# 6

# Solid State Stability

**JENS T. CARSTENSEN**

*Madison, Wisconsin*

The stability of drugs in solid dosage forms is the most important, since solid dosage forms are more common than the other types, and because the first clinical trials are usually carried out in this type of dosage form.

The author was, for several years, in charge of the investigational stability program at Hoffmann-La Roche, Nutley, N.J., and in these years accumulated a feel for the manner in which such dosage forms behaved. Some of these behavior profiles were, at the time, explainable, others not. The ones not explainable formed the basis for a great deal of research in the university setting he later enjoyed.

The general pattern that emerges is that solid dosage forms decompose by either first- or zero-order profiles, after adjustment has been made for initial events. Before attempting to elucidate why, it is necessary to know what happens to a solid compound itself, when it is exposed to adverse storage conditions.

The 1993 ICH Stability Guidelines pay particular attention to the intrinsic stability of the drug substance, the bulk drug, as witnessed by the following lines of the Guidelines:

> DRUG SUBSTANCE
> General
> Information on the stability of the drug substance is an integral part of the systematic approach to stability evaluation (36–39).
> Stress testing helps to determine the intrinsic stability of the molecule by establishing degradation pathways in order to identify the likely degradation products (41–43).

They formally introduce the concept of a re-test period for a bulk drug substance:

> Primary stability studies are intended to show that the drug substance will remain within specifications during the re-test period if stored under recommended storage conditions (46–48).
> The degree of variability of individual batches affects the confidence that a future production batch will remain within specification until the retest date (124–126).
> A re-test period should be derived from the stability information (165).

This requires that this be done on at least three batches of raw material manufactured at a minimum of pilot scale level:

> Stability information from accelerated and long term testing is to be provided on at least three batches. The long term testing should cover a minimum of 12 months duration on at least three batches at the time of submission. The batches manufactured to a minimum of pilot plant scale should be by the same synthetic route and use a method of manufacture and procedure that simulates the final process to be used on a manufacturing scale.
> The overall quality of the batches of drug substance placed on stability should be representative of both the quality of the material used in pre-clinical and clinical studies and the quality of material to be made on a manufacturing scale. Supporting information may be provided using stability data on batches of drug substance made on laboratory scale.
> The first three production batches of drug substance manufactured post approval, if not submitted in the original Registration Application, should be placed on long term stability studies using the same stability protocol as in the approved drug application (50–64).

It is not only the chemical but also pertinent physical parameters that must be monitored, such as possible polymorphic transformations:

> The testing should cover those features susceptible to change during storage and likely to influence quality, safety and/or efficacy. Stability information should cover as necessary the physical, chemical ... characteristics (66–69).

It also addresses the formation of decomposition products and their limits, a point frequently elucidated through kinetics:

> Limits of acceptability should be derived from the profile of the material as used in the pre-clinical and clinical batches. It will need to include individual and total upper limits for impurities and degradation products, the justification for which should be influenced by the levels observed in material used in pre-clinical studies and clinical trials (73–77).

The length of the studies are tied in with the anticipated use of the bulk drug:

> The length of the studies and the storage conditions should be sufficient to cover storage, shipment and subsequent use. Application of the same storage conditions as applied to the drug product will facilitate comparative review (79–81).

The ICH 1993 Stability Guidelines recommend a minimum set of testing conditions. It emphasizes that one of the virtues of accelerated testing is to ascertain that the effects of "excursions outside the label storage condition" such as might occur during shipping, can be assessed.

| | *Conditions* | *Minimum Time Period at Submission* |
|---|---|---|
| ***Long term testing*** | 25°C±2°C/60% RH ±5% | 12 Months |
| ***Accelerated Testing*** | 40°C±2°C/75% RH ±5% | 6 Months |

Where 'significant change' occurs during six months storage under conditions of accelerated testing at 40°C±2°C/75 percent RH ±5 percent, additional testing at an intermediate conditions (such as 30°C±2°C/60% RH ±5%) should be conducted for drug substances to be used in the manufacture of dosage forms tested long term at 25°C/60 percent RH and this information included in the Registration Application. The initial Registration Application should include a minimum of 6 months data from a 12 month study. 'Significant change' at 40°/75 percent RH or 30°C/60 percent RH is defined as failure to meet specification.

The long term testing will be continued for a sufficient period of time beyond 12 months to cover all appropriate re-test periods, and the further accumulated data can be submitted to the Authorities during the assessment period of the Registration application.

The data (from accelerated testing or from testing at an intermediate condition) may be used to evaluate the impact of short term excursions outside the label storage conditions such as might occur during shipping (90–109).

The frequency of testing is also specified:

> Frequency of testing should be sufficient to establish the stability characteristics of the drug substance. Testing under the defined long term conditions will normally be every three months, over the first year, every six months over the second year and then annually (111–114).

The containers are assessed as well, but in this respect the effect of oxygen and moisture, as covered in the next chapter, are probably more à propos.

> The containers to be used in the long term, real time stability evaluation should be the same as or simulate the actual packaging used for storage and distribution (116–118).

The 1993 ICH Guidelines address the evaluation of data as well. It is noted here that it is necessary to attempt to establish the "degradation relationship", i.e., attempt to assess the mechanism of degradation:

> The nature of any degradation relationship will determine the need for transformation of the data for linear regression analysis. Usually the relationship can be represented by a linear, quadratic or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve (138–143).

There is the admission of limited extrapolation of data, but here again, it is necessary to know the degradation pattern:

> Limited extrapolation of the real time data beyond the observed range to extend expiration dating at approval time, particularly where the accelerated data supports this, may be undertaken. However, this assumes that the same degradation relationship will continue to apply beyond the observed data and hence the use of extrapolation must be justified in each application in terms of what is known about the mechanism of degradation, the goodness of fit of any mathematical model, batch size, existence of supportive data etc. (149—155).

The guidelines again emphasize the need for assessment of degradation products and "appropriate attributes":

> Any evaluation should cover not only the assay, but the levels of degradation products and other appropriate attributes (156–157).

Such "appropriate attributes" are most commonly, for a bulk drug substance, morphology, particle size, shape, and fractal dimension.

## 1. SIMPLEST DECOMPOSITION MODES OF PURE SOLIDS

If a solid is placed in a vacuum and exposed to temperatures at which it decomposes at a measurable rate, one of the following situations may arise:

I Solid → solid + solid
II Solid → solid + liquid
III Solid → liquid + liquid
IV Solid → solid + gas
V Solid → liquid + gas
VI Solid → gas + gas

Other schemes are theoretically possible, but not likely. Of the above, it is schemes IV and V which will be treated in some detail below, because they are the ones most investigated in the pharmaceutical sciences. It will later be shown that most pharmaceutical systems will not be of such a purist nature, but the experiences gathered from examining them will throw light on several important real-life situations.

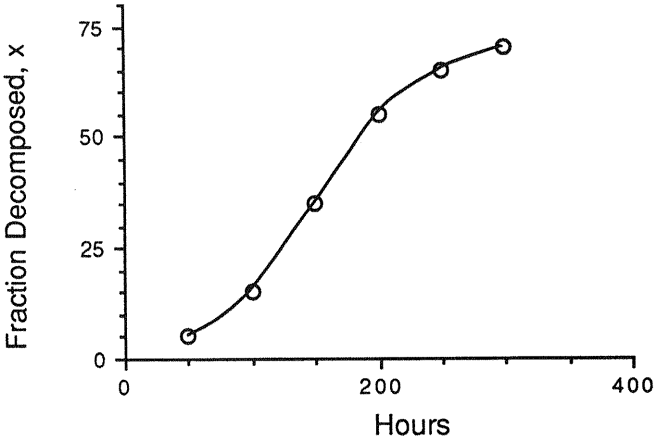


**Fig. 1** Decomposition of *p*-aminosalicylic acid at 65°C in vacuo. (Figure constructed from data by Carstensen and Pothisiri, 1975.)

