

Efficient Delivery of Photosensitizer for Rheumatoid Arthritis (RA) Treatment by Photodynamic Therapy (PDT)

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INTRODUCTION: Rheumatoid arthritis (RA)

is an inflammatory disease involving the destruction of the joints by activated macrophages. The treatments presently available for RA are not perfect and new efficient local treatments with reduced side effects are desirable.

Photodynamic therapy (PDT) is a powerful tool to treat oncological and inflammatory disorders¹. PDT is based on the injection of a photosensitizer, which is activated by light to produce cytotoxic molecules. For successful application in RA, the locally injected photosensitizer must target joint macrophages.

Biomaterial-based nanoparticles are proposed as system for the uptake of photosensitizer by the joint macrophages. Our proposition is therefore to entrap the photosensitizer in a polymeric nanoparticle to both reduce diffusion of the photosensitizer out of the joint and increase its uptake by joint macrophages.

MATERIALS & METHODS: Nanoparticles were based on chitosan and other natural polysaccharides² known for their biocompatibility. The process of nanoparticle formation and photoactive drug incorporation was entirely water-based. During formulation the surface properties were designed to target activated macrophages. The final formulation was designed to withstand physiological environments and particularly the specific environment in inflamed joints. The size distribution determined by scanning electron microscopy was between 50 and 300 nm (Fig. 1).

Entrapment efficiency of the photosensitizers into the nanoparticle was >98% (w/w). Loading capacity was >15% (w/w).

In vitro experiments: These photosensitizer-loaded nanoparticles were assayed on various cell populations, evaluating their uptake and efficacy in PDT protocols to induce cell death. Uptake of the nanoparticles was observed by fluorescence microscopy and fluorimetric reading. Cytotoxicity was assessed by the MTT survival test.

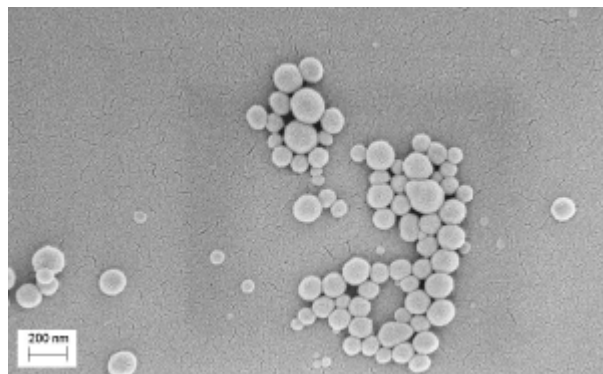


Fig. 1: Electron microscopy (SEM) picture of chitosan based nanoparticles loaded with photosensitizer. Dried from water based dispersion, platinum sputter coated.

In vivo experiments: The albumin-induced arthritis (AIA) model³ was used for *in vivo* test in mice. Inflamed mice knees were injected with the photosensitizer-loaded nanoparticles and exposed to laser light. The level of inflammation of the joints was quantified measuring the serum amyloid A (SAA), an inflammatory acute phase protein.

RESULTS: *In vitro*, optimal uptake of the photosensitizer-loaded nanoparticles was achieved after 3 hr incubation. These nanoparticles did not induce cytotoxicity in the absence of light in the murine RAW 264.7 macrophage cell line, whereas good phototoxic activities were observed in these cells exposed to red laser light.

In vivo, nanoparticles were well tolerated by the mice. Statistical evidence of a decreased status of inflammation after PDT treatment of inflamed mice knees was found using the SAA assay.

REFERENCES: ¹Dolmans, D.E.J.G.J. et al., *Nat. Rev. Cancer*, 2003, 3, 380-387. ²WO2007/031812 (PCT patent). ³Brackertz D. et al, *Arthritis and Rheumatism*, 1977, 20, 3, 841-850.

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