovine serum albumin (BSA) nanoparticles through intermolecular disulfide bonds as a PTX carrier for efficient tumor targeting. We also conducted a comparative evaluation of *in vitro* colloidal stability and PTX release property in serum between PTX-loaded BSA nanoparticles and Abraxane®.

2. Materials and methods

2.1. Preparation of PTX-loaded BSA nanoparticles

Two mg of BSA (FUJIFILM Wako Pure Chemical Co., Osaka, Japan) was washed with acetone and dissolved in 1 mL of phosphate-buffered saline (PBS) with 0–2 M of guanidinium chloride (GuHCl) and 5 mM of dithiothreitol. Following 30-min incubation at 37 °C, GuHCl and dithiothreitol in the solution was removed by gel filtration using a PD-10 desalting column (Global Life Sciences Technologies Japan K.K., Tokyo, Japan). Then, 0.1 mL of ethanol dissolving 10 mg/mL of PTX was added to the solution, and diamide was also added at a final concentration of 0.2 mM, followed by 1-h incubation at 15 °C. The resultant dispersion was incubated in ultrasonic bath at 37 °C for 10 min, and the precipitates were removed by membrane filtration with 0.22 μm pore size. To remove reagents and ethanol from the final preparation, the dispersion medium of PTX-loaded BSA nanoparticles was replaced twice with PBS by gel filtration using PD-10 column. The encapsulation efficiency of PTX in BSA nanoparticles were analyzed by gel filtration using a PD-10 column. The particle sizes, ζ-potentials and polydispersity indexes (PDIs) of the nanoparticles were measured using a Zetasizer Pro (Malvern Instrument, Worcestershire, UK).

2.2. In vitro stability assay of PTX-loaded BSA nanoparticles in fetal bovine serum (FBS) by gel filtration

PTX-loaded BSA nanoparticles or Abraxane® were incubated with fetal bovine serum at a volume of 1:1 at 37 °C for 3 h. The mixture was loaded onto the Sepharose CL-4B gel column (Global Life Sciences Technologies Japan K.K.) and eluted with PBS, followed by collecting 100 samples of 1 mL fractions. The concentration of PTX in each sample was determined by HPLC.

2.3. PTX release experiment

The release of PTX from PTX-loaded BSA nanoparticles or Abraxane® was measured by the equilibrium dialysis method. PTX-loaded BSA nanoparticles or Abraxane® were mixed with an equal volume of FBS in a dialysis tube (Spectra/Por4 Membrane, MWCO: 12,000–14,000, Repligen, MA, USA). The dialysis tube was incubated in PBS containing 3 % BSA (w/v) at 37 °C for 48 h. The released PTX was determined by HPLC.

2.4. Analytical method

PTX quantified according to a reversed-phase HPLC (Shimadzu, Kyoto, Japan) with an ultraviolet detector (SPD-20A) and COSMOSIL $5C_{18}$-MS-II column (4.6 mm i.d. × 150 mm; Nacalai Tesque, Kyoto, Japan). The column temperature was 30 °C, and injection volume was 10 μL. The eluent was 0.1 % phosphoric acid: acetonitrile = 1 : 1, and total flow rate was 1.1 mL/min. PTX was detected at a wavelength of 227 nm.

2.5. Statistical analysis

Results are presented as the mean ± standard deviation (SD) of three experiments. Multiple comparisons among all groups were performed using Tukey-Kramer test.

3. Results and discussion

3.1. Physicochemical properties and encapsulation efficiency of PTX-loaded BSA nanoparticles

There are several reports on preparation of anti-cancer drug-loaded albumin nanoparticles, and many of them use a desolvation technique.[15,20,21] The formation of the nanoparticles by desolvation method is based on the aggregation of albumin by drop-wise addition of ethanol into the aqueous albumin solution, followed by crosslinking by glutaraldehyde. Although this method achieves a high recovery rate of albumin nanoparticles, it takes more than 18–24 h for preparation. On the other hand, in this study, we prepared BSA nanoparticles based on disulfide crosslinking facilitated by adding a thiol-specific oxidizing agent (diamide).[22,23] This method allows to prepare BSA nanoparticles within 3 h.