## 2. THE SOLID TO SOLID + GAS REACTION

This reaction has been investigated by Prout and Tompkins (1944) and later by Kornblum and Sciarrone (1964) and Carstensen and Pothisiri (1975). A typical example of such a reaction is that of p-aminosalicylic acid, shown in Table 1 and Fig. 1. It is noticed that the profile is S-shaped. The general explanation for this type of reaction is the following:

No solid has a smooth surface, i.e., there are always surface imperfections. These could be "steps" in the surface or they could be crystal defects. These sites are more energetic than the remaining sites. They are most likely to occur at surfaces, which in any event are populated with molecules that are unlike the molecules in the bulk of the crystal. For instance they have at least one less neighbor than bulk molecules. It is assumed that decomposition is more likely to occur at such "activated" sites (Fig. 2).

Once a molecule decomposes at an activated site it changes its geometry, and hence the neighboring molecules are more likely to decompose. There will then be a chain or plane of activated molecules forming, with a probability of $a$ (second figure in Fig. 2). The rate of formation of activated molecules, $N$ in number at time $t$, is $dN/dt$, and this is proportional to $N$. Initially this is then given by

$$\left[\frac{dN}{dt}\right]_0 = a \cdot [N + N_0] \tag{6.1}$$

**Table 1** Decomposition of *p*-Aminosalicylic Acid

| Time (hours) | 0 | 50 | 100 | 150 | 220 | 260 | 325 |
|---|---|---|---|---|---|---|---|
| Percent decomposed | 0 | 4 | 18 | 36 | 60 | 70 | 77 |

*Source*: After Carstensen and Pothisiri, 1975.

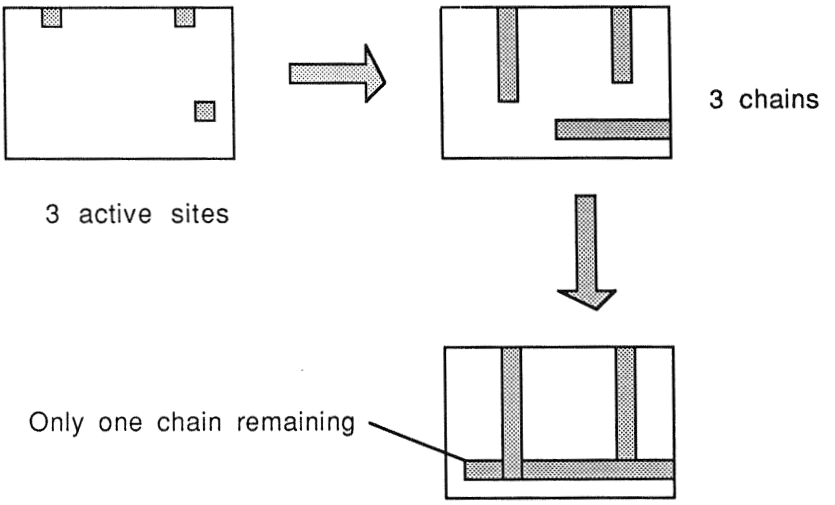


**Fig. 2** The propagation of active site chains from three surface sites.

It is obvious that after even a short period of time $N$ becomes much larger than $N_0$, so that this latter can be dropped at times even remotely larger than zero.

After a certain while (last figure in Fig. 2), planes will start to merge, and hence there will be a termination probability, $b$, so that at measurable times, Eq. (6.1) becomes

$$\frac{dN}{dt} = \{a - b\}N \tag{6.2}$$

Both $a$ and $b$ are functions of $t$ (or what is equivalent, to the fraction decomposed $x$). It is reasonable to assume that

$$a = b \quad \text{at} \quad t = t_{1/2} \quad (\text{or } x = 0.5) \tag{6.3}$$

i.e., at the point in time where one half of the substance has decomposed. Also,

$$b = 0 \quad \text{at} \quad t = 0 \quad (\text{or } x = 0) \tag{6.4}$$

since there can be no termination probability at time zero. One (not necessarily the correct) function which satisfies this condition is

$$b = 2xa \tag{6.5}$$

When this is inserted into Eq. (6.2) one obtains

$$\frac{dN}{dt} = a[1 - 2x] \cdot N \tag{6.6}$$

The decomposition rate, $dx/dt$, is proportional to $N$, i.e., $dx/dt = k \cdot N$ or

$$N = \frac{1}{k}\frac{dx}{dt} \tag{6.7}$$

Equation (6.6) can now be written

$$\frac{dN}{dt} = \frac{a}{k}[1 - 2x]\frac{dx}{dt} \tag{6.8}$$

Chain differentiation of $dN/dt$ gives

$$\frac{dN}{dt} = \frac{dN}{dx}\frac{dx}{dt} \tag{6.9}$$

Introducing Eq. (6.8) into Eq. (6.9) gives

$$\frac{dN}{dt} = \frac{dN}{dx}\frac{dx}{dt} = \frac{a}{k}[1 - 2x]\frac{dx}{dt}$$

$dx/dt$ is cancelled out of the last part of this equation to give

$$\frac{dN}{dx} = \frac{a[1 - 2x]}{k} \tag{6.10}$$

which integrates to

$$N = \frac{a}{k}(x - x^2) \tag{6.11}$$

Equation (6.7) is now introduced to give

$$\frac{1}{k}\frac{dx}{dt} = \frac{a}{k}x(1 - x) \tag{6.12}$$

which integrates to

$$\ln\left[\frac{x}{1 - x}\right] = a(t - t_{1/2}) \tag{6.13}$$

The equations have a zero time problem, since the equation is not defined for $x = 0$. This is a consequence of neglecting $N_0$. Similar paradoxes exist in the scientific literature. The Gibbs adsorption isotherm, for instance, is not defined for $C = 0$, i.e., liquid without surfactant. In the case of solid state stability, it might be thought of in the vein, that as the material is being produced, i.e., at time zero (e.g., through recrystallization), it is already decomposing (however little).

*Example 6.1.*

A set of decomposition data for a sample of a 5.52 mmoles of a solid are as shown in Table 2. Obtain the rate constant and the value of $t_{1/2}$.

*Answer.*

The transformation of data into the form of Eq. (6.13) is shown in Table 3. These data are plotted in Fig. 3. The least squares fit of the line according to Eq. (6.13) is

$$\ln\left[\frac{x}{1 - x}\right] = 0.868(t - 4) \tag{6.14}$$

**Table 2** Prout–Tompkins Data at 55.6°C

| Time | 0 | 1 | 2 | 3 | 4 | 4.5 | 5 |
|---|---|---|---|---|---|---|---|
| Gas (mmoles) | 0 | 0.48 | 0.86 | 1.56 | 2.77 | 3.71 | 4.96 |

**Table 3** Data in Table 4.2 Treated According to Eq. (6.13)

| Time | 0 | 1 | 2 | 3 | 4 | 4.5 | 5 |
|---|---|---|---|---|---|---|---|
| Gas (mmoles) | 0 | 0.48 | 0.86 | 1.56 | 2.77 | 3.71 | 4.96 |
| $x$ | 0 | 0.087 | 0.155 | 0.28 | 0.50 | 0.668 | 0.893 |
| $\ln[x/(1-x)]$ | | −1.75 | −1.17 | −0.58 | 0 | 0.291 | 0.581 |

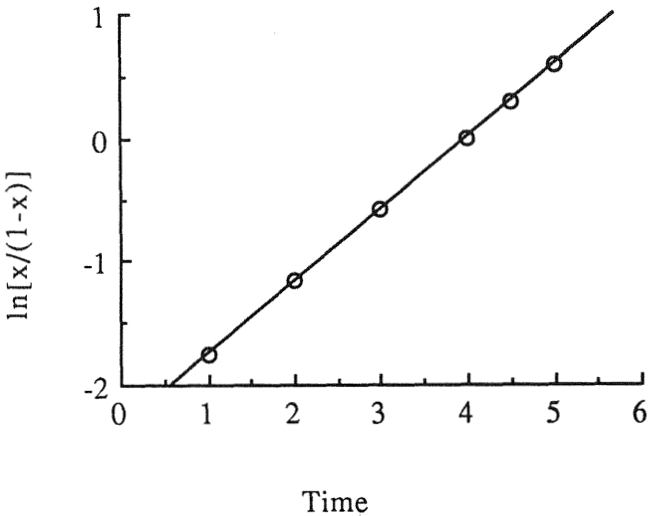


**Fig. 3** Data from Table 2 plotted according to Eq. (6.13). The least squares fit is $\ln[x/(1-x)] = -2.334 + 0.5832t$ with an $R$ value of 1.00.

