Hydrogel

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The purpose of this study was to evaluate the effects of various enhancers on the in vitro rat skin permeation of ciclopirox olamine from novel soft hydrogel (S-Gel).
A number of 1% ciclopiroxe S-Gel formulations with and without one of various enhancers were prepared and compared with each other. The in vitro rat skin permeation of drug was investigated using Keshary-Chien permeation cells at 37℃. The drug concentrations were determined by gas chromatography and the fluxes of ciclopiroxe were calculated from the slope of linear portion of the permeation profiles.
Among various enhancers used in this experiment, dodecylamine, HPE-101 and oleic acid were the most effective enhancers. The fluxes of 1%ciclopiroxe S-Gel containing one of the three enhancers, dodecylamine,
HPE-101 and oleic acid were 2.35, 2.24 and 2.12㎍/㎠/hr, respectively, comparing with 1.80㎍/㎠/hr of the control S-Gel without any enhancers.
From these results, this study demonstrated a good feasibility of a new dosage form, ciclopirox S-Gel for the treatment of cutaneous candidiasis, and other fungal skin infections, namely dermatophytosis and pityriasis versicolor.

[PE2-1] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

IN VITRO METABOLISM OF A NEW PROTON PUMP INHIBITOR KR60436 IN RAT AND HUMAN LIVER MICROSOMES

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KR60436, 1-(2-methyl-4-methoxyphenyl)-4-[(2-hydroxyethyl)amino]-6-trifluoro methoxy-2,3-dihydropyrrolo-[3,2c]-quinoline is a new proton pump inhibitor under development for the treatment of gastric ulcer. The objectives of this study were to investigate the in vitro metabolism of KR-60436 in rat and human liver microsomes, and to identify the KR60436 metabolites.
KR60436 was incubated individually with male rat and human liver microsomes in the presence of NADPH generating system. Unchanged KR60436 plus five oxidized metabolites were profiled, and tentatively identified from the incubation using electrospray LC/MS and MS/MS techniques. Electrospray-MS and MS/MS analysis of unchanged KR60436 and its metabolites revealed intense protonated molecular ions and prominent as well as informative daughter ions for stuctural elucidation of metabolites. Four metabolic pathways are proposed for the formation of metabolites in both species: O-demethylation, N-dehydroxyethylation, hydroxylation and N-acetylation. OH-KR60436 (M1) and O-demethyl-KR60436 (M2) was major metabolites in rats and human, respectively. In conclusion, KR60436 is substantially metabolized in rat and human liver microsomes.

[PE2-2] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

METABOLISM OF A NEW PROTON PUMP INHIBITOR DBM-819 by LC-MS/MS

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The in vitro and in vivo metabolism of the new proton pump inhibitor DBM-819, 1-(2-methyl-4-methoxyphenyl)-4-[(3-hydroxypropyl)amino]-6-methyl-2,3-dihydropyrrolo-[3,2c]quinoline in the rat were identified using LC/MS/MS. Four metabolites (M1, M2, M3 and M4) were produced using rat liver microsomes in the presence of NADPH-generating system. They were identified as desmethyl-DBM819 (M2), 8-hydroxy-DBM-819 (M3), 1-(2-methyl-4-methoxy-phenyl)-4-amino-6-methyl-2,3-dihydro-pyrrolo-[3, 2c]-quinoline (M4) and hydroxylated DBM-819 (M1), respectively. The metabolites M1-M3 obtained from in vitro studies were also confirmed in the bile after an oral administration of DBM-819 to rats. Enzymatic hydrolysis of the bile samples suggested that those metabolites were excreted as glucuronic acid-conjugated forms as well. Based on the results obtained metabolic map of DAM-819 is proposed.

[PE2-3] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Pharmacokinetics of cyclosporin A in lymph on rats

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Cyclosporin A (CSA), a cyclic endecapeptide with potent immunosuppressive activity, was derived from extracts of Tolypolcladium inflatum Gams. CSA inhibits lymphocyte proliferation at the cytokine transcription levels. CSA has large molecular weight, is highly lipophilic and virtually insoluble in water, because of these properties, oral and intravenous formulations of CSA are available as an oil-based solution or a microemulsion. Lipid-soluble vitamins and other lipophilic compounds are generally transported in the lacteals of the mesenteric lymphatic system in association with the chylomicron, and liposome, emulsion, macroconjugate and so on have been used for lymphatic delivery. So, we attempted to investigate the pharmacokinetic characteristics of cyclosporin in rat lymph node and blood after CIPOL Inj. (Chong Kun Dang Pharm., Seoul, Korea), intravenous commercial product as a microemulsion formulation, was administered (10 mg/kg). We measured simultaneously the CSA concentrations of mesenteric, brachial node, spleen and whole blood using TDxFLx (Abott Labaratores, Abott Park, U.S.A.). The pharmacokinetic parameters were evaluated by fitting the proposed catenary model with WinNonlin. The profiles of CSA concentrations in lymph node and whole blood were well fitted to this pharmacokinetic catenary model.

[PE2-4] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Metabolite kinetics of triflusal to 2-hydroxy-4-trifluoromethyl benzoic acid in rats

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In order to elucidate the fraction of hydrolysis in the over all in vivo metabolism of triflusal, the hydrolysis of triflusal to 2-hydroxy-4-trifluoromethyl benzoic acid (HTB) was studied in rats. Triflusal and HTB were injected into the rat femoral vein, respectively. And the pharmacokinetic parameters were obtained from the plasma concentration-time profiles of triflusal and HTB determined by the simultaneous analysis using high-performance liquid chromatography. It was supposed that triflusal was almost metabolized in vivo because the total excreted amounts of triflusal via urinary route were elusive. And also triflusal hydrolysis to HTB in aqueous media is