We first evaluated the particle size distribution, zeta potential and PDI value of PTX-loaded BSA nanoparticles. When BSA nanoparticles were prepared without denaturation of BSA by GuHCl, its size distribution was heterogeneous with the higher PDI values (Fig. 1A, Table 1). On the other hand, the nanoparticles composed of denatured BSA by GuHCl had a uniform size distribution around 100 nm with lower PDI value (Fig. 1B–E, Table 1), which is expected to be suitable for passive tumor targeting via EPR effect. Sun et al. have reported that reduced BSA molecules without denaturation by GuHCl tend to go back to native-like conformation, and therefore the BSA hydrogels stabilized by the intermolecular disulfide crosslinking undergo inter-to-intramolecular disulfide transformation in the absence of GuHCl.[24] Based on this information, we assume that not only intermolecular but also intramolecular disulfide bond formation would be responsible for the heterogenous size distribution of the nanoparticles composed of BSA without denaturation. In addition, we also confirmed that zeta potential of BSA nanoparticles was not changed with or without denaturation of BSA by GuHCl (Table 1). Therefore, we decided to use denatured BSA by 1.5 M GuHCl for preparation of PTX-loaded BSA nanoparticles. The BSA nanoparticles prepared by this method maintained its particle size and PTX-encapsulation efficiency after the storage for at least 14 d at 4 °C (data not shown).

With regard to the PTX-encapsulation efficiency, BSA nanoparticles prepared without denaturation of BSA showed higher encapsulation efficiency than the nanoparticles composed of denatured BSA by GuHCl (Table 1). This result suggests that BSA nanoparticles with larger particle size have the capacity to entrap larger amount of PTX. In an attempt to increase the PTX-encapsulation efficiency of BSA nanoparticles, we added different amount of PTX during the formation of BSA nanoparticles. However, PTX was scarcely entrapped into BSA nanoparticles when the added amounts of PTX was increased from 10 mg/mL to 20 mg/mL (data not shown). This would be because the solubility of PTX was saturated in the reaction solution and severely precipitated. Further studies on the optimization of the added amount of PTX and its solvent

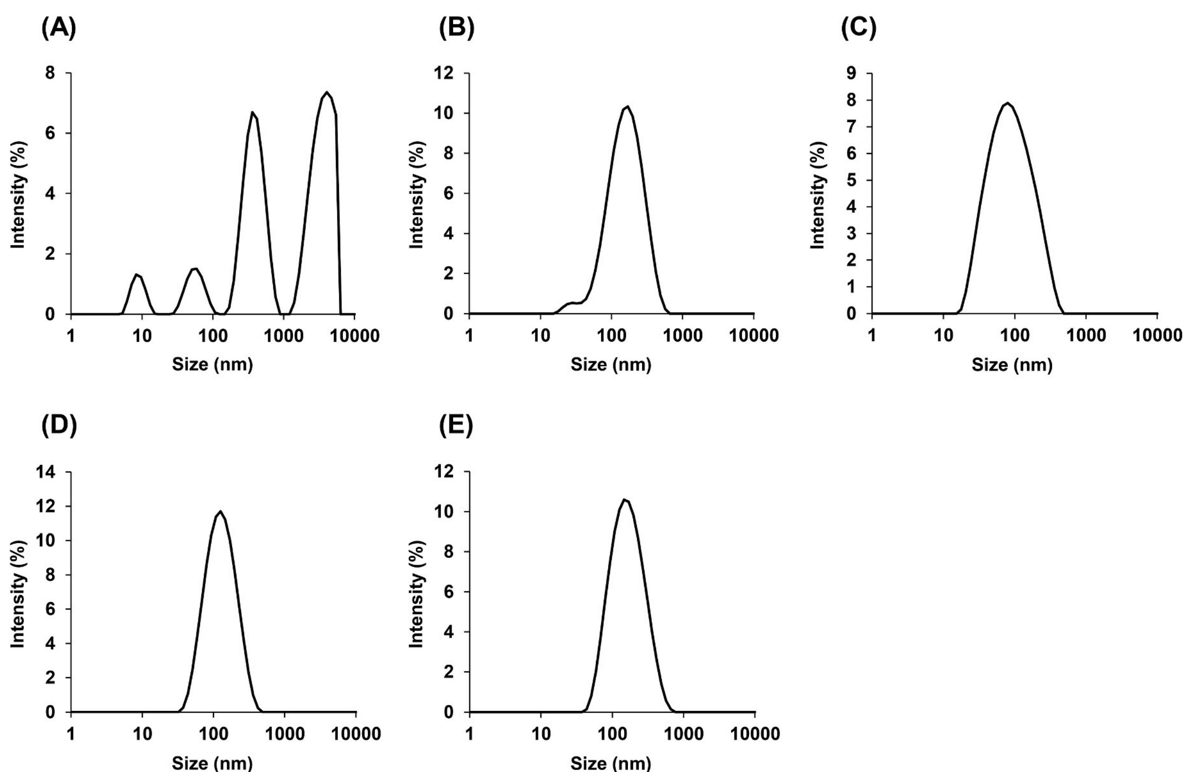

Fig. 1. Size distribution of PTX-loaded BSA nanoparticles prepared with or without denaturation of BSA by GuHCl. Particle sizes of PTX-loaded BSA nanoparticles prepared without denaturation of BSA (A) or with denaturation by 0.5 (B), 1.0 (C), 1.5 (D), or 2.0 (E) M GuHCl were measured by dynamic light scattering.