This type of reaction embodies the dehydration of solid hydrates. Leung et al. (1998a,b) have shown that aspartame 2.5 hydrate cyclizes by Prout–Tompkins kinetics and that the rate constants follow an Arrhenius equation.

## 3. TEMPERATURE DEPENDENCE OF THE SOLID TO SOLID + GAS REACTION

The rate determining parameter in Eqs. (6.12) and (6.13) is $a$. In general, activation energies encountered in pharmaceutical systems are between 15 and 30 kCal/mole. However, the parameter $a$ is a stoichiastic parameter and is not necessarily of this order of magnitude. Figure 4 shows the data from Table 3 extended to several temperatures. The least squares equation for the Arrehenius plot is

$$\ln[a] = 83.553 - 28.42\frac{1000}{T} \tag{6.15}$$

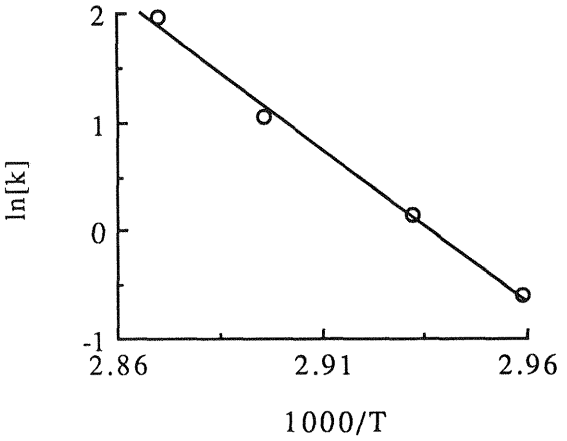


**Fig. 4** Arrhenius plot of $a$ values from data of the type shown in Table 2 carried out at 65 (Table 2), 68, 72, 75°C. Least squares fit: $\ln[k] = 83.553 - 28.421\{1000/T\}$ with $R = 0.997$.

and it is seen that $E_a/R = 28.42$ kCal, i.e., $E_a$ is about 57 kCal. In most solid to solid + gas reactions the activation energy will be excessively high (up to 80 kCal/mole). This means that the decomposition will occur at a measurable rate over a narrow temperature range, $T_1$ to $T_2$. Below $T_1$ it is too slow to allow detection of the entire curve in a reasonable length of time, and above $T_2$ it is too fast to measure with precision. In the data in Fig. 4 the rate constants increase 10-fold in a 10° span. $T_1 - T_2$ is frequently denoted a *decomposition range*, under melting point, in chemical tables.

It should be pointed out that the solid to solid + gas reaction may be so only over a certain temperature range, or to a certain degree of decomposition. Fig. 5 shows the eutectic diagram of a compound with its solid decomposition product.

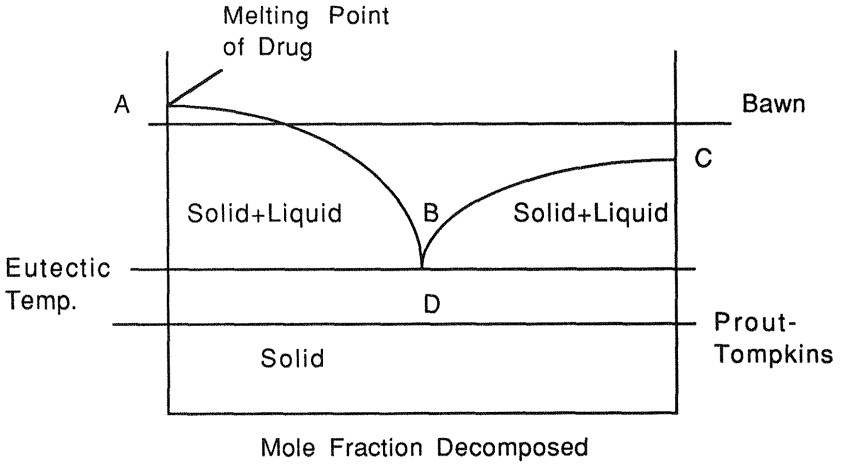


**Fig. 5** Binary melting point diagram showing areas where Bawn kinetics apply and where Prout–Tompkins kinetics apply.

If the study is carried out at temperatures below the eutectic temperature, $T^*$, then the reaction will be solid to solid + gas. If above the eutectic temperature, then the reaction will be solid to solid + liquid + gas. The compounds reported in literature to be of the solid to solid + gas type are most often inorganic salts, e.g., potassium permanganate (Prout and Tompkins, 1944), silver permanganate (Goldstein and Flanagan, 1964), and some organic compounds, such as oxalic acid and *p*-aminosalicylic acid (Kornblum and Sciarrone, 1964; Pothisiri and Carstensen, 1975; Carstensen and Pothisiri, 1975).

Olsen et al. (1997) showed cefaclor monohydrate to decompose (as judged by related substances) by first-order kinetics. The rate constants could be plotted by Arrhenius plotting and were consistent with ambient rate constants. The reaction scheme, when amorphous material was present, was such that the rates were faster at early time points and then became equal to those of the crystalline modification. The conclusion was that the initial phase was decomposition of amorphous content parallel to conversion of amorphous to crystalline drug.

At times the solid state reaction cannot be completely specified yet can be descried in analytical terms. Tzannis and Prestrelski (1999) described the effect of sucrose on the stability of trypsinogen during spray-drying by plotting denaturation temperatures as a function of melting temperature and found a linear increase between residual activity after spray-drying and melting temperature. Adler and Lee (1999) have reported on the stability of lactate dehydrogenase in spray-dried trehalose.

## 4. THE SOLID TO LIQUID + GAS REACTION

Many more compounds seem to decompose by this reaction scheme than by the solid to solid + gas. The reaction kinetics are usually referred to as Bawn kinetics (Bawn, 1955). This situation at time $t$ is as shown in Fig. 6, and as seen there will be a certain amount of liquid decomposition product. This amount corresponds to the amount of drug decomposed. However, the liquid decomposition product will dissolve parent compound to the extent, S (mole drug/mole decomposition product), to which it is soluble, so that the amount present in the solid state at time $t$ is the original number of moles, $A_0$, minus the amount decomposed, $A_0x$, minus the amount dissolved, $A_0Sx$.

