Albumin Nanoparticles for Intra-Articular Delivery of Celecoxib to Treat Osteoarthritic Inflammation

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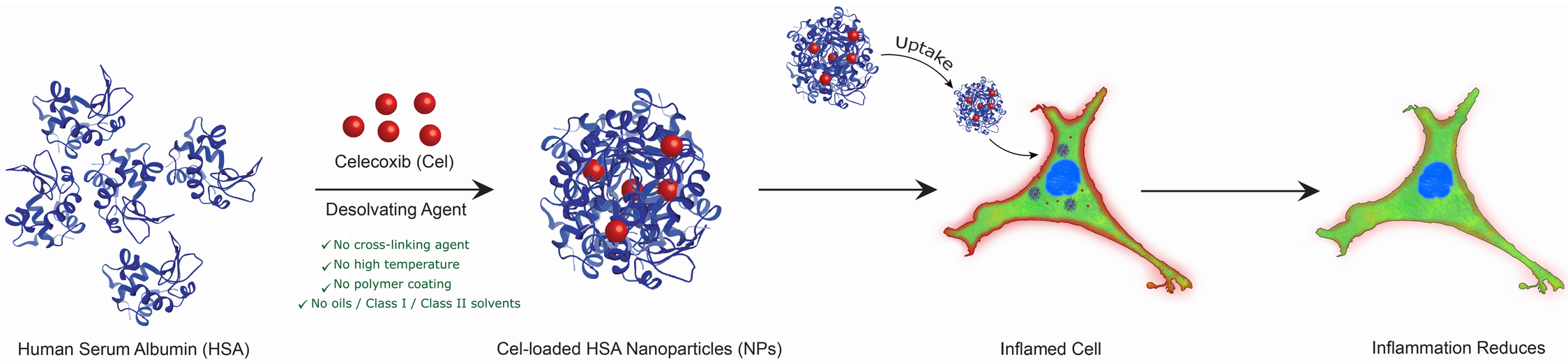
GRAPHICAL ABSTRACT



BACKGROUND

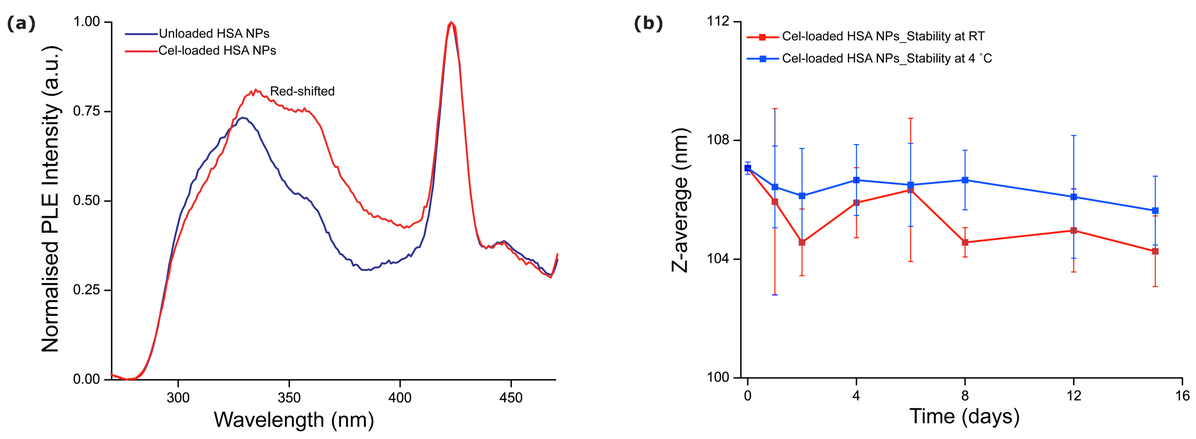
Osteoarthritis (OA) is a leading cause of chronic disability. Oral non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely recommended treatments. Of these, selective cyclooxygenase type 2 (COX-2) inhibitors have some advantages over other NSAIDs. The only selective COX-2 inhibitor approved both by FDA and EMA for OA treatment is CELEBREX® (having celecoxib as active pharmaceutical ingredient) capsules, but it has a black box warning of cardiovascular events and gastrointestinal bleeding. One possible way to avoid these side effects is direct intra-articular (IA) delivery of Cel to the OA knee. However, IA-delivered Cel is removed from the joints rapidly due to its small molecular size. Moreover, Cel is soluble in organic solvents which cannot be safely administered in the body. One option to counter these problems is to load Cel in a NP and inject the Cel loaded NP in the inflamed joint through IA injection. NPs of size less than 100 nm are known to enter the dense collagen matrix of cartilage to target chondrocytes. Thus, we have developed biocompatible, stable and homogenous Cel-loaded HSA NPs of average size 66 nm for IA delivery to treat OA.

