liver functions were observed in rabbits with acute and chronic diabetes based on plasma chemistry data and tissue microscopy. After intravenous administration of diltiazem to rabbits with acute and chronic diabetes, the plasma concentrations were higher and this resulted in a significantly greater area under the plasma concentration-time curve from time zero to time 24hrs than controll rabbits. The effects of diabetes on the pharmacokinetics of intravenouse diltiazem were more considerable in rabbits with chronic diabetes ; the AUC was significantly greater in acute AIDRs (1,111 ± 209 ng/ml·hr) and in chronic AIDRs (1,263±236 ng/ml·hr) than that (853 ± 155 ng/ml·hr) in control rabbits. And maximum plasma concentration were significantly higher than that in control rabbits. No significant change has been shown in cumulative urinary excretion of diltiazem among acute and chronic AIDRs and control rabbits. These findings suggest that in acute and chronic AIDRs, the hepatic metabolism of diltiazem was inhibited due to liver impairment and elimination rate constant was decreased due to kidney impairment.

[PE1-16] [04/19/2001 (Thr) 15:30 - 16:30 / Hall 4]

Encapsulation of lectin-conjugated ellagitannin(LET) into sterically stabilized liposomes

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Lectin-conjugated ellagitannin (LET), a newly introduced melanoma-specific anti-tumor agent which has been synthesized by conjugation of wheat germ agglutin(WGA) with praecoxin A, was encapsulated into sterically stabilized liposomes. To determin the encapsulation efficiency of LET, calibration curve was plotted with the bovine serum albumin(BSA) as pure standard protein and the contents of lectin was quantified by modified Folin phenol protein quantitation method. Employing solvents extraction methods, the interference of phospholipid during protein assay was eliminated efficiently. The extraction efficiency was 94.54±2.32%, and the encapsulation efficiency of lectin of 2.5mg LET/ml was 46.95%. In future, the in vivo profile of LET will be further investigated.

[PE1-17] [04/19/2001 (Thr) 15:30 - 16:30 / Hall 4]

Preparation of Fine Particles for DDS using Supercritical Antisolvent (SAS) process.

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A continuous supercritical antisolvent (SAS) recrystallization process has been used to prepare fine poly(L-lactic acid) (L-PLA) particles. A difficult-to-comminute biodegradable polymer was precipitated successfully through a carbon dioxide supercritical antisolvent (SAS) recrystallization process. In this study, the solubility of substance (L-PLA) to be crystallized was reduced sharply by adding the primary solvent (methylene chloride) into a second, so-called antisolvent (scCO2). SAS recrystallization is applied to L-PLA that is insoluble in supercritical carbon dioxide but highly soluble in methylene chloride, being itself completely miscible with carbon dioxide. Because the supersaturation of the L-PLA occurs dramatically by quick diffusion of CH2Cl2 into CO2, narrow distributed ultra-fine L-PLA particles are formed.
Experimental runs in a continuous flow crystallizer were performed changing process parameters such as the pressure (77.5-150 bar) and temperature (25-40℃) at 0.5wt% L-PLA concentration. Also, L-PLA concentration in methylene chloride was changed from 0.3 to 1wt% at 150 bar and 40℃. It is found that supercritical fluid process gives fine tuning of particle size and particle size distribution by simple manipulations of the process parameters. In all cases of our SAS recrystallization experiments, the spherical L-PLA particles were obtained. Mean particle size of the precipitated product could be

varied between 0.2 and 2㎛ by means of adjusting the system pressure and/or temperature. The proposed method is attractive as the basis of a new process for the preparation of drug delivery system.

[PE1-18] [04/19/2001 (Thr) 15:30 - 16:30 / Hall 4]

Formulation of microemulsion-based hydrogel containing prostaglandin E1 ethyl ester

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Prostaglandin E1 analogues, especially prostaglandin E1 ethyl ester(PGE1-EE), have been focused as a therapeutic agent for erectile dysfunction due to its higher skin penetration property than that of PGE1. A microemulsion-based hydrogel(MHG) containing PGE1-EE was formulated through phase diagram with polyoxyl castor oils, EtOH and medium chain triglycerides(MCTs). In vitro drug penetration characteristics of MHG was investigated using Franz diffusion cell and receptor solution (pH 7.4 PBS : EtOH = 90 : 10) containing PGE1 was assayed by validated HPLC method. PGE1-EE was stable in receptor solution for 6hrs but PGE1-EE was cleaved to PGE1 by skin esterase during penetration. Microemulsion promoted penetration of PGE1-EE, showing the result of 2~3 times higher penetration than that of control hydrogels, e.g. sodium alginate gel. Finally, in vivo pharmacodynamic effects of MHG, such as ICP(Intra Cavernosal Pressure), duration of erection, increment of penile length were investigated with wild male cats.

[PE1-19] [04/19/2001 (Thr) 15:30 - 16:30 / Hall 4]

Formation of peptide adduct during in vitro release of GHRP-6 containing poly(dl-lactide-co-glycolide) microspheres

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GHRP-6 is a synthetic growth hormone-releasing hexapeptide (His-DTrp-Ala-Trp-DPhe-Lys-NH2) which elicits a dosage-related release of growth hormone in vitro and in vivo. GHRP-6 was encapsulated into 50:50 poly(d,l-lactide-co-glycolide) (PLGA) microspheres using oil in water solvent extraction/evaporation method. Spherical microspheres with smooth surface structures were obtained with high encapsulation efficiency. In vitro release test was carried out in 33 mM phosphate buffer, pH 7.0 at 37°C. During in vitro release test, several degradation and/or adduct peaks were detected and some of them were identified by LC/MS/MS. Glycolic acid and lactic acid attributed to the erosion of PLGA during the incubation seemed to be conjugated to the free amino group of N-terminal His and epsilon amino group of Lys5 of GHPR-6. These results indicate that peptide adduct formation should be considered when planning to develop a sustained release peptide formulation using PLGA polymers.

[PE1-20] [04/19/2001 (Thr) 15:30 - 16:30 / Hall 4]

Increased Stability of Recombinant Human Epidermal Growth Factor by Poly(Ethylene Glycol) Conjugation