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