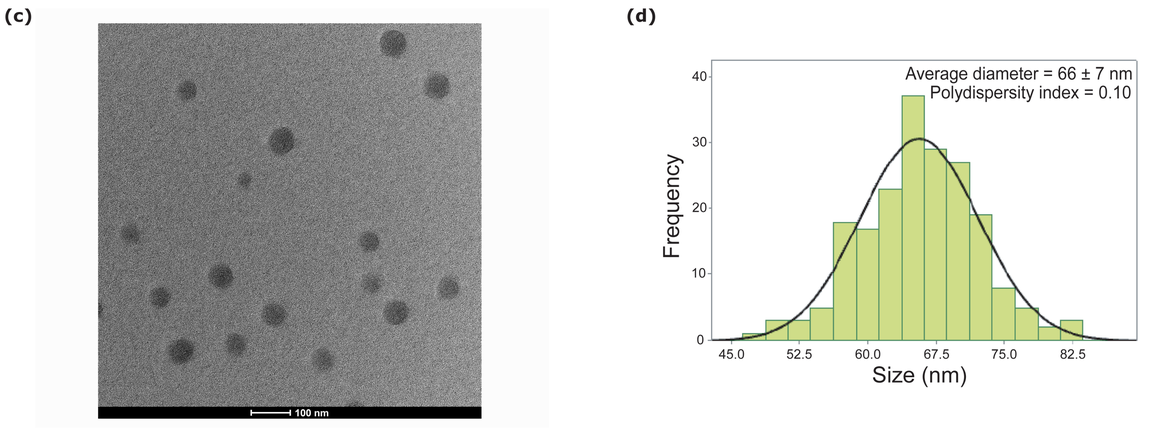
METHODS

The Cel-loaded HSA NPs were synthesised by a novel process and characterised using several spectroscopic, microscopic, and scattering techniques. Finally, the cytotoxicity and anti-inflammatory efficacy of the Cel-loaded HSA NPs were tested on a lipopolysaccharide (LPS)-stimulated human leukemia monocyte (THP-1) cell line, in primary chondrocytes and in cartilage explant from the knee joint of OA patients.

