Cho HeaYoung°, Lee Suk, Kang HyunAh, Lee YongBok

College of Pharmacy and Institute of Bioequivalence and Bridging Study,Chonnam National University, Gwangju 500-757, Korea

On the basis of recognizing that physicochemical properties (lipophilic/hydrophilic), intestinal absorption clearance and pharmacokinetic characteristics of drug are the fundamental parameters controlling the rate and the extent of drug absorption, the biopharmaceutics classification system for the correlation between drug lipid-solubility and intestinal absorption clearance is proposed. The aim of this study was to assess whether the partition coefficient in n-octanol/buffer (pH 7.4) and intestinal absorption clearance of nine beta-blockers such as atenolol, sotalol, nadolol, acebutolol, pindolol, metoprolol, timolol, labetalol, propranolol can be correlated or not. In vivo intestinal absorption clearance was determined by using in situ single-pass perfusion at steady state. So as to do, a constant concentration of each drugs were applied to rat intestinal lumen side. At the steady state, we measured the concentration of each drugs to be remained of intestinal lumen side using HPLC with UV or fluorescence detection. From the results, we know that the higher partition coefficient of beta-blockers, the more permeable except sotalol, acebutolol and timolol.

[PE1-11] [10/18/2002 (Fri) 13:30 - 16:30 / Hall C]

Preparation and release characteristics of PVP-based solid dispersion capsules containing solubilizers

Cao QingRi°, Kim TaeWan, Choi ChoonYoung, Lee BeomJin

Biological Rhythm and Controlled Release Lab., College of Pharmacy, Kangwon National University; Pharm Tech Research Incorp.

Purpose. To prepare PVP-based solid dispersions containing lovastatin (LOS) and solubilizers (sodium lauryl sulfate, Tween80, oleic acid) to enhance dissolution of practically insoluble LOS. Methods. Solid dispersions containing LOS were prepared by dissolving two different organic solvent systems (acetone/ethanol or acetonitrile/ethanol). Results. The stickiness and flowability of solid dispersion powders were dependent on the composition and ratio of the solubilizers. LOS contents was decreased when acetone/ethanol was used instead of acetonitrile/ethanol. The solubilizers were useful to increase dissolution rate of LOS in gastric or intestinal fluid. Most of all, simultaneous use of the solubilizers in PVP-based solid dispersion capsule gave the best dissolution, reaching 76 and 60% in gastric and intestinal fluid, respectively. Conclusions. The various solubilizers could be applicable to solid dispersion system for enhanced dissolution and bioavailability of poorly water-soluble drugs. Supported by ministry of health & welfare (02-PJ1-PG11-VN02- SV01-0002).

[PE1-12] [10/18/2002 (Fri) 13:30 - 16:30 / Hall C]

Solubilization of poorly water-soluble drugs using solid dispersions

Kim TaeWan°, Choi ChoonYoung, Cao QingRi, Lee BeomJin

Biological Rhythm and Controlled Release Lab., College of Pharmacy, Kangwon National University;Pharm Tech Research Incorp.

Purpose. To prepare polymer based physical mixtures or solid dispersions containing solubilizing compositions using a spray-dryer. Methods. Lovastatin,simvastatin,aceclofenac and cisapride were selected as poorly water-soluble drugs. Dextrin, poly(vinylalcohol), poly(vinylpyrrolidone)and polyethylene glycol were chosen as solubilizing carriers for solid dispersions. The solid dispersions containing solubilizing compositions without drug were prepared without using organic solvents or tedious changes of formulation compositions. This system could be used to quickly screen the dissolution profiles of poorly water-soluble drugs by simply mixing with drugs thereafter. In case of solid dispersion containing drug, organic solvent systems could be used to solubilize model drugs. Results. The dissolution rates of the drugs were higher when mixed with drug and solid dispersions containing solubilizing compositions. However, solid dispersions of LOS, AFC, and CSP simultaneously containing drug and solubilizing compositions in organic solvent systems were more useful than physical mixtures of drug and solid dispersions without drug except SIMS. Conclusions. Based on solubilizing capability of polymer based physical mixtures in gelatin hard capsules, optimal solid dispersion system of poorly water-soluble drugs

could be formulated. However, it should be noted that dissolution rate of poorly water-soluble drugs were highly dependent on drug properties, solubilizing compositions and polymeric carriers. Supported by ministry of health & welfare (02-PJ1-PG11-VN02-SV01-0002).

