

was calculated. Eventhough (S)-(-)- $\alpha$ -methylbenzylamine was most effective for the preferential recrystallization of (S)-(+)-ibuprofen, chemical shift differentiation ability was weak. (-)-Cinchonidine discriminated the methyl, methylene and benzyl protons of (S)-(+)-ibuprofen and (R)-(-)-ibuprofen effectively.

[PD4-34] [ 2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function ]

### **High throughput automated 96-well solid-phase extraction and liquid chromatography-tandem mass spectrometric analysis of beraprost in human plasma**

**Chang Kyu Young**<sup>o</sup>, Kim Hohyun, Lee Hee Joo, Lee Kyung Ryul

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A sensitive and selective liquid chromatographic method coupled with tandem mass spectrometry (LC-MS/MS) was developed for the determination of beraprost in human plasma. Plasma samples were transferred into 96-well OASIS HLB extraction plate using an automated sample handling system and the drugs were eluted with methanol. The eluents were then evaporated and reconstituted with water. All sample transfer and solid-phase extraction (SPE) was automated through the application of both the PerkinElmer MultiPROBE II HT and TOMTEC Quadra 96 workstation. The reconstituted samples were analyzed by a reversed-phase LC-MS/MS using an electrospray ionization (ESI) interface. The mobile phase was composed of 1 mM ammonium acetate and acetonitrile (50:50, pH 5.0), with a flow rate at 0.2 mL/min. The limit of quantification (LOQ) was 20 pg/mL, using a sample volume of 1.5 mL for the analysis. Beraprost produced a protonated precursor ion ([M-H]<sup>+</sup>) at m/z 397, and a corresponding product ion at m/z 269. Internal standard produced a protonated precursor ion ([M-H]<sup>+</sup>) at m/z 367 and a corresponding product ion at m/z 249. Based on a signal-to-noise level (S/N) of 10, the limit of quantification for beraprost was found to be 20 pg/mL. This simple, rapid and robust assay will enable the complete processing of large sample for pharmacokinetic studies of beraprost in human plasma.

[PD4-35] [ 2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function ]

### **Liquid Chromatographic Resolution of Pyrethroid Acids and Their Esters on Chiral Stationary Phases**

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Pyrethroid acids are essential chiral intermediates of the pyrethroids, which account for about 25% of the world insecticide market and are found to be some of the most effective commercially available pesticides. It was demonstrated that polysaccharide-derived chiral stationary phases (CSPs) are very efficient for the separation of the enantiomers of pyrethroid acids. It was observed that the enantioseparation of pyrethroid methyl ester and ethyl derivatives was well accomplished on brush-type WhelkO-1. The observed enantioselectivity is suitable for the determination of enantiomeric purity of pyrethroid acids and their ester derivatives on these CSPs.

[PE1-1] [ 2003-10-11 09:00 - 12:30 / Grand Ballroom Pre-function ]

### **Skin penetration enhancement of prostaglandin E1 and its ethyl ester for topical formulations**

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Purpose. To investigate the effect of different terpene enhancers on skin penetrations of prostaglandin E1 (PGE1) and its ethyl ester (PGE1-EE), a therapeutic agent for erectile dysfunction, external gel systems were formulated with the specific enhancers having different values in their lipophilicity (log P was ranged in 2.23-

4.58). Methods. Topical gels containing PGE1 (0.5 %) and PGE1-EE (0.1 %) were formulated with ethanol and propylene glycol as a vehicle, selective terpenes as a penetration enhancer, and HPC-H as a thickening agent. In vitro skin penetration profiles of the drug through the rat's dorsal skin using modified Franz diffusion cell were observed by the simultaneous HPLC assay of [PGE1] and [PGE1-EE] in the receptor compartment. Results. In the skin penetration study for 6 hr, combination of ethanol and propylene glycol in 1:3 v/v ratio as a vehicle increased the flux of PGE1 and its ethyl ester up to 15- and 3-fold, respectively, showing the result of an order of magnitude difference compared to the control formulation (ethanol only). In addition, employment of terpene enhancers to the above gel system further increased the flux of both drugs in decreasing order as follows: limonene > cineole > menthone ≥ carvone > thymol, which was consistent with the degree of lipophilicity. Limonene which possessed the highest lipophilicity (log P of 4.58±0.23) provided the greatest enhancement for PGE1 and its ethyl ester, revealing increased flux about 6- and 7-fold, respectively. Conclusions. Terpene enhancers in combination with the selective cosolvent mixture in gels exhibited pronounced enhancement for skin penetration of the tested drugs. And the lipophilicity of the enhancer showed a key role in the penetration enhancement.

[PE1-2] [ 2003-10-11 09:00 - 12:30 / Grand Ballroom Pre-function ]

### **Pharmacokinetic behavior of lipid nanodispersion system for parenteral delivery of paclitaxel in rats**

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Purpose. Paclitaxel has demonstrated significant activity in clinical trials against a wide variety of tumors. The clinical application of Taxol<sup>®</sup>, a commercial product of solubilized paclitaxel with cosolvents of ethanol and Cremophor, however, has been limited largely by hypersensitivity of the excipient. The aim of this study was to formulate paclitaxel-loaded lipid nanodispersions (Px-LN) for i.v. administration without toxic excipients, and to evaluate in vitro characteristics and in vivo pharmacokinetic behaviors. Methods. Hot homogenization method was adopted to prepare Px-LN using a Microfluidizer. The mean diameter and polydispersity index (PI) of LN were determined by PCS. Zetapotential was measured by Zetasizer. The content of paclitaxel in the LN was analyzed by HPLC after dilution with 60% acetonitrile. Px-LN or the reference formulation (Taxol<sup>®</sup>) at a dose of 5 mg/kg as paclitaxel was given to male Sprague-Dawley rats through the femoral vein for 30 sec. Blood samples were deproteinated with acetonitrile and assayed for paclitaxel by the validated HTLC/MS/MS method. Results. Paclitaxel was successfully incorporated into the lipid nanoparticles with mean particle size of 50 nm (PI<0.3) and the zetapotential of -40mV, which considered to be acceptable for intravenous administration. The content of paclitaxel in the LN was ca. 1.5 mg/ml. The formulation of Px-LN was stable for over 8 months under refrigerated condition. The AUC of Px-LN was 1.7-fold higher than that of Taxol<sup>®</sup>. The elimination half-life of paclitaxel in terminal phase for the Px-LN was increased more than two times compared to Taxol<sup>®</sup>. Conclusion. The incorporation of paclitaxel in lipid nanodispersion could increase the bioavailability resulted in extended blood level of the drug with reduced elimination. The LN might be a prospective carrier for the parenteral delivery of water-insoluble lipophilic drugs.

[PE1-3] [ 2003-10-11 09:00 - 12:30 / Grand Ballroom Pre-function ]

### **Improvement of bioavailability of poorly water-soluble drugs by size reduction technique.**

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The prolonged mechanical grinding process may enhance the bioavailability of the drugs due to the change of solid state such as micronization and decrease of crystallinity. A series of attempts to enhance the bioavailability of insoluble drugs have been made by the fine grinding technique using a planetary mill. The objective of the present study is to investigate the possibility of improving the dissolution properties of poorly water-soluble drugs