RESULTS

Characterisation





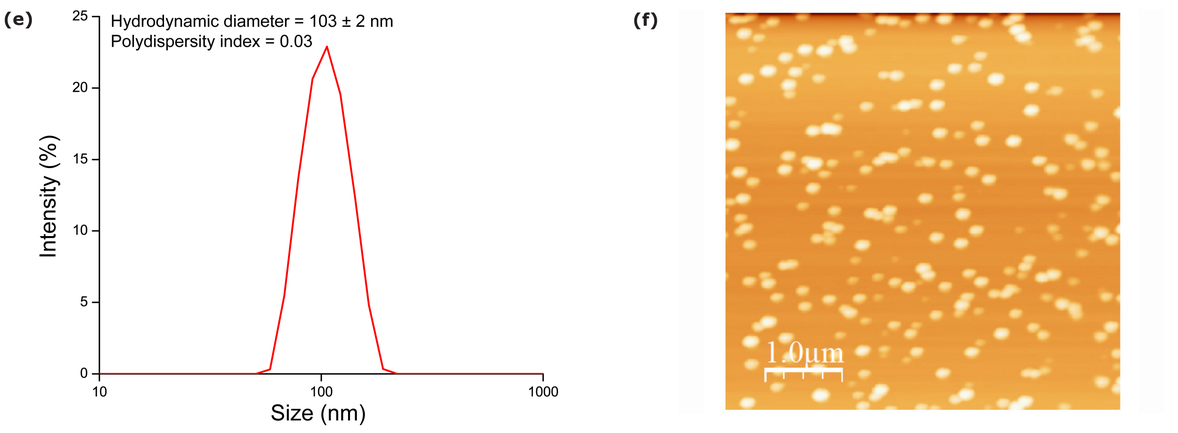


Figure 1: **(a)** Fluorescence spectrum, **(b)** plot of z-average versus time incubated at RT and 0 ºC, **(c)** TEM micrograph and the corresponding **(d)** size distribution, **(e)** DLS-based particle size distribution and **(f)** AFM image of Cel-loaded HSA NPs.

In-vitro results

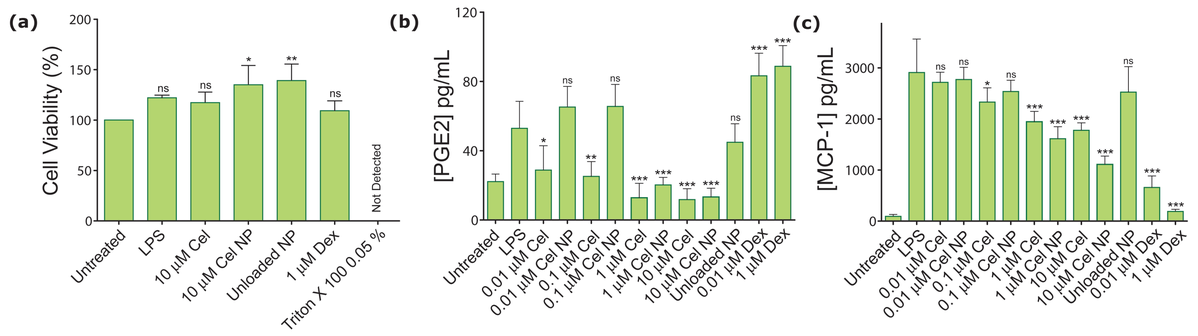


Figure 2: (a) Cell viability, **(b)** prostaglandin E2 (PGE2) ELISA and **(c)** monocyte chemoattractant protein-1 (MCP-1) ELISA results of THP-1 cells pre-treated with different samples and then stimulated with 1 µg/mL LPS for 24 hrs. *P < 0.05; **P < 0.01; ***P < 0.001; n.s., not significant compared to untreated for figure a and to LPS treated for figures b and c.

