ution rate constant (cm/s) can be obtained by Eq. (9.10), which under sink conditions (i.e., when C is less than 15% of S) becomes

$$C = \frac{SkA}{V}t \tag{9.12}$$

It has been suggested (Riegelman, 1979) that if k is obtained under sink conditions over a pH range of 1 to 8 at 37°C in a USP vessel by way of Eq. (9.12) at 50 rpm, then if the dissolution rate constant (kA/V) is greater than 1 mg min^{-1} cm^{-2}, the drug is not prone to give dissolution-rate-limited absorption problems. On the other hand, if the value is less than 0.1, such problems can definitely be anticipated, and compounds with values of kA/V of from 0.1 to 1 mg min^{-1} cm^{-2} are in a gray area. For compound selectivity it is frequently useful to express dissolution findings in terms of k (i.e., in cm/s).

For a small amount of powder, dissolution of the particulate material can often be assessed (and compared with that of other compounds) by placing the powder in a calorimeter (Iba et al., 1991) and measuring the heat evolved as a function of time. The surface area must be assessed microscopically (or by image analyzer), and the data must be plotted by a cube root equation (Hixson and Crowell, 1931):

$$1 - \left[\frac{M}{M_0}\right]^{1/3} = -\frac{2kS}{\rho r}t \tag{9.13}$$

where M is mass not dissolved, M_0 the initial amount subjected to dissolution, ρ true density, S solubility, and r the mean "radius" of the particle. The method is simply comparative, not absolute, because the hydrodynamics are different in the calorimeter from what it would be in a dissolution apparatus.

It is obvious that the dissolution rate is a function of the exposed surface area, but how this changes during dissolution is not quite obvious. Sunada et al. (1989) measured the change in surface area during dissolution of *n*-propyl-*p*-hydroxybenzoate and found dissolution rates proportional to surface area.

5.1. Solubility of Unstable Compounds

Quite often a compound is rather unstable in aqueous solution. Hence the long exposure to liquid required for traditional solubility measurements will cause decomposition, and the resulting solubility results will be unreliable. In this particular case Nogami's method may be used. If a solution experiment is carried out as a dissolution experiment with samples taken at equal time intervals, δ, it can be shown (Nogami et al., 1966) that when the amount dissolved at time $t+\delta$ is plotted versus the amount dissolved at time t, a straight line will ensure. The following relationship holds:

$$C(t+\delta) = S[1 - \exp(-k\delta)] + \exp(-k\delta)Ct \tag{9.14}$$

hence such a plot as shown in Fig. 7 will give k from the slope; inserting this in the intercept expression will give S. The advantage of the method is that it can be carried out in a short period of time, and reduce the effect of decomposition; the disadvantage is that it is not as precise as ordinary solubility determinations.