Table 1
Physicochemical properties and encapsulation efficiency of PTX-loaded BSA nanoparticles.

GuHCl concentration (M)	Average particle size (nm)	Zeta potential (mV)	Polydispersity index (PDI)	Encapsulation efficiency (%)
0	570.9 ± 133.9	−10.6 ± 2.5	0.77 ± 0.12	71.4 ± 12.5
0.5	138.3 ± 5.8**	−11.9 ± 1.2	0.29 ± 0.05**	42.7 ± 8.1**
1	128.2 ± 6.6**	−10.8 ± 1.8	0.40 ± 0.05**	39.0 ± 5.3**
1.5	134.1 ± 17.5**	−10.4 ± 2.3	0.20 ± 0.03**††	31.3 ± 3.5**
2	145.2 ± 8.1**	−12.3 ± 2.7	0.22 ± 0.02**††	29.7 ± 3.8**

Each value represents the mean ± SD ($n = 3$).
**$p < 0.01$, compared with 0 M GuHCl.
††$p < 0.01$, compared with 1 M GuHCl.

(ethanol) during encapsulation process of PTX into BSA nanoparticles are needed to improve their PTX-encapsulation efficiency.

3.2. *Comparison of in vitro stability in serum between PTX-loaded BSA nanoparticles and Abraxane®*

We comparatively assessed the stability of PTX-loaded BSA nanoparticles and Abraxane® in serum by gel filtration. We preliminarily confirmed that 100-nm nanoparticles, albumin molecules, and free PTX were eluted at fractions 25–35 mL, 55–70 mL, and 75–90 mL, respectively. As shown in Fig. 2A, PTX elution from Abraxane® was only detected at fractions around 80 mL, indicating that Abraxane® nanoparticles were completely collapsed and PTX was dissociated from human serum albumin (HSA) in the presence of serum. This would be because Abraxane® nanoparticles were not stabilized by any intermolecular chemical bonds. On the other hand, in the case of BSA nanoparticles, approximately 60 % of PTX were eluted as PTX-loaded BSA nanoparticle at fractions around 25 mL (Fig. 2B). These results indicate that PTX-loaded BSA nanoparticles had higher colloidal stability than Abraxane® in the presence of serum.

We further evaluated the PTX release from PTX-loaded BSA nanoparticles and Abraxane® in the presence of serum by the dialysis method. More than 80 % of PTX was released from Abraxane® within 9 h, whereas BSA nanoparticles showed much slower PTX release and it reached approximately 50 % at 48 h (Fig. 3). Thus, owing to its higher colloidal stability, BSA nanoparticles enable the sustained release of PTX in the presence of serum.

In our previous study, we prepared two PTX-loaded nanoparticles, emulsions and liposomes, and compared their *in vitro* colloidal stability and *in vivo* anti-tumor efficacy. It was demonstrated that liposomes have significantly higher *in vitro* colloidal stability in the presence of serum compared with emulsions, which leads to more efficient tumor distribution of PTX and consequent potent anti-tumor efficacy in mice.[25] In addition, we also reported that liposomes showing slower release rate of encapsulated doxorubicin exhibited higher tumor accumulation and anti-tumor efficacy of doxorubicin than liposomes showing faster release rate of doxorubicin.[26]) Based on these observations, we found that the colloidal stability and sustained release property of anti-cancer drug-loaded nanoparticles strongly influence their anti-tumor efficacy. Since PTX-loaded BSA nanoparticles prepaed in this study possess both properties, we expect that PTX-loaded BSA nanoparticles would exert a remarkable anti-tumor efficacy *in vivo*.

Recently, Hama et al. have reported that gp60, known to be responsible for the uptake of normal albumin, is not involved in the uptake of Abraxane®-derived HSA by vascular endothelial cells.[27]) They mentioned that this is because Abraxane®-derived HSA is denatured by organic solvent during preparation. On the other hand, they

