• 系統編號	RN9705-1018
• 計畫中文名稱	利用經個別皮膚的生化參數與基因多型性因子標準化之皮膚滲透係數以建構 滲透係數與結構特質之定量相關性 滲透係數與結構特質之定量相關性(III)
• 計畫英文名稱	Construction of Quantitative Structure Permeability Relationship (QSPR) with Skin Permeability Normalized to Biological Parameters/Genetic Polymorphism of Individual Skin (III)
• 主管機關	行政院國家科學委員會
• 計畫編號	NSC95-2320-B038-002
• 執行機構	台北醫學大學藥學系
• 本期期間	9508 ~ 9607
• 報告頁數	29 頁
• 使用語言	中文
• 研究人員	許明照 Sheu, Ming-Thau
• 中文關鍵字	滲透力; 滲透係數與結構關係式; 經皮水分散失
• 英文關鍵字	Permeability; QSPR; TEWL
• 中文摘要	由於皮膚滲透力(permeability)是描述滲透質經由皮膚吸收之效能的重要指標,所以藥物分子之皮膚滲透力常被用於評估藥物傳遞系統經由皮膚吸收的效力。而傳統結構與滲透力定量關係式(QSPR)是建立在以平均的皮膚滲透力與滲透質之分子量、正辛醇與水分配係數(Ko／w)之間的定量關係。本研究擬以 aspirin、diclofenacsodium、diflunisal、flufenamicacid、ibuprofensodium、ketoprofen、nabumetone、naproxen、piroxicam 和 tenoxicam 爲模式藥物進行體外穿皮實驗，計算其對個別鼠皮的皮膚滲透力以考慮到 BALB／nu 品系之裸鼠皮生理特性參數(經皮水分散失、皮膚水分含量、皮膚油脂含量、真皮層彈性纖維量及皮膚彈性係數)之可能影響性。而在 QSPR 建構模式除考慮分子量與正辛醇與水分配係數之外，進一步將模式藥物依照分子極性分爲兩群組(clogP 值小於 2 及 clogP 值大於 2)，分析探討藥物本身之分子量及分子極性與不同個體間皮膚結構差異性對於藥物皮膚滲透力之影響，並評估不同極性之模式藥物經由皮膚滲透吸收其可能的路徑與機制。實驗結果顯示，如只將本次研究所選用之十個模式藥物的分子量及分子極性與其體外穿皮吸收實驗所得之皮膚滲透係數進行回歸分析，證明本研究所獲得的皮膚穿透力數據具有足夠的可信度。若將上述 QSPR 方程式依照分子極性細分爲兩群組探討，再一併考慮皮膚生理特性參數對於皮膚滲透力的影響，兩群組模式藥物之 kp 預測關係式皆可證實，除了藥物分子量與分子極性會影響皮膚滲透力以外，本研究所探討五種皮膚生理特性之中，與藥物皮膚滲透力最爲相關的爲經皮水分散失數值，兩者均呈現正相關之關係；此外，在依不同極性模式藥物分組而建立的 kp 預估關係式中，藥物分子量皆呈現負相關影響而藥物分子極性皆呈現正相關影響，其中

clogP>2 之模式藥物受其分子特性的影響較 clogP<2 之模式 3 藥物更爲顯著。另一方面，藥物穿透過角質層的路徑主要分爲三種路徑：直接穿透過角質細胞(transcellular)、穿透角質細胞間隙脂質部分(intercellular)與經由皮膚器官吸收(transappendageal)；實驗結果顯示較爲親水性之藥物(clogP<2)其穿透角質層的路徑可能爲直接穿透過角質細胞，較爲親脂性之藥物(clogP>2)可能爲穿透角質細胞間隙的脂質組成部分。其原因可能爲在於 intercellular 滲透路徑多爲脂質緻密組成，而 transcellular 滲透路徑則爲親水性的纖維角質蛋白，因此經由 intercellular 路徑滲透的藥物其皮膚滲透力受到分子大小(分子量)與分子極性的影響較爲顯著。總結來說，分析探討皮膚的生理特性參數將有助於改善以藥物的分子特性所建構之 QSPR 模式的預測結果。

- 英文摘要

Skin permeability is used as a key parameter for describing the percutaneous transport of solutes, and as such, it is essential for designing and evaluating the efficacy of drug delivery system through the skin. Historically, quantitative structure-permeability relationships (QSPR) have been constructed between the average permeability coefficient (kp) of solutes through the skin and their molecular weight (MW) and octanol water partition coefficient, Ko／w. However, it was recognized that QSPR model evaluation should take into consideration of the possible impact of biological parameters of skin (transepidermal water loss (TWEL), hydration content, lipid content, resonance running time, and elasticity) on drug permeation and the permeation through different penetration routes in the skin for those drugs with different lipophilicity (calculated octanol-water partition coefficient, clog P) was influenced by various physicochemical factors of drug at different extent. In this study, the in vitro permeation study of ten model drugs divided into two groups (clog P < 2, ibuprofen sodium, diclofenac sodium, flufenamic aicd, aspirin and tenoxicam; and clog P > 2, ketoprofen, naproxen, piroxicam, nabumetone and diflunisal) through individual nude mice skin was examined to determine individual kp and the biological parameters for each individual skin were measured as well. The MW and clog P of model drugs and the biological parameters of skin all were then taken into consideration in the construction of QSPR model for individual kp. The preliminary results show that a simple relationship between the kp and the MW and clogP of ten model drugs was obtainable: 0.61). TEWL MW Both relationships demonstrate that except MW and clog P, TEWL was the only biological parameters of the skin was statistically examined to be positively influential at the similar extent on kp for both groups of model drug. The MW and clog P of drugs have the same negative and positive effects, respectively, on kp for two groups of drugs with clog P > 2 and clog P < 2, but the influential extent for the former greater than that for the latter. In terms of three main routes for drugs penetration through the stratum corneum: transcellular, intercellular and transappendageal route, hydrophilic drugs (clog P < 2) might be mainly transported through the transcellular pathway while lipophilic drugs (clog P > 2) through the intercellular pathway. It was reasoned that lipid compositions and integrity in the intercellular route might have greater influence on drug permeation in term of molecular size (MW) and lipophilicity than that for the transcellular route that was filled with hydrophilic and fibrous keratin. In conclusion, QSPR model evaluation for kp based on the lipophilicity of model drugs could be statistically improved with taking into consideration of the biological parameters of the skin.