The rate of decomposition would be the sum of the rates of decomposition in the solid state (assumed first order with rate constant $k_s$, time$^{-1}$ and in the dissolved state (assumed first order with rate constant $k_1$ time$^{-1}$. The rate equation, hence, is

$$\frac{dA}{dt} = -k_s[A_0(1-x) - A_0xS] - k_1[A_0xS] \tag{6.16}$$

Noting that

$$\frac{A}{A_0} = (1-x) \tag{6.17}$$

it follows, by division through by $A_0$, that

$$\frac{d(1-x)}{dt} = -k_s[1-x-xS] - k_1xS \tag{6.18}$$

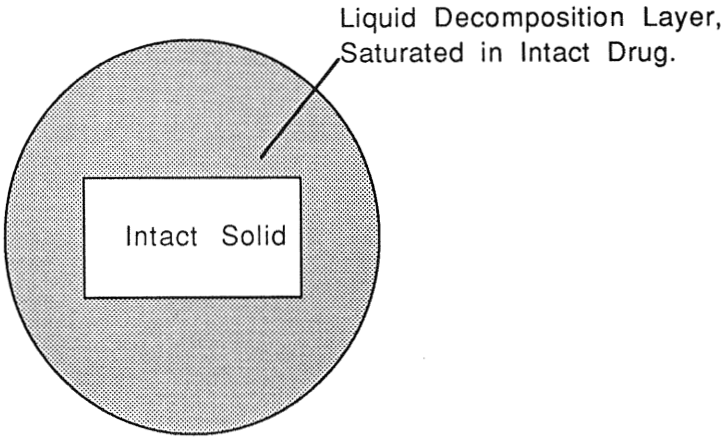


**Fig. 6** Situation leading to Bawn kinetics.

or, noting that $d(1-x) = -dx$,

$$\frac{dx}{dt} = k_s[1 - x - xS] - k_1 Sx = k_s[1 + Bx] \tag{6.19}$$

where

$$B = \frac{k_1}{k_s} - 1 - S \tag{6.20}$$

Eq. (6.19) can be integrated, and it then yields

$$\ln[1 + Bx] = Bk_s t \tag{6.21}$$

Using $B$ as an adjustable parameter, it is possible to find the value that makes the data profile through the origin, as dictated by Eq. (6.21), and also gives the best fit.

Figure 7 and Table 4 show an example of data from decomposition of *p*-methylaminobenzoic acid.

To plot this according to Eq. (6.21) it is necessary to assume values of $B$, plot the data, and assess the goodness of fit by some criterion. A different value of $B$ is then chosen, and this process is repeated until a "best" value of $B$ is arrived at. It can be shown that in general the sums of the squares of the deviations $[s^2_{yx} = \Sigma(y - \hat{y}\backslash\text{wedge})^2/(n-2)]$ of the points from the ensuing line can be used as a criterion. A different criterion is the correlation coefficient. In many cases this is also *not* a good criterion, and criteria for linearity (e.g., Durbin–Watson statistics) are the best. With data fitting to Eq. (6.21), the line must pass through the origin. Fitting the data in this fashion is shown in the table for three values of $B$ (0.1, 0.85, and 2.0). It is, of course, best to do this by computer, and a simple program in BASIC is shown in Table 5.

The number of data points are inserted, the assumed value of $B$ is inserted, and the program is run. One can then in three or four tries arrive at a "best" value for $B$.

In the case of Eq. (6.21), using the correlation coefficient is not a good parameter, because it simply increases with increasing values of $B$ up to a very high

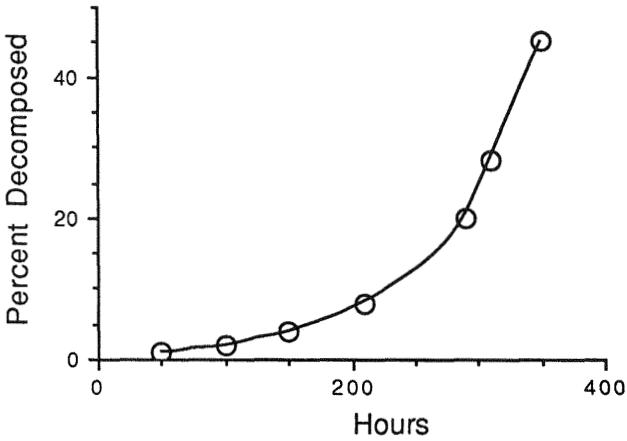


**Fig. 7** Data from Table 4. Decomposition of *p*-methylaminobenzoic acid. (Graph constructed from data published by Carstensen and Musa, 1972.)

**Table 4** Decomposition Data for *p*-Methylaminobenzoic Acid

| Time (h) | 0 | 50 | 110 | 150 | 210 | 290 | 310 | 350 |
|---|---|---|---|---|---|---|---|---|
| % Decomposed | 0 | 1 | 2 | 4 | 8 | 20.5 | 27.9 | 45 |

(unrealistic) value and also results in a very high intercept (see Table 6). All the correlation coefficients are good. The best criterion would be a criterion that dealt with curvature, but a simpler one, as stated, is simply to note the intercept, which should be zero (see Fig. 8).

Studies of this type are usually done on a vacuum rack. In this, the pressure is monitored as a function of time, and the sample can be observed. At a given point in time (which is quite reproducible), the last trace of solid will disappear. At this point in time, $t^*$, the amount not decomposed, $A_0(1-x)$, is just sufficient to dissolve the amount of liquid, $A_0x$, present, i.e., at time $t^*$:

$$S = \frac{1 - x^*}{x^*} \tag{6.22}$$

where $x^*$ is the mole fraction decomposed at time $t^*$. Therefore Eq. (6.21) is valid from time 0 to time $t^*$. If $t^* = 350$ (as in the example used here), and $x^* = 0.45$ at this point, it follows that

$$S = \frac{0.55}{0.45} = 1.22 \text{ moles/mole} \tag{6.23}$$

The slope in the above case is 0.01 $h^{-1}$. Since the slope is $[B \cdot k_s]$ it follows that

$$k_s = \frac{\text{slope}}{B} = \frac{0.01}{0.85} = 0.012 \text{ h}^{-1} \tag{6.24}$$

**Table 5** Program for Obtaining Best Values by Manual Iteration

```
100  PRINT "Type in data as x,y, in 400 block"
110  INPUT "Number of Data Points=";N1
120  INPUT "Iteration Parameter, B=";B
130  PRINT "T";SPC(6);"X";SPC(6);"LN(1+BX)
140  PRINT "----------"
200  READ A, C
210  X=A
220  Y=LOG(1+B*C)
230  X1=X1+X
240  X2=X2+(X^2)
250  Y1=Y1+Y
260  Y2=Y2+(Y^2)
270  Z1=Z1+(X*Y)
280  N2=N2+1
300  PRINT X;SPC(6);C;SPC(6);Y
310  IF N2=N1 goto 700
400  DATA 50,1
410  DATA 100,2
420  DATA 150,4
430  DATA 210,8
440  DATA 290,20
450  DATA 310,28
460  DATA 350,45
700  Z2=X2-((X1^2)/N2)
710  Z3=Y2-((Y1^2)/N2)
720  Z4=Z1-(X1*Y1/N2)
730  Z5=Z4/Z2
740  Z6=(Y1-(Z5*X1))/N2
750  PRINT
760  PRINT "Slope="; Z5
770  PRINT "Intercept="; Z6
780  Z7=(Z4^2)/(Z3*Z2)
790  Z8=(Z7)^(0.5)
800  PRINT "Correlation Coefficient=";Z8
810  Z9=(Z3-((Z5^2)*Z2))/(N2-2)
820  PRINT "syx^2=";Z9
```

$k_1$ is now calculated from Eq. (6.20):

$$0.86 = \frac{k_1}{0.012} - 1 - 1.22 \tag{6.25}$$

i.e.

$$k_1 = 3.08 \times 0.012 = 0.037\ \text{h}^{-1} \tag{6.26}$$

Beyond $t^*$ the system is a solution system and should decompose by first-order kinetics. The density of the liquid will actually change with time, but it is assumed that both parent drug and decomposition product have approximately the same

**Table 6** Data in Table 5 Treated by Eq. (6.21)

| | $\ln[1+Bx]$ | | |
|---|---|---|---|
| Time (h) | $B=0.1$ | $B=0.85$ | $B=2$ |
| 50 | 0.095 | 0.615 | 1.099 |
| 100 | 0.182 | 0.993 | 1.610 |
| 150 | 0.334 | 1.481 | 2.200 |
| 210 | 0.588 | 2.054 | 2.830 |
| 290 | 1.099 | 2.890 | 3.710 |
| 310 | 1.335 | 3.210 | 4.040 |
| 350 | 1.705 | 3.677 | 4.510 |

