To improve solubility and bioavailability of a poorly water-soluble anti-fungal agent, Itraconazole, we prepared its solid dispersion particles using supercritical fluid processes with water-soluble carriers. Itraconazole and water-soluble polymer, HPMC were dissolved in mixture of methylene chloride and ethanol(60 : 40 w/w) as a feed solution. And then prepared solid dispersion particles by spraying the solution into the vessel filled with supercritical carbon dioxide as an anti-solvent. Various experimental parameters including temperature(45~80℃), pressure(80~150 bar), and concentrations of feed solution were investigated. In each cases, characterized its morphology by scanning electron microscopy and investigated polymorphic characteristics by differential scanning calorimetry(DSC) analysis. And determined its water-solubility. At the DSC profile, all the processed products showed a wider melting endotherm with a lower heat-flow peak than that of pure itraconazole. After the processing, we obtained its solid dispersion nanoparticles, together with remarkable water-solubility.

[PE1-16] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Chemical Stability of Prokidin in Buffered Aqueous Solutions

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The effects of pH and temperature on the degradation of prokidn in various buffered aqueous solutions (pH 1.32 ~ 9.66) and temperatures (35, 45 and 60 ℃) were investigated. The effect of ionic strength on the degradation of prokidin was also measured by varying ionic strength (0.0466 ~ 1.5) at pH 7.35 and 45 ℃. The effect of metal ions on the degradation of prokidin at pH 7.35 and 3.98 was observed. The degradation of prokidin followed the pseudo-first-order kinetics. The degradation rate of prokidin showed pH-dependent and temperature-dependent patterns. Prokidin was very stable at the pH below 3.98, where half-lives at 35, 45 and 60 ℃ were 294, 206 and 107 day, respectively. However, it degraded very rapidly at pH above 6.49, the half-lives at 35, 45 and 60 ℃ were 60, 25 and 13 day, respectively. As ionic strength increased, the degradation rate of prokidin increased. Some metal ions increased the degradation rate in the rank order of Mn2+ > Fe3+ > Cu2+ > Fe2+. On the other hand, other metal ions such as Bi3+, Ba2+, Zn2+, Ni2+, Co2+ and Mg2+ did not show unfavorable effect.

[PE1-17] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Hydrolysis of Prostaglandin E1(PGE1) ethyl ester, a prodrug of PGE1, in rat's skin homogenate

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Ester type prodrugs are hydrolyzed generally in a quantitative manner to produce a parent drug by the esterase in vivo. PGE_1-EE, a prodrug of PGE_1 showing improved skin permeation due to its lipophilicity, was also expected to be hydrolyzed during transdermal absorption process. Therefore, in this experiment, in vitro hydrolysis of the ester in rat's skin homogenates was studied by the quantitation of residual [PGE_1-EE] and produced [PGE_1], revealing the results of the decrease in [PGE_1-EE] and the increase in [PGE_1]. However, mass balance between [PGE_1-EE] and [PGE_1] was not established. This difference was possibly due to another mechanism involved in degradation or hydrolysis pathway and it was verified by unknown peak in HPLC chromatogram. As a result, a complicated hydrolytic degradation was proposed as follows: PGE_1-EE hydrolyzed by the skin esterase to PGE_1 directly (k_1), at the same time, PGE_1-EE degraded to the unknown intermediate compound (k_x) then hydrolyzed sequentially to PGE_1 finally (k_2). In order to verify the above hypothesis,computer simulation technique using Grapher^{TM} has been carried out. The approximate rate constants for k_1, k_x, and k_2 were calculated as 0.003~0.009, 0.019~0.021 and 0.018~0.020, respectively. The observed rate constants for changes in

[PGE_1-EE] and [PGE_1] were well consistent with the simulated k values. In addition, the skin penetration study also supported the newly postulated hydrolysis pathway as explained above. .

[PE1-18] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Enhanced Dissolution of Tenoxicam by Solid Dispersion Technique

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The effects of solid dispersions with cyclodextrins (CDs) on the dissolution rate of tenoxicam, which is known to be a very slightly soluble drug, were investigated. The solubility of tenoxicam was determined in the presence of various CDs [α-, β- and γ- CD, 2-hydroxypropyl- β- CD (HPCD), sulfobutyl ether- β- CD (SBCD), dimethyl- β-CD (DMCD) and trimethyl- β- CD (TMCD)] by shaking in water bath at 30℃. Solid dispersions were prepared with β- CD using solvent evaporation and freeze-drying process. The ratios of drug to carrier were 1:1 and 1:2 molar ratio. Tenoxicam was dissolved in ammonium hydroxide solution, mixed with CD solutions and dried. Dissolution tests were performed in gastric and intestinal juice. Solid dispersions were also formulated to tablets and then dissolution rates were compared with that of a commercial product. The solubility of tenoxicam increased in the rank order of SBCD > γ- CD > β- CD > HPCD > DMCD > α- CD > TMCD. Dissolution rate of the solid dispersions was higher than that of drug alone. As the ratio of carrier was higher, dissolution rate increased more. The dissolution rate of tenoxicam from the tablets prepared by freeze-drying at 1:2 molar ratio was fast, more than 80% was released within 15 min in gastric juice. All solid dispersion tablets prepared with β-CD at 1:2 molar ratio showed more rapid dissolution than commercial product. The formation of solid dispersion is an effective method for increasing the dissolution rate of poorly water soluble tenoxicam. β- CD was thought be a candidate carrier for solid dispersion.

[PE1-19] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Saturable Elimination of Tacrine from the Rat Cerebrospinal Fluid

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Tacrine is clinically used in the treatment of Alzheimer's disease. In this study, we have examined in vivo kinetics of elimination of tacrine from the cerebrospinal fluid to understand better the kinetics of tacrine in the brain. Sprague-Dawley rats were undergone a surgery involving catherterization of lateral ventricle (LV, drug administration) and cisterna magna (CM, CSF collection). Tacrine was administered via LV cannulae at the doses of 5, 25 or 125 ㎍ (in 5 ㎕). CSF (5 ml/sample) was collected at pre-determined times via the CM cannulae. Tacrine level in the CSF sample was assessed by an HPLC assay for tacrine. Clearance and volume of distribution of tacrine was estimated from the temporal profiles by the standard moment analysis. In some cases, phenol red was included in the injection mixture (dose, xx mg/rat) as a CSF volume marker. In all experimental condition, temporal profiles of tacrine concentration in the CSF were declined in a multi-exponential manner. Tacrine clearance from the CSF was 1970 ± 257 ㎕/min for 5 ㎍ dose. Since the reported bulk flow clearance ranges from 2-5 ml/min for rats, tacrine is apparently eliminated from the CSF via mechanism in addition to the bulk flow. Interestingly, apparent clearance for tacrine in CSF was decreased with dose, indicating that the elimination pathway, probably through the choroid plexus, the blood-CSF barrier, is saturable. Since Tacrine is not likely to be metabolized in the brain and, thus, saturable elimination from the CSF may represent a saturable efflux process for tacrine via choroids plexus.