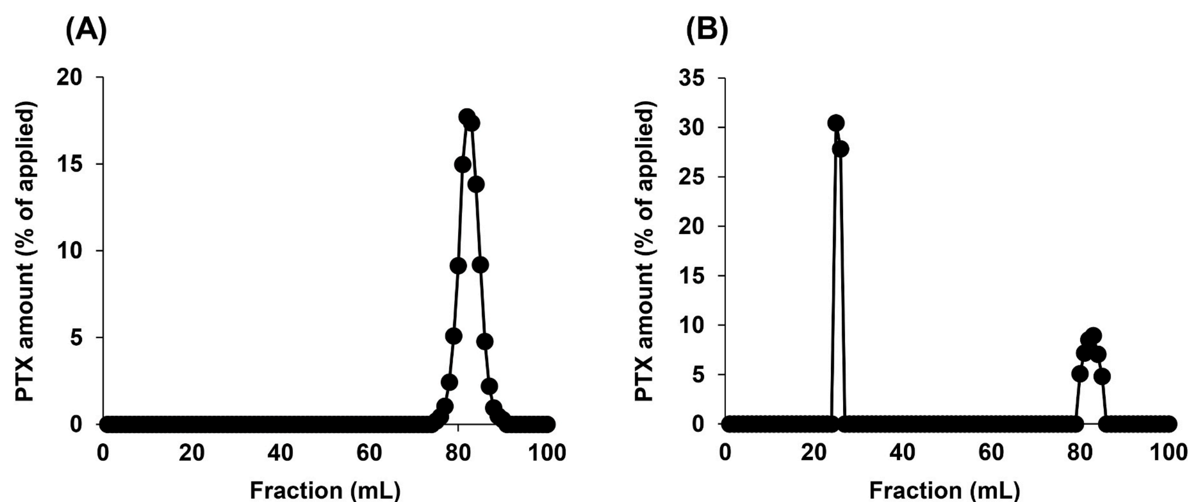

Fig. 2. Stability of PTX-loaded BSA nanoparticles in serum. Abraxane® (A) or PTX-loaded BSA nanoparticles (B) were incubated with FBS at 37 °C for 3 h, and analyzed
by gel filtration. The concentration of PTX in each sample was determined by HPLC.

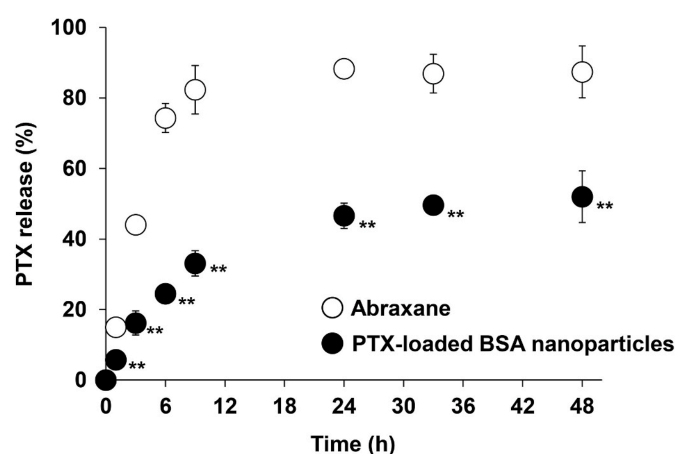

Fig. 3. Release profile of PTX from BSA nanoparticles in the presence of serum. Abraxane® or PTX-loaded BSA nanoparticles were mixed with an equal volume of FBS in a dialysis tube, and incubated at 37 °C for 48 h. The concentration of PTX in each sample was determined by HPLC. **$p < 0.01$, compared with Abraxane®.

have also demonstrated that Abraxane®-derived HSA is taken up by vascular endothelial cells through denatured albumin receptors, gp18 and gp30, and its uptake amount is comparable to that of normal albumins through gp60. Therefore, PTX-loaded BSA nanoparticles prepared in this study have the potential to accumulate in tumor tissue not only by passive extravasation via EPR effect but also by possible active mechanisms via receptor-mediated transcytosis. We are now investigating the *in vivo* tumor targeting efficiency and trying to elucidate uptake mechanisms of PTX-loaded BSA nanoparticles into tumors.

In conclusion, we demonstrated that denaturation of BSA by GuHCl significantly affects the size distribution of BSA nanoparticles, and denatured BSA by 1.5 M GuHCl can form intermolecular disulfide-crosslinked PTX-loaded BSA nanoparticles with more uniform size distribution around 100 nm. Moreover, rapid preparation of BSA nanoparticles was achieved by using diamide. Furthermore, the prepared BSA nanoparticles showed a higher stability and sustained PTX release property in serum than Abraxane®. Thus, PTX-loaded BSA nanoparticles have great promise for improving therapeutic efficacy and reducing adverse effects of PTX.

4. Ethic statements

This work does not include any human subjects, animal experiments, or data from social media platforms.

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Please note that all *Biochemistry and Biophysics Report* authors are required to report the following potential conflicts of interest with each submission. If applicable to your manuscript, please provide the necessary declaration in the box above.

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CRediT authorship contribution statement

Yusuke Kono: Writing – original draft, Supervision, Data curation, Conceptualization. **Tomoyuki Sugaya:** Methodology, Investigation, Data curation. **Hikaru Yasudome:** Methodology, Investigation, Data curation. **Hideo Ogiso:** Investigation, Data curation, Conceptualization. **Ken-ichi Ogawara:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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