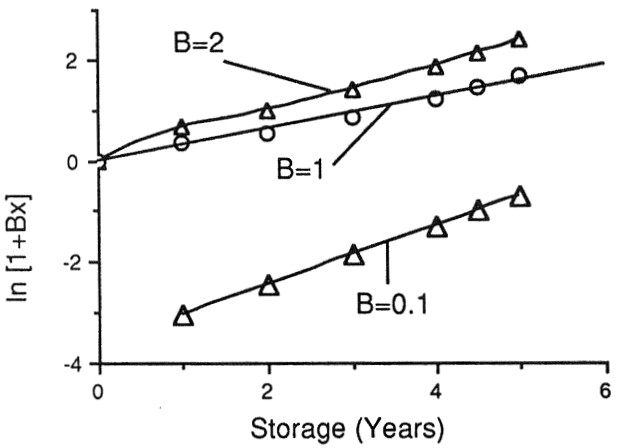


**Fig. 8** Data from Table 4 treated by Eq. (6.21).

density. The common density is denoted $\rho$, and since there is a total number of $A_0$ moles, the volume of liquid is $A_0\rho$. The initial molar concentration (at time $t^*$) is, therefore, $A_0(1-x*)/[A_0/\rho] = (1-x*)/\rho$. The time is counted from $t=t^*$ and the concentration at time $t-t^*$ is $(1-x)/\rho$, so that

$$\ln\left[\frac{1-x}{\rho}\right] = -k_1 t + \ln\left[\frac{1-x^*}{\rho}\right] \tag{6.27}$$

or

$$\ln\left[\frac{1-x}{1-x^*}\right] = -k_1(t-t^*) \tag{6.28}$$

or

$$x = 1-(1-x^*)e^{-k_1 t} \tag{6.29}$$

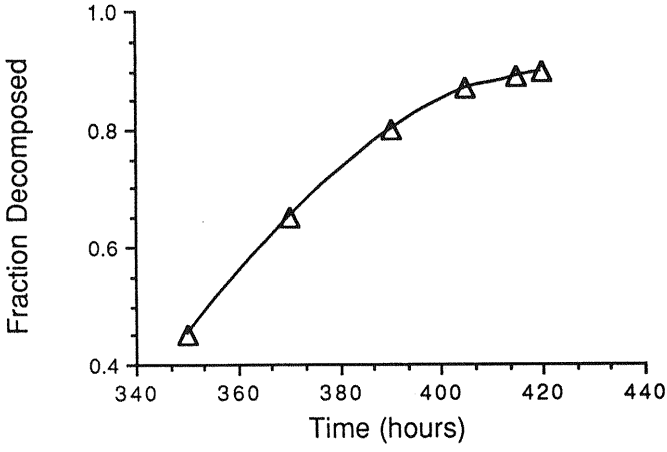


**Fig. 9** Decomposition of *p*-methylaminobenzoic acid after $t^*$ (350 hours) at which point $x = 0.45$ (i.e., $1 - x = 0.55$, as used in Fig. 10). (Graph constructed from data published by Carstensen and Musa, 1972.)

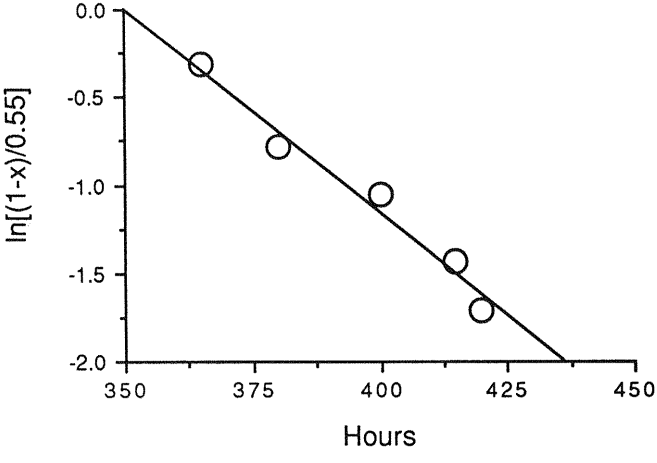


**Fig. 10** Data in Fig. 9 treated according to Eq. (6.28). (Graph constructed from data published by Carstensen and Musa, 1972.)

Data of this type, for *p*-methylaminobenzoic acid, are presented in Figs. 9 and 10. It is seen that the data are quite first order. The first-order rate constant obtained from this plot is $k_1 = 0.040\ \text{h}^{-1}$ in quite good agreement with the value of 0.037 found from the first part of the curve.

When the total curve is plotted (i.e., when Fig. 7 and Fig. 9 are combined), then an S-shaped curve results. Unlike the Prout–Tompkins curve, the Bawn curve is a two-phase curve, one part relating to the phase where there is solid present, the other to the part where all solid has dissolved.

The values of $x^*$ obtained at $t^*$ will differ from temperature to temperature, since the solubility is a function of temperature. This is actually the value of the

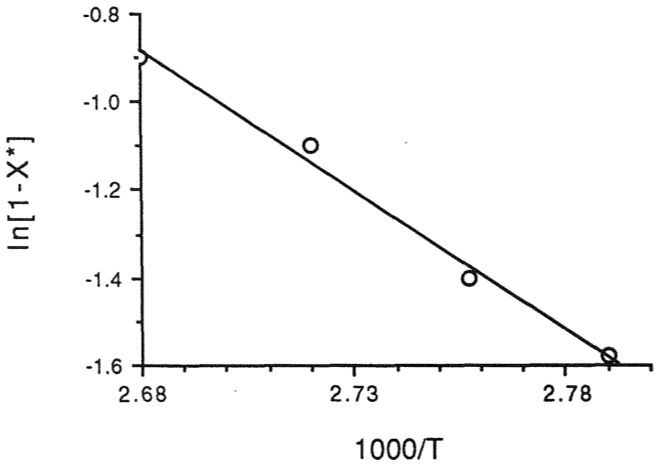


**Fig. 11** $\ln[1-x^*]$ as a function of $1000/T$. Least squares equation: $y=16.19-6.37x$ ($R=1.00$). (Graph constructed from data by Carstensen and Kothari, 1983.)

liquidous line on a eutectic diagram. The melting point depression curve (Maron and Prutton, 1965) is given by

$$\ln(1-X^*)=\frac{\Delta H}{R}\left[\frac{1}{T_f}-\frac{1}{T}\right] \tag{6.30}$$

Such plots are quite linear, as shown in Fig. 11.

## 5. THE NG EQUATION

Ng (1975) suggested the following global equation for solid state decomposition:

$$\frac{dx}{dt}=x^n(1-x)^p \tag{6.31}$$

As pointed out earlier, a modification of this equation is

$$\ln\left\{\frac{x^n}{(1-x)^p}\right\}=-k'(t-t_i) \tag{6.32}$$

which may be written as

$$\ln\left\{\frac{x^q}{1-x}\right\}=-k(t-t_i) \tag{6.33}$$

where

$$k=\frac{k'}{p} \tag{6.34}$$

and

$$q = \frac{n}{p} \tag{6.35}$$

## 6. TOPOCHEMICAL REACTIONS

There are theories akin to the above, which simply, empirically state that (a) decomposition starts at the surface of the solid and works inwards. If, for instance, the solid were a cube originally with side $a_0$ cm, then, after a given time the side length, $a$, would be

$$a = a_0 - kt \tag{6.36}$$

i.e., it is assumed that the decomposition "front" progresses in a linear fashion. This is akin to physical phenomena such as crystal growth (the so-called McCabe law). At time $t$ there will, therefore, be an amount undecomposed given by

$$N\rho a^3 = N\rho[a_0 - kt] \tag{6.37}$$

where $N$ is the number of particles in the sample and $\rho$ is the density of the solid. The original volume of the solid was $Na_0^3$, so that the fraction not decomposed, $x$, would be given by

$$x = \frac{N\rho a^3}{[N\rho a_0]^3} = \left[\frac{a}{a_0}\right]^3 = \left[1 - \left(\frac{k}{a_0}\right)t\right]^3 \tag{6.38}$$

It is noted from Eq. 38 that the rate constant $(k/a_0)$ is particle size dependent. This property will be touched on frequently in the following.

