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• 英文關鍵字	insoluble drugs；bioavailability；pharmaceutical parameter；pharmacokinetic characteristic；computer simulation
• 中文摘要	本研究計劃之目的在於探討藥劑學參數對於不同藥動學特質藥物的低生體可用率之提昇效果，以瞭解利用改善藥劑學參數以解決低口服生體可用率問題的可行性範圍以及藥動學參數的關鍵性影響因子。本計劃將先建立電腦模擬程式進行模擬計算，以比較探討藥劑學參數改善程度對於不同藥動學特質藥物之生體可用率的影響性，依此而做爲選擇藥物進行臨床驗證之依據。模擬的藥劑學參數包括溶解度改善與粒度大小及分布範圍等；而模擬的藥動學參數包括藥物的滲透係數 (permeability) 高低，於胃腸道的吸收模式 (absorption pattern) 差異，首渡代謝效應 (first-pass effect) 程度，以及吸收分布與排除常數大小。在本模擬中的顆粒分佈區分割爲 16 等份，以減少運算的時間而又不會失去模擬所要求的準確度。但由初步的模擬試驗結果顯示，爲使難溶性的藥物容易達到生體相等性，仍首要謹慎的控制藥物的溶解度和顆粒分佈的標準偏差這兩個因素。因此選用固定相同滲透係數與胃腸道吸收模式的藥物於相同的首渡代謝程度下進行模擬，而在交叉的生體相等性試驗模擬顯示，試驗藥物的溶解度必需落在文獻藥物溶解度的 75%-150%，才可通過生體相等性試驗。在溶解度，顆粒分佈和受試者差異之三因素的交叉生體相等性試驗結果，可以發現受試者的 inter-error 和 intra-error 是試驗藥物是否能通過生體相等性試驗的關鍵因素。另外，增加受試者的人數，確實能夠改善通過生體相等性試驗的百分比，且可改善 Cmax，Tmax 和 AUC 之間的變異程度。預期未來能驗證電腦模擬程式之預估能力，確認改善藥劑學參數對於生體可用率的影響程度與相關性，以提供國內廠商應用相關資訊於有效改善低生體可用率藥物之用，研發得到良好品質的學名藥產品，進一步提昇臨床治療的有效性。
• 英文摘要	The aim of the study was to explore the pharmaceutical factors improving the low bioequivalence of drugs with different pharmacokinetic

characteristics and to understand these possible critical factors for oral dosage forms containing drugs with low bioavailability. In this study, computer simulation was conducted to examine factors affecting bioequivalence and to compare the influence of those factors on the drugs with different pharmacokinetic property. The pharmaceutical factors examined included solubility, particle size and its distribution. On the other hand, the pharmacokinetic parameters compared involved permeability, absorption pattern, first-pass effect, absorption rate constant, and elimination rate constant. Results of preliminary simulation illustrated that 16 size fractions for a distribution was appropriately generated in the following simulation to reduce execution time of computer without sacrificing the accuracy of simulation. The preliminary simulation further demonstrated that the solubility and the standard deviation of a particle size distribution were two main factors that needed to be carefully controlled for a practically insoluble drug in order to achieve bioequivalence. Since that, a drug with the same permeability and absorption pattern was selected to conduct simulation at a constant extent of the first-pass effect. With the simulation of a cross-over design for bioequivalence study, drug solubility in test formulation must be in the range about 75-150% of drug solubility in reference formulation to pass bioequivalence test. Simultaneous influence of drug solubility, standard deviation, and inter- and intra-error of volunteer on the bioequivalence test was concluded that inter- and intra-error of volunteer was the critical factor to have a higher pass percentage for Cmax, Tmax, and AUC. Furthermore, the passing percentage of bioequivalence test could be improved by increasing the number of volunteer as a result of improving the variability for these three test criteria. In the future, we expect to verify the prediction of computer simulation program and to confirm the correlation between pharmaceutical factors and bioequivalence. Offering these information to the industry would improve the passing percentage of bioequivalence of drugs with low bioavailability, in addition to promote the effect of clinical therapy.