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Poly (DL lactic acid) Microspheres for Controlled Drug Delivery Systems

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A new antiinflammatory drug was entrapped into the ploy (DL lactic acid) (PDLLA) (MW 3000) microspheres. The microspheres were prepared by an oil-in-oil emulsion polymerisation method. The morphology and degradation of the microspheres were analysed by optical and scanning electron microscopy. The *in vitro* release pattern of the drug from the microspheres was analysed by HPLC. The *in vitro* degradation and the percent weight loss determination of the PDLLA microspheres were also analysed. It was found that the release of the new anti inflammatory drug from the above poly (DL lactic acid) microspheres followed zero order fashion and lasted for about 14 days.

DRUG delivery systems using various kinds of biodegradable polymers have been extensively studied. In the case of microspheres as drug delivery systems, a wide variety of biodegradable materials and manufacturing methods using various kinds of biodegradable polymers encapsulating a variety of bioactive agents are available[1-5]. Controlled release systems based on biodegradable microspheres have gained much attention for extracorporeal therapy and targeted release.

Long time experience with poly(lactic acid) polymers has shown that these materials are biocompatible in physiological environments and degrade to toxicologically acceptable products that are ultimately eliminated from the body[6,7]. All these characteristics make poly(lactic acid) and poly (lactic acid/glycolic acid) to hold a considerable promise for the controlled drug delivery. Hence they have been widely used as release systems for a variety of drugs such as narcotic antagonists[8], local anaesthetics[9], immunopotentiators[10,11] and steroid hormones[12].

In the present investigation, the preparation, characterisation, *in vitro* degradation studies and *in vitro* release studies of a new anti inflammatory drug from biodegradable microspheres prepared with poly (DL lactic acid) (PDLLA) of molecular weight 3000 were evaluated. The drug, ONO-5046 is a newly synthesised drug with antiinflammatory activity, which consists of two benzene rings in the structure.

Poly (DL-lactic acid) was prepared by poly condensation method using DL-lactic acid aqueous solution at the Research Centre for Biomedical Engineering. The molecular weight was regulated by changing the polymerisation time and the vacuum. All other chemicals were of analytical grade and supplied by Nakalai Tesque Inc., Japan.

PDLLA microspheres were prepared by taking 200 mg of PDLLA and dissolving in 3 ml of acetonitrile. The PDLLA solution was added to 120 ml of olive oil containing 120 mg of lecithin. The reaction mixture was kept for stirring overnight at 320 rpm at 40°. The spheres thus formed were centrifuged, washed 3 or 4 times with hexane and dried. For preparing the drug loaded microspheres, 10% of drug was added to the PDLLA solution before adding to the mixture of lecithin and olive oil.

Shape and size of microspheres was estimated on an optical microscope. The amount of drug in microspheres was determined by directly recovering the drug from

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microspheres. About 11 mg of microspheres were dissolved in 200 µl of acetonitrile and the drug was extracted into 1.8 ml of ethanol. The solution was filtered through a Millipore filter and the amount of drug was estimated by High Performance Liquid Chromatography (HPLC) procedure using an internal standard method with an ultra violet detector (UV) under the following conditions: Column, Capcell pack C 18 (15 mm length and 4.6 mm in diameter); Column temperature 40°; Mobile phase, a mixture of 5 mM tetra-n-butyl ammonium chloride/acetonitrile 11/8; Flow rate, 1 ml/min; Wave length, 240 nm with an internal standard, p-Hydroxy benzoic acid-n-propyl ester in ethyl alcohol.

Morphology and degradation of PDLLA microspheres were studied on a scanning electron microscope at an accelerating voltage of 15 kV. The percent material weight loss of microspheres was determined by collecting the microspheres from the release medium at different intervals. The samples were freeze-dried and the weight was determined.

The *in vitro* release studies of the drug from PDLLA microspheres were carried out by taking 22 mg of microspheres (containing approximately 2 mg of drug) in 2 ml of PBS (pH 7.4). The release experiments were conducted at 37°under constant shaking. The PBS solution was collected at different intervals and the amount of drug was analysed by HPLC.

The morphological changes of the microspheres at different degradation stages were observed using scanning electron microscopy. Immediately after the preparation the microspheres were found to be spherical with smooth surface. After 1 day in the release medium, small cracks and pores were seen, the pores increased in size and number after 4 days in the release medium. After 14 days in the release medium only porous remnants remained.

The remaining material weight of the PDLLA microspheres was determined at different time intervals. There was a gradual decrease in the mass of the microspheres and about 17% of the microspheres remained in the release medium on day 15. Figure 1 shows the percent weight loss of microspheres as a function of time.