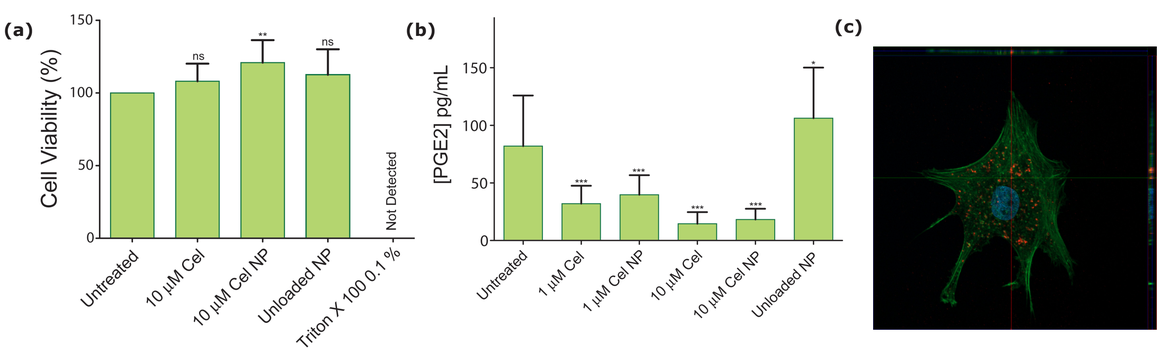


Figure 3: **(a)** Cell viability and **(b)** PGE2 ELISA results of primary chondrocytes from OA patients treated with different samples for 24 hrs. *P < 0.05; **P < 0.01; ***P < 0.001; n.s., not significant compared to untreated. **(c)** Orthogonal view of confocal image of primary chondrocyte treated with Alexa Fluor 568 tagged Cel-loaded HSA NPs for 4 hrs.

Ex-vivo results

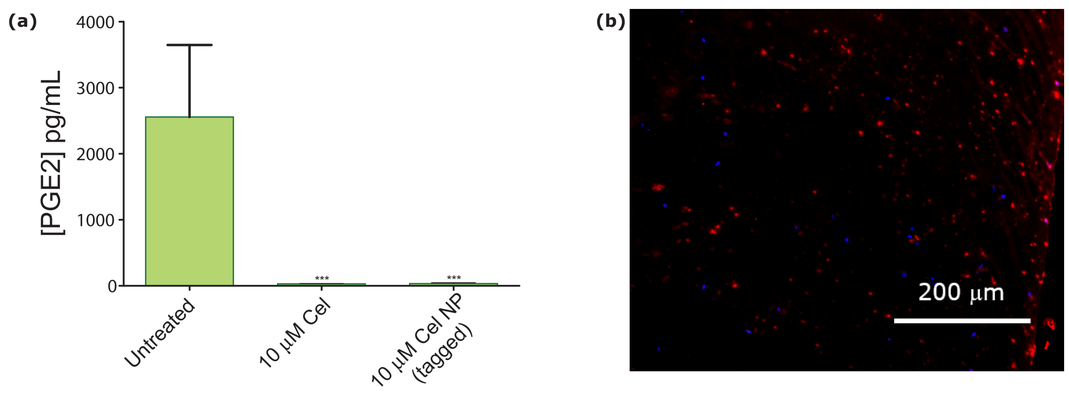


Figure 4: **(a)** PGE2 ELISA result of cartilage explant from OA patient treated with different samples for 24 hrs. ***P < 0.001 compared to untreated. **(b)** Fluorescence image of the cartilage explant (cross sectioned) treated with Alexa Fluor 568 tagged Cel-loaded HSA NPs for 72 hrs.

CONCLUSION

We have developed a novel method for the synthesis of Cel-loaded HSA NPs of size less than 100 nm without using any external agents, high temperatures, polymer coatings, oils and Class I/II solvents for IA delivery to treat OA. The Cel-loaded HSA NPs were stable, and spherical with low polydispersity index. The Cel-loaded HSA NPs were found not to reduce the cell viability and efficiently reduced the inflammation in stimulated THP-1 cells, OA patient's primary chondrocytes and cartilage explant. The ex vivo data indicated that the Cel-loaded HSA NPs were able to penetrate the dense collagen matrix of cartilage to target chondrocytes.

VALUE PROPOSITION

- Elimination or reduction of the side-effects associated with Cel.
- Increase in drug bioavailability and reduction in overall treatment cost.
- The Cel-loaded HSA NPs could potentially be used to treat other forms of arthritis.
- The HSA NPs could also be loaded with other drugs and can be used for passive targeting of cancer through enhanced permeation and retention effect.
- The formulation method allows the loading of temperature-sensitive drugs.

REFERENCES & ACKNOWLEDGEMENT

1. Maudens, P. et al. Recent advances in intra-articular drug delivery systems for osteoarthritis therapy. Drug Discov Today 2018, 23, 1761.
2. Yan, H. et al. Suppression of NF-κB activity via nanoparticle-based siRNA delivery alters early cartilage responses to injury. Proc. Natl. Acad. Sci. 2016, 113, E6199.

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