An example of this type of decomposition pattern is aspirin in an alkaline environment (Nelson et al., 1974). This is shown in Fig. 12.

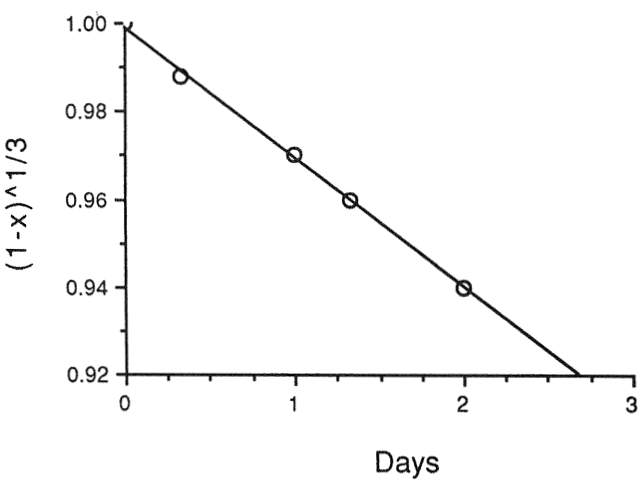


**Fig. 12** Decomposition of aspirin in alkaline environment. Least squares fit: $y = 1.0 - 0.0295x$ ($R = 1.00$). (Graph constructed from data by Nelson et al., 1974.)

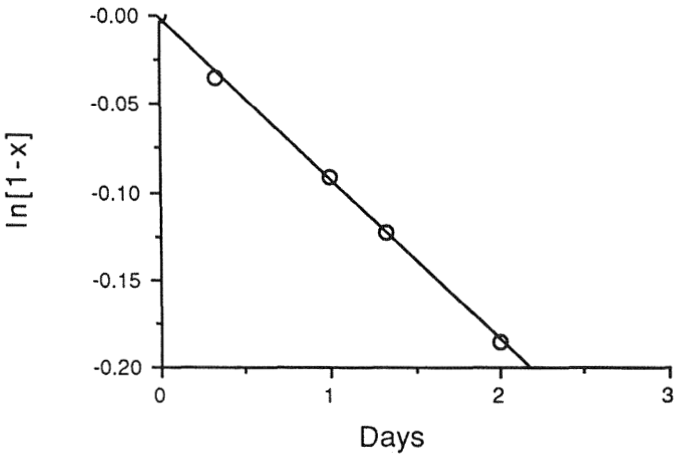


**Fig. 13** Data in Fig. 12 treated as first order.

In general it is not possible to distinguish between a reaction of the type described by Eq. 38 and a first-order reaction. Only with excellent precision, with a fairly large number of assays, and with a sufficiently large decomposition will it be possible to distinguish between the two. The data in Fig. 12 are shown treated as first order in Fig. 13.

## 7. DIFFUSION CONTROLLED INTERACTIONS

Figure 14a shows a situation where a solid, A, is in contact with another solid, B. The contact area is assumed to be 1 $cm^2$. It is assumed that A can react with B in this situation, i.e.,

$$A + B \rightarrow C \tag{6.39}$$

As the reaction proceeds (Fig. 14b), decomposition product, C, will accumulate between A and B, and at a given time $t$, compound A must diffuse to the surface of compound B through a layer of compound C, $h$ cm thick, in order for the reaction to take place. The density of B is denoted $\rho$. A layer of B $h$ cm thick would contain $h\rho$ g of B, and hence

$$\frac{dB}{dt} = D\frac{dh}{dt} \tag{6.40}$$

By Fick's first law, $dB/dt$ is inversely proportional to $h$, so that we may write

$$\rho\frac{dh}{dt} = \frac{q}{h} \tag{6.41}$$

or

$$h \cdot dh = \left[\frac{q}{\rho}\right]dt \tag{6.42}$$

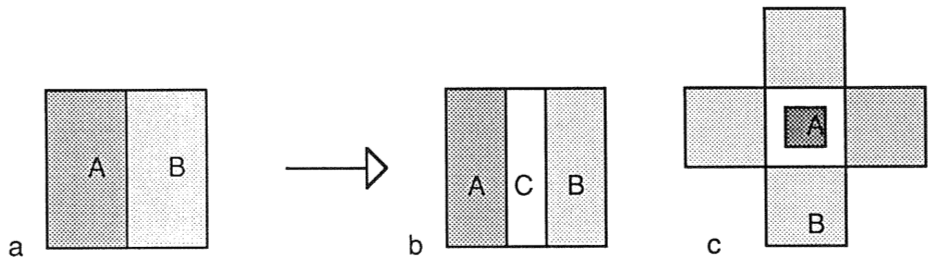


**Fig. 14** Stages in Jander kinetics.

This may be integrated to

$$h^2 = \left[\frac{2q}{\rho}\right] t = k't \tag{6.43}$$

or

$$h = [k't]^{1/2} \tag{6.44}$$

where $k' = 2q/\rho$. If, as shown in Fig. 14, A and B are cubical, of side length $a_0$ initially, and a at time $t$, and if B is surrounded by A as shown, then

$$h = a_0 - a \tag{6.45}$$

The amount retained at time $t$ is

$$\begin{aligned}(1-x) &= \left[\frac{a}{a_0}\right]^3 = \left[\frac{a_0 - a_0 + a}{a_0}\right]^3 \\ &= \left[1 - \frac{h}{a_0}\right]^3 = \left[1 - \frac{\{kt\}^{1/2}}{a_0}\right]^3\end{aligned} \tag{6.46}$$

or

$$\{1 - (1-x)^{1/3}\}^2 = \frac{kt}{a_0^2} \tag{6.47}$$

where $x$ is fraction decomposed. It is seen that the rate constant is related to the particle size, i.e., the finer the particles the larger the rate constant. A system of this type is, again, the aspirin–sodium bicarbonate system, but at lower temperatures. At higher temperatures, the autodecomposition of aspirin is higher than the diffusion coefficient (related to $q$), and the reaction at higher temperatures then follows Eq. (6.40) (Nelson et al., 1974).

Recently it has become customary to compare polymorphic and pseudo-polymorphic transformation data with prevailing solid state equations, e.g. forms of the Ng-equation. Several such equations, some of them already alluded to, are listed in Table 7.

