 © The Authors

Poster Session 2 – Biopharmaceutics

114
Inhibition of CYP450 activity by Chinese herbal enhancers: in-vitro and in-vivo study

C.-J. Wang, L.-H. Pao* and Oliver O.-Y. Hu**

Tri-Service General Hospital, *School of Pharmacy and **Pharmaceutical Research Institute, National Defense Medical Center, P.O. Box 90048-508, NeiHu, Republic of China

To evaluate the effect of herbal enhancers on skin and liver cytochrome P450 activity, three herbal enhancers were examined in nude mice by in-vitro and in-vivo studies. In-vitro results showed that HUCHE044 (100 μM), HUCHE010 (100 μM), and HUCHE046 (100 μM) inhibited 7-ethoxyresorufin hydroxylase (EROD) activity by 99 ± 5.1%, 100 ± 2.5% and 97 ± 8.2%, respectively, in skin microsomes. HUCHE044 (100 μM) and HUCHE010 (100 μM) inhibited 7-methoxyresorufin hydroxylase (MROD) activity by 91 ± 6.5% and 82 ± 8.4%, respectively, in liver microsomes, while HUCHE046 (100 μM) had no significant inhibition on MROD activity. In addition, after transdermal treatment of mice with these herbal enhancers (4 mg kg^{-1}), mice were sacrificed and skin and hepatic microsomes were taken to analyse the EROD and MROD activity for skin and liver. Results demonstrated that HUCHE044, HUCHE010 and HUCHE046 inhibited EROD activity by 28 ± 14%, 76 ± 7.5% and 42 ± 17%, respectively, in skin microsomes, while they did not inhibit MROD activity in hepatic microsomes. Moreover, HUCHE010 and HUCHE046 suppressed cytochrome P4501A (examined by Mab 1-7-1 antibody) by 74% and 28%, respectively, in skin microsomes.

115
Caco-2 cell monolayer guided optimisation of an oral lipid formulation

B. Forbes, G. Ghibellini*, G. P. Martin and G. A. Magee*

Department of Pharmacy, King's College London, 150 Stamford Street, London SE1 9NN, UK and *GlaxoSmithKline R & D, Park Road, Ware, SG12 0DP, UK

Many therapeutically promising compounds are difficult to deliver on account of low intestinal permeability. Accordingly, the current trend is to predict the permeability of drug candidates early in the discovery/development process using Caco-2 cell monolayers. The scope for formulation to enhance epithelial permeability (compared with solubility) is debatable, but if permeability-enhancing strategies are to succeed, formulations should be optimised in–vitro before proceeding to time-consuming and expensive in-vivo studies. Caco-2 cells are not usually used to evaluate the permeability-enhancing potential of oral drug formulations. The aim of this study was to evaluate the use of cell-culture methodology for identifying the contribution of individual components of a lipid formulation to epithelial permeability enhancement.

Stat-Ease DX-5 software was used to produce an investigation of variable proportions of a potential permeability-enhancing formulation. Formulations comprising Tween 80 (5.25–8.5% w/v), capric acid (6.5–16% w/v), Capmul MCM (9–23% w/v) and caprylic acid (6.5–16% w/v) in a Miglyol 812 base were evaluated. The responses measured for each formulation (0.2% w/v in Hank's balanced salt solution) were surface tension, transepithelial electrical resistance (TER) of Caco-2 cell monolayers and solute flux across Caco-2 cell monolayers. Surface-tension measurements were made using the De Noüy ring method using a Kruss K12 tensiometer. Standard methods were used to culture Caco-2 cell monolayers on diffusion chamber inserts for 18 days and to evaluate the permeability modifying effects of the formulations (Delie & Rubas 1997). Formulations were applied to the apical surfaces of the cell monolayers and TER was measured after 15 min using an epithelial voltohmmeter. Incorporation of ^{14}C-mannitol in the formulations allowed transepithelial solute flux to be measured over 30 min.

Preliminary experiments indicated that 0.2% w/v of lipid formulation (equivalent to the dispersion of 500 mg of formulation in 250 mL intestinal fluid) was an appropriate concentration to use to produce discriminatory effects on monolayer permeability. The transport of mannitol was enhanced by up to 30 fold compared with control after application of the formulations and by approximately 10 fold by application of a reference formulation (Miglyol 812 65% w/v, Capmul MCM 23% w/v and Tween 80 12% w/v). An inverse relationship between mannitol permeability and TER was observed. However, no clear relationship was observed between the permeability-enhancing and surface-tension-lowering (detergent) effects of the formulations. Perturbation plots constructed using the StatEase software revealed fatty-acid composition to be primarily responsible for permeability-enhancing effects, whereas Capmul MCM had the greatest effect on surface tension. In conclusion, the combination of computer-assisted design with Caco-2 cell permeability allowed fatty acids to be identified as the important active components of a complex formulation.

Delie, F., Rubas, W. (1997) *Crit. Rev. Ther. Drug Carrier Syst.* **14**: 221–286