NONISOTHERMAL KINETICS APPLIED TO DRUGS IN PHARMACEUTICAL SUSPENSIONS

J.-O. Waltersson and P. Lundgren, Department of Galenical Pharmacy, Biomedical Center, University of Uppsala, Box 580, S-751 23 Uppsala, Sweden.

Studies on the stability of drug substances in aqueous suspensions are seldom reported in the literature. There are several problems connected with this type of study e.g. of experimental nature, complicated kinetic calculations due to the change in solubility with temperature, low degradation rates at moderate temperatures.

A simplified method for the determination of the chemical stability of drugs in pharmaceutical suspensions has been published (Tingstad et al 1973). We have developed a nonisothermal version of this method and this technique has been applied to the pseudo zero-order degradation of four different drugs in aqueous suspensions viz. acetylsalicylic acid, chloramphenicol, hydrocortisone and procaine penicillin G.

The suspensions were exposed to nonisothermal degradation within the temperature range of 40-90°C in buffer solutions (Waltersson & Lundgren 1982). The amount of drug degraded was plotted versus time. The change in slope of such a concentration-time-temperature curve reflects the increase in pseudo zero-order rate constant with increase in temperature. The rate constant at any particular time was calculated from the slope of the tangent to the curve at that time, obtained from the first derivative of the function (Waltersson & Lundgren 1982). Thus the pseudo zero-order rate constants at different temperatures during the nonisothermal run were obtained. The logarithms of these k_{obs}-values were plotted versus the reciprocal of the absolute temperature giving straight lines. The slopes of these lines are equal to $-(\Delta H_a + \Delta H_f)/2.303R$, where ΔH_a is the heat of activation and ΔH_f the heat of fusion (Tingstad et al 1973).

Using this simplified procedure the room temperature stability of a drug substance in suspension can be estimated from accelerated temperature studies without determining solubilities or first-order rate constants and thus can be performed within a days work.

From Table 1 it can be seen that the obtained results show no significant difference between available isothermal values and the nonisothermal ones obtained with the proposed method. One drawback, as in the case of hydrocortisone, is that for drug substances with very low water solubility, the nonisothermal degradation curve can not be obtained during one day.

Table 1. Stability results from degradation in aqueous suspension

Drug substance	$-\Delta H_a$ (kJ mol^{-1})	$-\Delta H_f$ (kJ mol^{-1})	$-(\Delta H_a + \Delta H_f)$[a] (kJ mol^{-1})	
Acetylsalicylic acid	70.6	27.1	108.7	112.7
Chloramphenicol	100.8	25.3	122.7	126.1
Hydrocortisone	65.3	19.5	-[b]	85.1
Procaine penicillin G	83.3	25.9	110.2	109.2

[a] Experimentally determined nonisothermal and isothermal values resp.;
[b] Not obtained within one day

Tingstad, J. et al (1973) J. Pharm. Sci. 62: 1361-1363
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