[PE1-13] [10/18/2002 (Fri) 13:30 - 16:30 / Hall C]

A study on the Physico-chemical Properties of CB-ph, a New Anti-cancer drug

Kim SuYoen^{O}, Kim DaeDuk, Lee ChiHo

College of Pharmacy, Pusan University, Pusan 609-735

Purpose To investigate the physico-chemical properties of CB-ph[2-benzoyloxycinnamaldehyde], an anticancer drug obtained from *Cinnamomum cassia* using methylenechloride, and its stability in various aqueous solutions. Results CB-ph was rarely soluble in water but soluble in methanol and very soluble in ether. Kinetic salt effect on degradation of CB-ph in buffer solutions at pH 4.0 and 60℃ showed a linear relationship having a positive slope that means reactions between hydronium ions and protonated substrates. By plotting the logarithm of the degradation rate constants of CB-ph as a function of temperature(40-80℃) in aqeous solutions vs. 1/temperature was obtained a linear relationship and the t_{90} of CB-ph was calculated from Arrhenius plot. From the pH-rate profile, it was found that CB-ph was most stable in pH range of 2 - 4 at 60℃. The weight change of CB-ph in desiccator storage for 5 weeks under various relative humidity(21 to 88%) were not found. Conclusions Melting point of CB-ph was 82.5℃. The solubilities of CB-ph were 0.4ug/mL in water, 18mg/mL in methanol, and 49mg/mL in ether. The pH-rate profile of CB-ph at 60℃ showed a general acid-base catalysis reaction in the range of pH 1-9. The degradation rate constants(K) of CB-ph at 60℃ and pH 1, 4, 5 and 9 were 0.0041, 0.0004, 0.0019 and 1.5828 h^{-1}, respectively. t_{90} of CB-ph in distilled water at 20℃ was approximately 170 days. The degradation of CB-ph in buffer solutions at pH 4.0 and 60℃ may be affected through both of a primary and a secondary salt effect.

[PE1-14] [10/18/2002 (Fri) 13:30 - 16:30 / Hall C]

Pharmacokinetics of New Solubilizer in Intravenous Micelle Formulation of Paclitaxel in Mice

Lee SunA^{O}, Han KyuWon, Um SoYoung, Kim KilSoo

College of Pharmacy, Ewha Womans University

Paclitaxel is an antitumor agent with poor water solubility and its pharmacokinetics are nonlinear. Cremophor EL, a surfactant used in the formulation of paclitaxel, may cause adverse effects. New solubilizer(Aceporol 460) was developed to reduce side effects of Cremophor EL and to increase the effect of drug as surfactant used in the intravenous micelle formulation of anticancer drug paclitaxel. We studied easy, rapid quantitative determination of Aceporol 460 in mouse plasma samples, which was achieved by complexation of the compound with the Coomassie brilliant blue G-250 dye in protein-free extracts. The binding of the dye to Aceporol 460 caused a shift of the absorption maximum in 400-700nm. Pharmcokinetics of New solubilizer were studied by this method. Mice were treated with Cremophor EL, Aceporol 460, each at dose levels of 0.83, 0.625, 0.417mL/kg(29.3, 22.1, 14.7mL/m2). Mouse samples were collected up to 90 minute after injection. AUCs(0-90) of Aceporol 460 were 85.46μ
Lmin/mL(at 0.417mL/kg), 194.83μLmin/mL(at 0.625mL/kg), 252.99μLmin/mL(at 0.83mL/kg).

[PE1-15] [10/18/2002 (Fri) 13:30 - 16:30 / Hall C]

Tissue Distribution of Novel Polymeric Micellar Paclitaxel in Mice

Kim HyeJin^{O}, Kang MinKyung, Kim KilSoo

College of Pharmacy, Ewha Womans University