College of Pharmacy, Chonnam National University

The techniques that can potentially enhance the dissolution rate and extent of absorption of poorly soluble drugs is the formation of solid dispersion with polymeric materials. To increase the dissolution rate of furosemide, vitamin E TPGS (d-alpha tocopheryl polyethylene glycol 1000 succinate) was used as a drug carrier. The 1:2(w/w) solid dispersion was prepared by solvent method. The dissolution test, X-ray diffraction, Infrared spectra, thermal analysis of furosemide test systems were carried out. The dissolution rate of furosemide-vitamin E TPGS solid dispersion was enhaced markedly than that from the physical mixture or intact furosemide. The X-ray diffraction, IR, DTA, and TGA studies showed the physiochemical modification of the furosemide from the solid dispersion. The crystalline peaks of furosemide alone or furosemide contained within a physical mixture were disappeared in the solid dispersion indicating the amorphous form. An interaction, in the solid dispersion such as an association between the functional groups of furosemide and vitamin E TPGS might have occurred at the molecular level, changing the physicochemical property and increased the dissolution of furosemide. The results showed that the extent of dissolution was significantly enhanced, following formation of the solid dispersion, and the solid dispersion techniques with vitamin E TPGS provide a promising way to increase the dissolution rate of poorly soluble drug.

[PE1-14] [04/19/2001 (Thr) 15:30 - 16:30 / Hall 4]

Circadian Changes in Pharmacokinetics of Acebutolol Orally Administered to Rabbits

Burm JP°, Lee JH and Choi JS

College of Pharmacy, Chosun University and Chosun Nursing College

Effect of circadian rhythm on the pharmacokinetics of acebutolol and its metabolite, deacetylacebutolol was studied in rabbits after a single oral administration of acebutolol, 20mg/kg, in the morning (09:00 A.M.) and in the evening (21:00 P.M.). The plasma data were subjected to simultaneous computer nonlinear least squares regression analysis using a two-compartment pharmacokinetic model.

The elimination rate constant(β) of acebutolol were 0.072 ±0.016 hr^{-1} in the morning and 0.066 ± 0.013 hr^{-1} in the evening. The total body clearance(CLt) and area under the plasma concentration-time curve(AUC) of acebutolol were 3.02 ±0.52 L/hr/kg and 6.79 ±1.21 μg/ml·hr in the morning and 2.41 ±0.43 L/hr/kg and 9.16 ±1.69 μg/ml·hr in the evening. The plasma concentrations of acebutolol in the evening were increased during 4-12hr compared to those of acebutolol in the morning. The CLt of acebutolol in the evening were decreased significantly ($p < 0.05$) compared to that of acebutolol in the morning and the AUC of acebutolol in the evening were increased significantly ($p < 0.05$) compared to that of acebutolol in the morning.

However, the pharmacokinetic parameters of its metabolite were not significantly different between in the morning and in the evening.

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

Pharmacokinetic Changes of Intravenous Diltiazem in Alloxan-Induced Diabetes Mellitus Rabbits

Choi JS° and Jung EJ

College of Pharmacy, Chosun University

Because physiological changes occurring in diabetes mellitus patients could alter the pharmacokinetics of the drugs used to treat hypertention resulting from diabetic complications,the pharmacokinetics of diltiazem were investigated after intrvenous administration of the drug (4 mg/kg) to control rabbits and rabbits with acute and chronic diabetes induced by alloxan. Impaired kidney and

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

Jeon HJ, Choi SU, Yun MK, Lee MW, Kim HH, Lee DI, Choi YW

College of Pharmacy, Chung-Ang University

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.

Song KH°, Lee C-H*, Lee Y-W

National Research Lab. for Supercritical Fluid, Korea Institiute of Science and Technology, Chemical Engineering Department, Yonsei University*

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