One manner in which different polymorphs are created is by way of recrystallizing them from different solvents, and at a point in time when sufficient quantities of material (and this need not be very much) are available, the preformulation scientist should undertake recrystallization from a series of solvents.

Knowledge of polymorphic forms is of importance in preformulation because suspension systems should never be made with a metastable form (i.e., a form other than the stable crystal form). Conversely, a metastable form is more stable than a stable modification, and this can be of advantage in dissolution [Eq. (9.11)].

6. VAPOR PRESSURE

In general, vapor pressures are not all that important in preformulation, but it should always be kept in mind that a substance may have sufficiently low vapor pressure to (a) become a lost to sufficient extent to cause apparent stability problems and content uniformity problems, and (b) exhibit a potential for interaction with other compounds and adsorption onto or sorption into package components (Pikal and Lukes, 1976).

Most drug substances are, substantially, not volatile. As an initial screen, it can be determined whether the drug is sufficiently volatile to cause concern, by placing a weighed amount of it in a vacuum desiccator and weighing it daily for a while. It is better to have a high-vacuum system for this, and the use of a vacuum electrobalance is best for this purpose. A good estimate of the vapor pressure can be obtained (Carstensen and Kothari, 1981) by using a pierced thermal analysis cell, placing it on a vacuum electrobalance, and monitoring the weight loss rate. A substance with known vapor pressure can then be used for calibration, the loss rates being proportional to the vapor pressures.

By using constant temperature TGA, graphs such as that shown in Fig. 8 will result. The weight rate (which should be established as due to evaporation of the compound) is given by

$$\frac{dW_a}{dt} = -kA'P_a \tag{9.15}$$

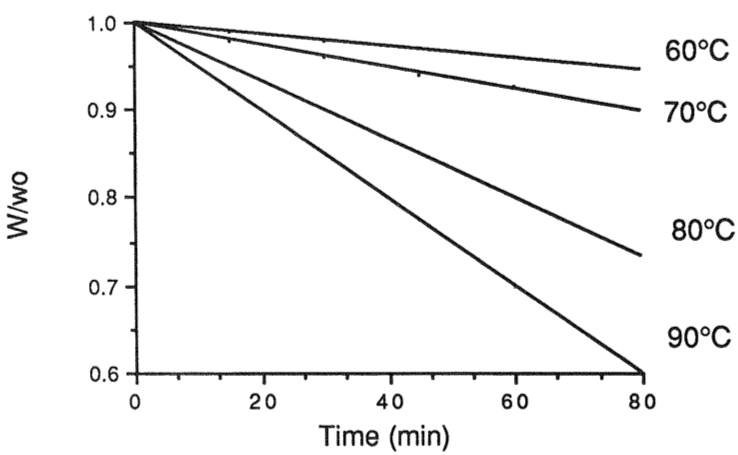

Fig. 8 Weight loss curves from constant temperature TGA.