**Table 7** Equations Relating to Decomposition in the Solid State

| | |
|---|---|
| $\ln(x/(1-x)) = kt$ | surface nucleation, Prout–Tompkins equation |
| $\{-\ln(1-x)\}^{1/n} = kt$ | $n$-dimensional nuclear growth (Avrami) |
| | $n$-dimensional nucleus growth |
| $1-(1-x)^{1/n} = kt$ | $n$-dimensional boundary reaction |
| $x^2 = kt$ | diffusion in one dimension |
| $(1-x)\ln(1-x)+x = kt$ | diffusion in two dimensions |
| $(1-(1-x)^{1/3})^2 = kt$ | diffusion in three dimensions (Jander equation) |

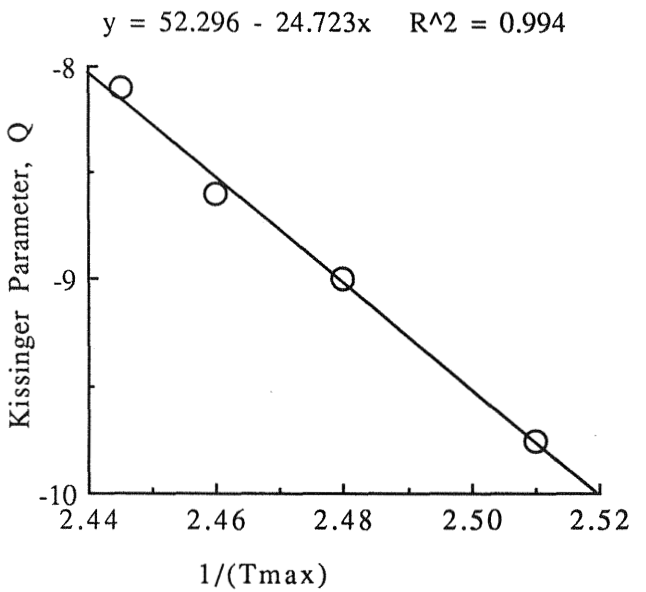


**Fig. 15** Kissinger plot of polymorph II of glybuzole. (Plot constructed from data published by Otsuka et al., 1999.)

There has been a tendency in recent literature to simply fit data to several (or all) of these equation, and the equation that gives the "best fit" is then assumed to be the mechanism. Figure 15, for instance, shows a literature example of such data. It is claimed that this data best fits a Jander equation (and such treatment is shown in Fig. 16), but first of all the fit is not good, and secondly, it is obvious that the phase, C, in the Jander model (Fig. 14) cannot possibly apply to a polymorphic transformation where the reaction is simply $A \rightarrow B$, not $A + B \rightarrow C$.

It is emphasized here that sorting out mechanisms by statistical analysis can be dangerous.

Several recent investigations in this field have appeared in recent years. Fini et al. (1999) have studied the dehydration and rehydration of diclofenac salt hydrate at ambient temperature. Otsuka et al. (1999) investigated three forms of glybuzole

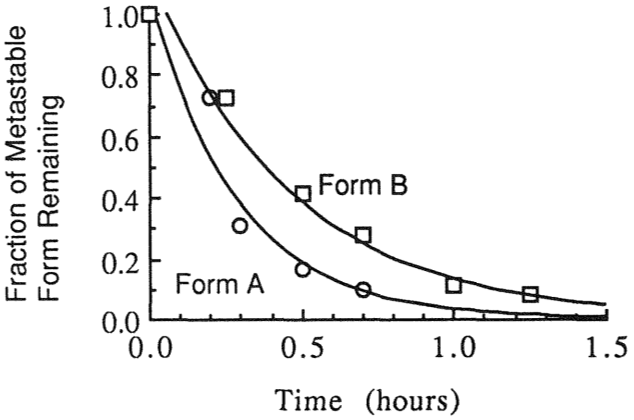


**Fig. 16** Literature data dealing with two polymorphic transformations allegedly diffusional because it adheres (somewhat) to a Jander model.

(I, II, and amorphate) and found all to have fairly much the same solubility. Neither form I nor form II changed after storage at 40°C/75% and 0% RH for 2 months. DSC for form I showed no peak other than a sharp melting endotherm at 167.4°; form II showed a slight endotherm at 116.8°C and a sharp endotherm at 166.6°C. The amorphate showed a (slight) exotherm peaking at 81.5°C, presumably due to crystallization, and a sharp endotherm at 167.3°C. From this it would be reasonable to conclude that form II is stable at room temperature and transform to I at 116.8°C, this latter form being stable at the higher temperatures.

The authors estimated the polymorphic stability of form II by way of the Kissinger equation (Kissinger, 1956):

$$\partial\left\{\frac{\ln(\phi/T_{\max}^2)}{\partial(1/T_{\max})}\right\} = \frac{-E}{R} \tag{6.48}$$

where $\phi$ is the rate of heating, $T_{\max}$ is the temperature at the peak maximum in the DSC, $E$ is the activation energy, and $R$ is the gas constant. If the experiment is conducted at different heating rates, different $T_{\max}$ values result, and in the case of glybuzole there were four such values.

It can be seen from the graph that the activation energy is $24.723 \times 1.99 = 49.2$ kCal/mol. Otsuka et al. (1991, 1993, 1999) employed the Jander equation to explain crystallization rates of compounds, e.g., amorphous glybuzole. As mentioned above, however, the Jander equation is based on an assumption of a layer of "reaction product," and such a layer (i.e., such a model) cannot be conceived of in a polymorphic transformation. What would be the "reaction product"?

## 8. GENERAL INTERACTIONS IN DOSAGE FORMS

It is tempting to think of a tablet as an agglomeration of individual particles, independent of one another, but this cannot be the case. By their mere nature, particles

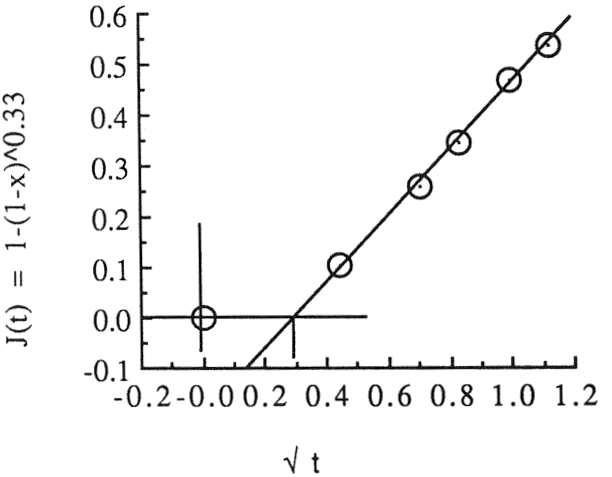


**Fig. 17** Data from form B in Fig. 15 treated according to a Jander model. The curve follows the least squares fit equation: $J(t) = -0.194 + 0.652\sqrt{t}$.

are fused together (either by brittle fracture or by plastic deformation in tablets or tamping in capsules), and if the created contact area is between two different components of the tablet (one being the drug), then there is the possibility of interaction. It is highly likely that moisture plays a part in all of these. In fact, in one of the cases to be discussed below (tartaric acid + sodium bicarbonate) this is the case (although the tablet can, for all practical purposes, be anhydrous at the onset).

The most common type of interaction in solid dosage forms is actually between water and drug. This is a large topic in itself, and the following chapter is devoted to it. The topic discussed here will be of special cases where water is not the interactant (or the main interactant).

The following cases are illustrative examples:

1. Tartaric acid and sodium bicarbonate
2. Aspirin and phenylephrine
3. Aspirin and lubricants

In addition to the points made, note that in the curve in Fig. 17 a lag time has to be invoked for the data to linearize.

### 8.1. Tartaric Acid and Sodium Bicarbonate

This is a common combination in effervescent tablets. When the tablet is added to water, the acid and the base will react, forming carbon dioxide, which produces the desired bubble effect:

$$R_2(COOH)_2 + 2NaHCO_3 \rightarrow R2(COO^-)_2 + 2Na^+ + 2H_2O + 2CO_2 \qquad (6.49)$$

To be strictly correct, the left hand side should be written in ionic form as well.

Of course, it is necessary that this reaction not take place prior to the time it reaches the consumer, because if the reaction does occur in the solid state, then

(a) carbon dioxide will form in the container, (b) the tablet will become softer, and (c) upon "reconstitution" the bubble effect will be reduced to the extent that carbon dioxide was lost in storage.

The evolution of carbon dioxide would normally build up pressure in a glass bottle, but the tubes in which effervescent products used to be sold were not tight, and the carbon dioxide could escape. The same is true to a great extent in plastic bottles and in plastic blister packs, but the problem that the reaction (as will be demonstrated below) is catalyzed by moisture, in other words the fact that the container is not hermetic in this aspect, is a disadvantage. This is so sensitive that during manufacture extra precautions are taken to keep the relative humidity of the processing areas low. Hence one must also pack the products in hermetic containers, and aluminum foil has become a popular means of doing this. If, however, the initial moisture is not low enough, then the reaction will proceed, and in this case the internal pressure will cause the aluminum foil to balloon.

