DDS Institute

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General Summary

We are investigating new drug delivery systems (DDS) using nanotechnology. We have developed poly (D, L-lactic acid) (PLA)/poly (ethylene glycol) (PEG)-PLA nanoparticles for targeting and sustained release of steroid/immunosuppressants and have found enhanced anti-inflammatory activity in experimental animal models of arthritis. These studies were partly supported by a Grant from the Ministry of Health, Labour and Welfare of Japan. We also prepared thermosensitive nanoparticles using N-isopropylacrylamide (NIPAAM) to control cellular uptake. The presence of CD208-positive keratinocytes was shown in psoriatic epidermis.

Research Activities

Nanoparticle preparations of a steroid for targeting and sustained release
The purpose of this study was to engineer nanoparticles with various sustained profiles of drug release and prolonged circulation by blending PLA/poly (D, L-lactic/glycolic acid) (PLGA) homopolymers and PEG-block-PLA/PLGA copolymers encapsulating betamethasone phosphate. Nanoparticles of different sizes, drug encapsulation/release profiles, and cellular uptake levels were obtained by mixing homopolymers and block copolymers with different compositions/molecular weights at various blend ratios with an oil-in-water solvent diffusion method. The *in vitro* release of betamethasone phosphate increased with nanoparticles of smaller size or of PLGA homopolymers instead of PLA homopolymers. Furthermore, the uptake of nanoparticles by macrophage-like cells decreased with nanoparticles of higher PEG content, and nanoparticles of PEG-PLGA block copolymers were taken up earlier than those of PEG-PLA block copolymers after incubation with serum. In addition, prolonged blood circulation was observed with nanoparticles of smaller size with higher PEG content, and nanoparticles of PEG-PLA block copolymers remained longer in circulation than did those of PEG-PLGA block copolymers. Analysis of betamethasone phosphate concentrations in organs and *in vivo* fluorescence imaging revealed reduced liver distribution of blended nanoparticles than of PLA nanoparticles. This is the first study to systematically design and characterize biodegradable PLA/PLGA and PEG-PLA/PLGA—blended nanoparticles encapsulating betamethasone phosphate with different release profiles and stealthiness. PLA nanoparticle preparations (about 150 nm in diameter) containing betamethasone phosphate with zinc ion was confirmed to be an appropriate DDS because of the lack of an initial burst. The pharmacological effects by single intravenous injection of this preparation were continued for 1 week in several experimental animal models of inflammation, including rheumatoid arthritis and asthma. The

pharmacological potency of this preparation was 2 to 4 times greater than that of betamethasone sodium phosphate. Because significant accumulation was observed with this preparation in the reticuloendothelial system of the spleen and liver, PEGylation of the nanoparticles has been performed with PEG-PLA block polymers. The anti-inflammatory effects of this stealth-type nanosteroid were 5 to 10 times greater than those of nonstealth nanosteroids in animal models, because stealth nanopartilces escaped from trapping in the liver and specifically accumulated in the inflammatory lesions, possibly helping to reduce the rate of adverse effects.

Publications

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