The *in vitro* release patterns of the drug from PDLLA microspheres was analysed by HPLC. Figure 2 shows the

Fig. 1: Loss of weight of microspheres with time

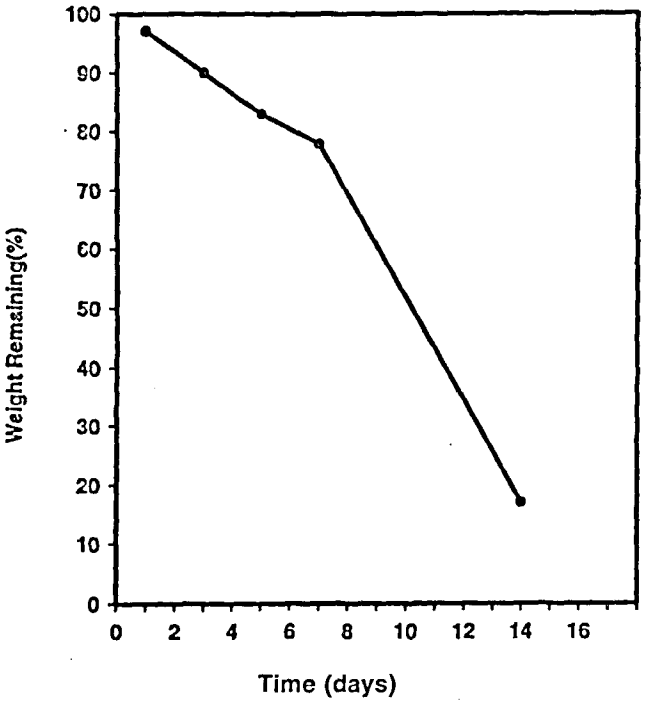
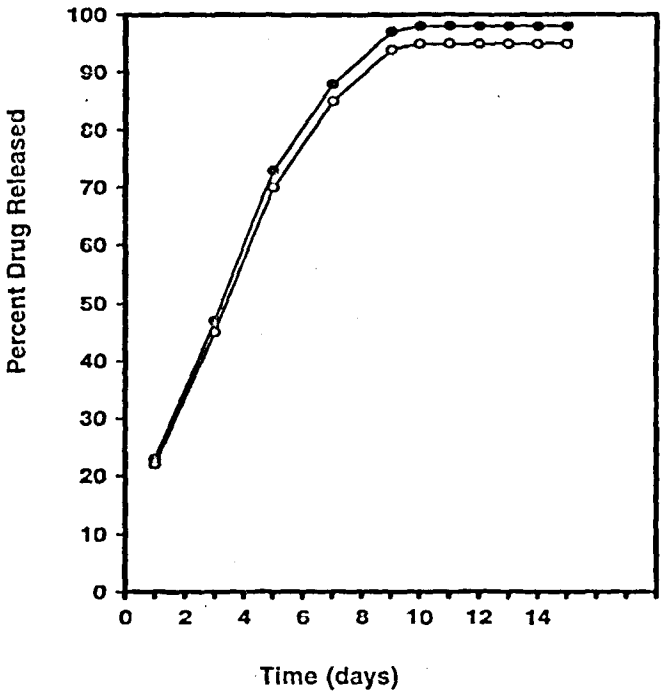


Fig. 2: *In vitro* release pattern of drug from PDLLA microspheres



-o- Drug released from the microspheres
-•- Drug + degraded drug released from the microsphers

release pattern of the drug from PDLLA microspheres at two different molecular weights. The release of the drug from microspheres followed zero order pattern and the release lasted for about 14 days. The HPLC analysis showed that the percent entrapment of the drug was about 5.2%. However, the maximum release (about 95%) occurred in the first 7 days. The release pattern of the degradation product of the drug also was analysed by HPLC. The amount of the degradation product in the release medium was very less indicating that the degradation of the drug was very insignificant.

The degradation of poly(lactic acid) is a critical factor in determining the release of the drug from the matrix. Morphological studies by scanning electron microscopy supported a mechanism of homogenous degradation of PDLLA showing a progressive formation of pores all over the matrix. Pores appeared after the first day in the dissolution medium and their size and number increased with time. By day 7 a highly porous matrix was seen. After 15 days only collapsed porous pieces of microspheres remained in the release medium. Further PDLLA degrades through hydrolysis of ester groups along the main chain of polylactide. Normally PDLLA mass loss begins when the molecular weight decreases. Hence it was clearly indicated that PDLLA molecular weight decreased with the drug release.

Drug release from the microspheres can be explained by two mechanisms: one by diffusion through polymer matrix and the other matrix bioerosion. The bioerosion occurs when the release of the drug from the matrix follows the erosion of the polymer surface or bulk matrix than by simple diffusion[13-17]. The progressive increase of pores and the decrease in the release of the drug from PDLLA microspheres is controlled mainly by matrix erosion. In the present investigation the goal of designing controlled release system for a new antiinflammatory drug for 2 weeks was achieved by selecting the polymers from PDLLA polymer family with suitable degradative properties and these microspheres have a potential to be used as carriers for physiologically active agents such as hormones, peptides and antigens.

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