A KINETIC ANALYSIS OF DRUG RELEASE FROM AQUEOUS SOLUTIONS OF POLYSORBATES 20 AND 80

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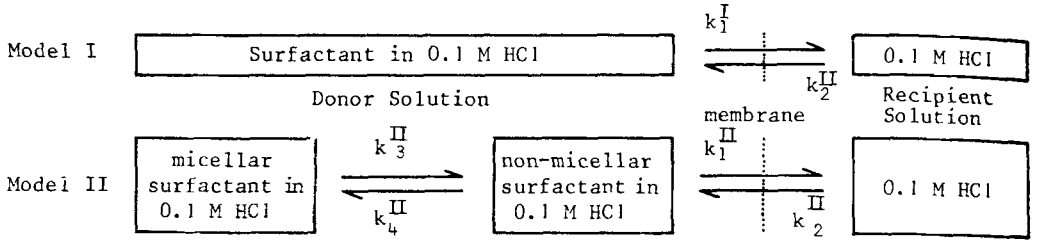
Interactions between solubilizates and aqueous solutions of non-ionic surfactants have been characterized previously using techniques such as solubility measurement and equilibrium dialysis. The technique of dynamic dialysis has been under utilized in such investigations probably due to difficulties in the analysis of the data. This report describes an attempt to characterize the interactions between salicylic acid and polysorbate solutions using a dynamic dialysis system and a statistical treatment of data based upon compartmental analysis.

A dialysis apparatus was used in which the donor cell contained polysorbate 20 or 80 in 0.1 M HCl and was separated by a semi-permeable membrane from a recipient cell. Salicylic acid was originally present only in the donor cell and then dialysis was allowed to proceed to equilibrium with the concentration of salicylic acid in the recipient solution being monitored continuously. Amongst the possible kinetic models that may be considered to describe the transfer processes in the terms of compartmental analysis are



Experimental data describing the increase in concentration of solubilizate in the recipient solution were fitted to each model. The 'best' fits were obtained using nonlinear least squares regression analysis (Metzler & others, 1974). In the case of model I it was expected and found that $k_1^I = k_2^I$ when the surfactant concentration was zero. When the surfactant was present in the donor cell it was found that $k_1^I \neq k_2^I$. However, systematic deviations from Model I were detected which were reduced when the data were fitted to Model II. The improvements were confirmed by F tests at the 95% significance level. Attempts have been made to fit the data to more refined compartmental models based upon the heterogeneity of micellar systems but, at this stage of the investigation, these models are not warranted from a statistical point of view. This study of the kinetics of transfer of salicylic acid supports the hypothesis that solutions of polysorbate 20 and 80 at concentrations over the range 1 to 5% $^w/_v$ in 0.1 M HCl do not behave as a single compartment from a kinetic point of view. Indeed significant improvements in the kinetic analysis were obtained if it was assumed that the surfactant solutions behave as if two compartments were present. The most probable interpretation of this conclusion is that the salicylic acid is distributed between micellar and non-micellar regions of the solution. In which case, the specific rate constants k_3^{II} and k_4^{II} refer to movement from, and to, the micellar region. If the micellar region of the surfactant solutions is regarded as a separate phase then distribution ratios may be obtained provided that relative quantities can be assigned to the two phases. Ratios obtained in this manner would provide alternatives to ratios obtained from equilibrium data for use in the estimation of fractions of solubilizate immediately available for absorption from micellar solutions in *in vivo* situations.

Metzler, C.M., Elfring, G.L. & Mc Ewen, A.J. (1974). A users manual for Nonlin and associated programs, The Upjohn Company, Kalamazoo, Michigan.