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Design and evaluation of albumin nanoparticles for the delivery of a β-tubulin polymerization inhibitor

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BACKGROUND

Albumin (Figure 1A) is one of the most abundant proteins in blood plasma. It is nontoxic, nonimmunogenic, biocompatible and biodegradable.
It strongly interacts with both hydrophilic and hydrophobic compounds, which makes it a versatile substance in drug delivery.

CR-42-024 (Figure 1B) is a novel tubulin polymerization inhibitor, synthesized and patented in the Department of Oncology, University of Alberta.
It has shown potent anti-cancer activity in cancer cell lines *in vitro* (IC_{50} of 3.28 and 4.29 nM in pancreatic and bladder cancer, respectively). The compound has particularly been effective in cancer cells resistant to paclitaxel.

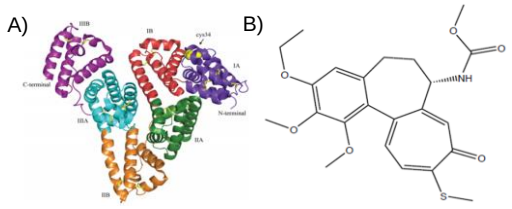

Figure 1. A) Albumin, B) CR-42-024.

PURPOSE

To load CR-42-024 into serum albumin (SA) generating CR-SA nanoparticles (CR-SA NPs), to improve the undesirable side effects of the compound, such as poor water solubility, poor uptake into tumor site, nonselective distribution and uptake by normal body cells and tissues.

METHODS

The nanoparticles were generated using a modified version of the desolvation method (Figure 2). Albumin nanoparticles were produced by addition of a desolvating agent, ethanol, to an albumin solution, while stirring. A crosslinker, glutaraldehyde, was added to the system and left overnight to stabilize the nanoparticles. The day after, already crosslinked albumin nanoparticles were incubated overnight at 37°C with different drug solutions and drug-loaded albumin nanoparticles were obtained.

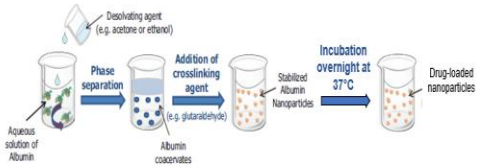

Figure 2. Modified version of desolvation.

The nanoparticles were freeze-dried and assessed for:

- Particle size and zeta potential
- Drug loading
- Release
- Morphology (Figure 3)
- Cell toxicity studies

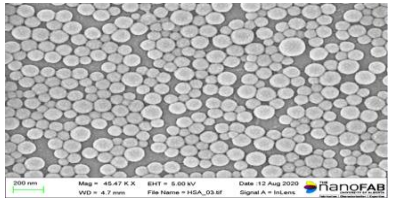

Figure 3. CR-42-024-loaded HSA NPs 45k-fold magnification.

RESULTS

The spherical nanoparticles obtained had an average diameter of ~ 130 nm with a narrow size distribution (Figure 4A) and they were negatively charged (zeta potential ~ -30 mV, Figure 4B).

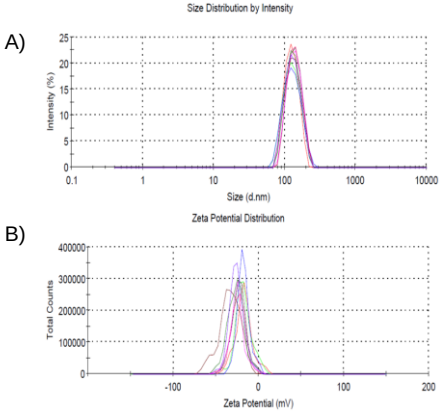

Figure 4. A) Size, B) Zeta potential.

The *in vitro* release of CR-42-024 showed a more sustained release pattern, compared to the free drug, without any initial burst release (Figure 5).

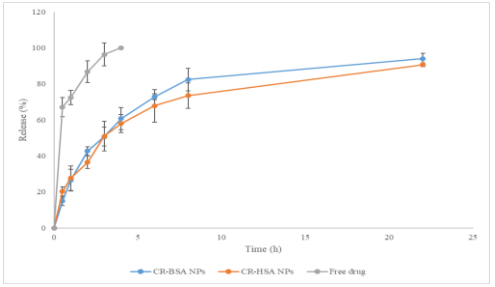

Figure 5. Release profile.

RESULTS

By reducing the amount of albumin used, the encapsulation efficiency remained the same. Therefore, it was preferable to reduce the quantity of albumin used, to increase the drug loading, which resulted to be ~ 6 µg drug/mg albumin (Figure 6).

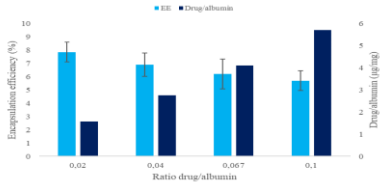

Figure 6.Encapsulation efficiency and drug loading.

Cellular toxicity studies of the CR-SA NPs exhibited even lower IC_{50}s compared to the positive control, the free CR-42-024.

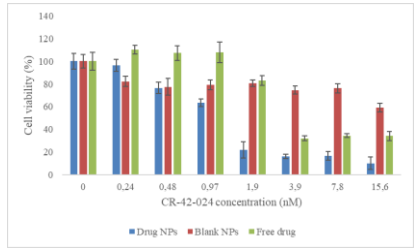

Figure 7.Cell toxicity on SW-620 cell line at 72h.

CONCLUSIONS

The formulation of such CR-SA NPs should be further modified and improved to provide higher loaded drug levels for *in vivo* evaluations and replace the use of glutaraldehyde with a less toxic crosslinking agent, to reduce the toxicity of the carrier.