DDS Institute

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General Summary

We are investigating a new drug delivery system (DDS) using nanotechnology. We have developed polylactic acid (PLA)/polyethylene glycol (PEG)-PLA nanoparticles for targeting and sustained release of steroid/immunosuppressants and have demonstrated enhanced anti-inflammatory activity in experimental animal models of arthritis. These studies were supported in part by a grant from the Ministry of Health, Labour and Welfare of Japan. We also prepared thermosensitve 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 (BP). 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 BP increased with smaller nanoparticles or 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 were nanoparticles 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 those of PEG-PLGA block copolymers. Analysis of BP concentration in organs and *in vivo* fluorescence imaging revealed that the liver distribution of blended nanoparticles was less than that of PLA nanoparticles. To our knowledge, this is the first study to systematically design and characterize biodegradable PLA/PLGA and PEG-PLA/PLGA-blended nanoparticles encapsulating BP with different release profiles and stealthiness.

The PLA nanoparticle preparations (about 150 nm in a diameter) containing BP with zinc ion was confirmed to be an adequate DDS because of the absence of an initial burst. The pharmacological effect of a single intravenous injection of this preparation continued for 1 week in several experimental animal models of inflammation. The pharmacological potency of this preparation was 2 to 4 times greater than that of

betamethasone sodium phosphate.
Because this preparation showed significant accumulation in the reticuloendothelial systems of the spleen and liver, PEGylation of the nanoparticles was performed with PEG-PLA block polymers. Because stealth nanoparticles escaped trapping in the liver and specifically accumulated in the inflammatory lesions, they showed an anti-inflammatory effect 5 to 10 times greater than that of nonstealth nanosteroids in animal models and had reduced adverse effects. Production at an industrial scale according to the guidelines of good manufacturing practices of active pharmaceutical ingredients is also under investigation.

Publications

Ishihara T, Takahashi M, Higaki M, Takenaga M, Mizushima T, Mizushima Y. Prolonging the in vivo residence time of prostaglandin E1 with biodegradable nanoparticles. *Pharm Res* 2008; **25:** 1686–95.