[S10-2] [11/28/2005(Mon) 09:25-09:50/Gumoono Hall C]

Consideration of Physical and Biological Factors for Oral Drug Bioavailability

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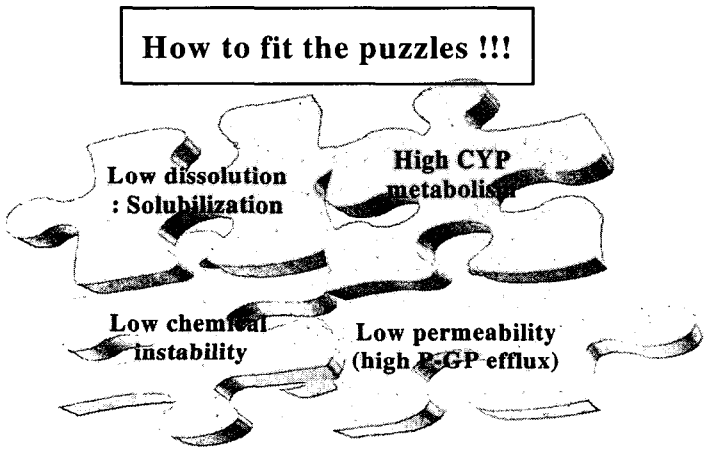
Bioavailability is defined as the rate and extent of drug to enter the systemic circulation in the body. When the dosage forms are administered, the drug bioavailability becomes decreased by experiencing the series of biological pathways such as low dissolution, chemical instability, low permeability, high P-glycoprotein efflux and the first pass metabolism in the gut. As a result, drug bioavailability is a function of various biological steps given as *f(BA) = f(sol) x f(chemical stability) x f(lymphatic absorption) x f(GI permeability) x f(P-GP efflux) x f(GI metabolism) x f(hepatic metabolism) x ·····x f(others)*. Therefore, controlling biological pathways like fitting puzzles is an important issue to get the smart drug products with good bioavailability as well as to satisfy regulatory guidelines and clinical benefits, depending on the physicochemical and biological properties of drugs as depicted below.

One of methods to overcome these physicochemical, biological and metabolic barriers is to efficiently utilize GRAS listed pharmaceutical excipients in the formulations. Pharmaceutical excipients are regarded as key ingredients not only to decide optimal dosage forms but also to change physicochemical properties of drugs and biological parameters. Therefore, pharmaceutical excipients such as surfactants, oils, fatty acids, solubilizers and stabilizers must be screened for their functionality and then selected at the early formulation stages to control bioavailability of drugs. The effectiveness and applications of these pharmaceutical excipients should be carefully decided according to their net contribution to the physicochemical properties of drugs and biological parameters.



In this study, contribution of various pharmaceutical excipients to dissolution, chemical stability

and hepatic metabolism in human liver microsomes of the various model drugs was widely described

Effect on dissolution rate-Sodium lauryl sulfate (SLS) and tween 80 in PVP solid dispersion increased the dissolution rate of aceclofenac but precipitation phenomenon was observed in the gastric fluid. Fatty oils and co-surfactants as emulsifying system prevented the precipitation of aceclofenac and resulted in nearly 100 % dissolution rate.

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Chemical stability-The solubility of simvastatin was highly improved by addition of pharmaceutical excipients. Simvastatin was very liphophilic and sensitive to chemical degradation. However, the cleavage of simvastatin to simvastatin acid was suppressed by addition of excipients, mainly cremophor EL and SLS. In case of rabeprazole-The degradation constant (K_b) was 0.0124 and 0.0463 min^{-1} when no pharmaceutical excipients were added. The chemical degradation of RPN highly protected when the pharmaceutical excipients were added. Poloxyl 20 cetyl ether showed a superior potentiality to protect chemical degradation of rabeprazole.

Hepatic metabolism in human liver microsomes-Hepatic metabolism of raloxifene only as a control was 41.02%. Inhibition of hepatic metabolism was observed when pharmaceutical excipients were added but varied as a function of concentration. Cremophor EL, sodium lauryl sulfate and polysorbate 80 showed dose-dependent inhibition of hepatic metabolism. Two UDPGA-dependent metabolite peaks [retention time: 4.0 min (MT2) and 7.8 (MT1)] were investigated using mass spectroscopy. The molecular weight of MT1 (MH^+ m/z = 650) was 176 units higher than RXH (MH^+ m/z = 474), indicating RXH-glucuronide. The fraction of nonenzymatic chemical degradation of olanzapine in phosphate and tris buffer at 37°C: for 120 min was insignificant, giving only 3.85 and 2.26%, respectively. The ratio of drug concentration and microsomal protein was an important factor for drug metabolism. The volume of organic solvent to dissolve drug appeared to be harmful against hepatic metabolism. When olanzapine (10 ppm) in 5 μl of methanol in the reaction mixture was incubated with 1.0 mg/protein of microsome for 120 min, over 20.3% olanzapine was enzymatically metabolized. Among five pharmaceutical excipients tested, Brij 97, span 20 and polysorbate 80 displayed significant inhibition of hepatic metabolism, giving 10.5, 8.3 and 6.8%, respectively when compared with control (20.3%). The polysorbate also inhibited hepatic metabolism in a dose dependent manner.

Chemical degradation rate of simvastatin was dependent on the buffer composition. The simvastatin was degraded about 80% at 0.1 M phosphate buffer, pH 7.4 and 50% in Tris buffer condition (0.06 M pH 7.4) when incubated at 37 °C for 60 min. However, when simvastatin was incubated with microsomal fraction, about 20% simvastatin was degraded. Of this degradable effect,

14% from enzymatic cleavage by CYP3A4, and 6% from chemical degradation were observed by examining chemical degradation in the presence of ketoconazole. The components of microsomal fraction such as Mg^{2+}, glycerol, fetal bovine serum and albumin were not the critical factors because chemical degradation of simvastatin was not blocked. Lipid-based components in microsomal fraction may be involved to protect chemical degradation of simvastatin by forming bilayered micelles or liposome. The hepatic metabolism of simvastatin was also changed by the pharmaceutical excipients. Moreover, SLS and PEG 4000 showed dose-dependent inhibition of hepatic metabolism.

In conclusions, the pharmaceutical excipients modified dissolution, chemical stability and hepatic metabolism of various drugs. The selection of proper pharmaceutical excipients could be a critical step at the early formulation approaches to control bioavailability of various low bioavailable drugs.

Acknowledgements: The work was partially supported by a grant of the Ministry of Science and Technology-NRL program (M1-0302-00-0080), South Korea.