CS02-1 PBPK Modeling of Transport and Metabolism on Drug Absorption and Disposition: Conceptual Frameworks

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Physiologically based pharmacokinetic (PBPK) modeling approaches encompassing transporters and enzymes for intestine, liver and kidney models are introduced to examine drug absorption, metabolism and excretion. The traditional intestinal (TM) and the segregated flow (SFM, with separate flows to the enterocyte and serosal regions) intestinal models were combined with the liver, kidney, brain, the highly perfused, poorly perfused and adipose tissues for construction of whole body PBPK models. Tissue to blood partition coefficients were calculated according to the method of Rodgers and Rowland or obtained experimentally. Parameters were optimized with Scientist® or the commercially available simulator, Simcyp®, in PBPK models to examine the sequential metabolism of codeine to morphine and to morphine 3β glucuronide (M3G) in the rat and man and the intravenous disposition of digoxin in mice. In both cases, the SFM was superior over the TM in the description of drug absorption and sequential metabolism.