The solid-state reaction has been investigated by Usui and Carstensen (1985) and by Wright and Carstensen (1986). When the reaction occurs in the solid state, there are two questions that present themselves:

1. Is moisture important and if so in what sense?
2. What is the stoichiometry? Is it that of Eq. (6.48) or is it

$$R_2(COOH)_2 + NaHCO_3 \rightarrow R_2(COOH)COONa + H_2O + CO_2 \qquad (6.50)$$

Usui checked the weight loss of heated samples in hermetic containers, utilizing different ratios of acid and base, and established that the stoichiometry is that of Eq. (6.50), i.e., the mole-to-mole interaction of tartaric acid and sodium bicarbonate.

He next studied the weight loss in open containers and demonstrated that the tartaric acid did not lose weight, and that the sodium bicarbonate, and the mixture of sodium bicarbonate and tartaric acid, lost weight at a low rate, corresponding to that of the sodium bicarbonate itself. In other words, in an open container there was no interaction, simply decarboxylation of the bicarbonate itself.

He next studied the effect of compression on the decomposition of sodium bicarbonate. Characteristic curves are shown in Fig. 18. It is noted that the decomposition rate are a function of applied pressure. In the following it is assumed that the particles are isometric and that the reaction rate is proportional to the surface area of unreacted sodium bicarbonate. The following nomenclature is used: there are $M$ g of unreacted sodium bicarbonate at time $t$, and $M_0$ initially. There are $N$ particles each of area $a$, volume $v$, and density $\rho$. The surface area is proportional to the two-thirds power of the volume by the isometry factor $Q$, i.e.,

$$a = Qv^{2/3} = Q\rho^{-2/3}m^{2/3} \qquad (6.51)$$

The total area, $A$, hence is given by

$$A = NQ\rho^{-2/3}m^{2/3} = N^{1/3}Q\rho^{-2/3}M^{2/3} \qquad (6.52)$$

It follows that

$$A_0 = N^{1/3}Q\rho^{-2/3}M_0^{2/3} \qquad (6.53)$$

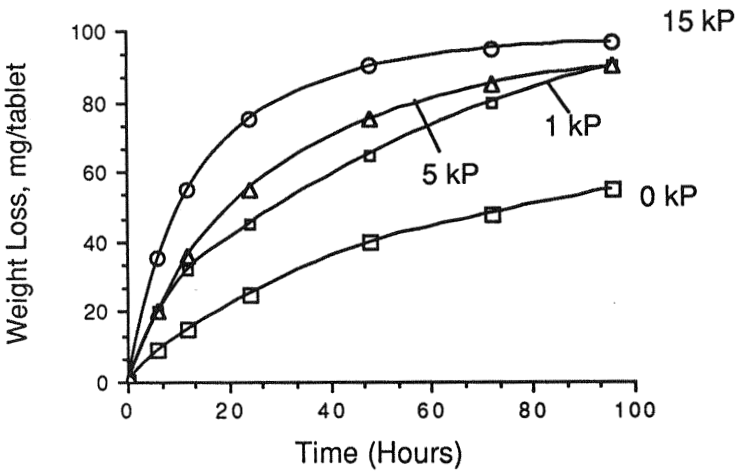


**Fig. 18** Effect of tableting pressure on sodium bicarbonate decomposition at 70°C. (Graph constructed from data by Usui and Carstensen, 1985.)

The decomposition rate is proportional to the surface area at time $t$, i.e.,

$$\frac{dM}{dt} = -k''A = -k'M^{2/3} \tag{6.54}$$

where

$$k' = k''N^{1/3}Q\rho^{-2/3} \tag{6.55}$$

Rearrangement of Eq. (6.55) gives

$$\frac{dM}{M^{2/3}} = -k't \tag{6.56}$$

This can be integrated, and when initial conditions are imposed the following expression results:

$$\left(\frac{M}{M_0}\right)^{1/3} = (1 - X)^{1/3} = 1 - kt \tag{6.57}$$

where $X$ is mole fraction decomposed, and where

$$k = \frac{k''N^{1/3}Q\rho^{-2/3}}{3M_0^{1/3}} \tag{6.58}$$

Eliminating $N$ by inserting Eq. (6.55) into Eq. (6.58) gives

$$k = \frac{k''A_0}{3M_0} \tag{6.59}$$

The data should, therefore, plot by a cube root equation and Fig. 19 shows this, indeed, to be the case.

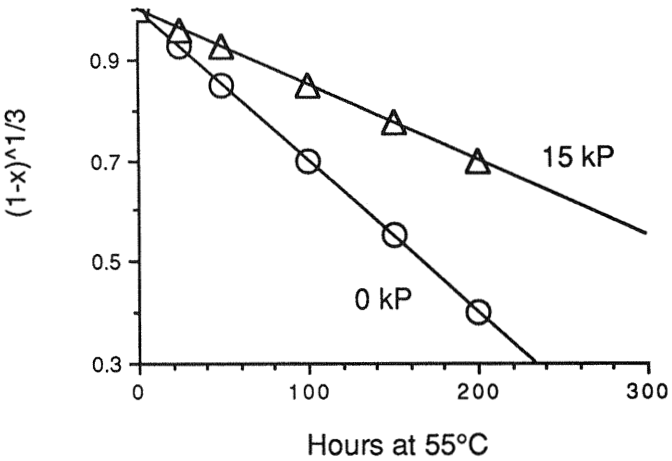


**Fig. 19** Cube root plot of sodium bicarbonate decomposition at 55°C. Least squares fit equations: 0 kP: $y = 1 - 0.0015x$ ($R = 1.00$); 15 kP: $y = 1 - 0.003x$ ($R = 1.00$). (Graph constructed from data by Usui and Carstensen, 1985.)

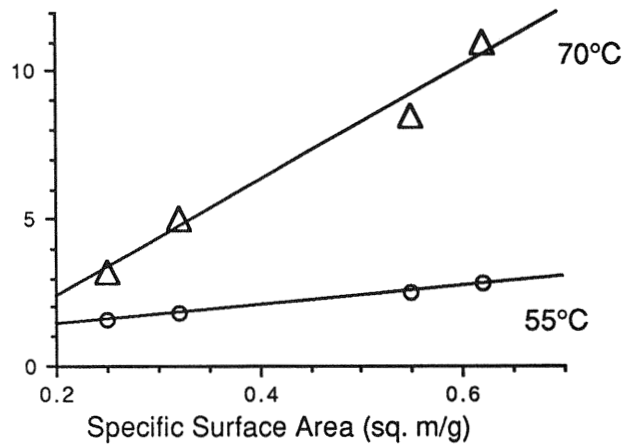


**Fig. 20** Cube root constants from Fig. 19 versus specific surface areas. Least squares fits: 70°C: $y = -1.534 + 19.447x$ ($R = 0.99$); 55°C: $y = 0.788 + 3.188x$ ($R = 1.00$) (Graph constructed from data by Usui and Carstensen, 1985.)

The rate constants according to Eq. (6.59) should be proportional to the surface area at time zero ($A_0/M_0$). That this is the case is shown in Fig. 20. The rate constants follow an Arrhenius plot (Fig. 21) and are in line with the data reported by Schefter et al. (1974).

In a closed system there is a rapid interaction between the sodium bicarbonate and the tartaric acid in compressed tablets. Even though the system is supposedly dry, it is assumed that there is a very slight amount ($z$ moles) of water present in the table initially and that the reaction starts in a dissolved stage. If this is the case, then, since water is produced in the reaction, there will be an acceleration.

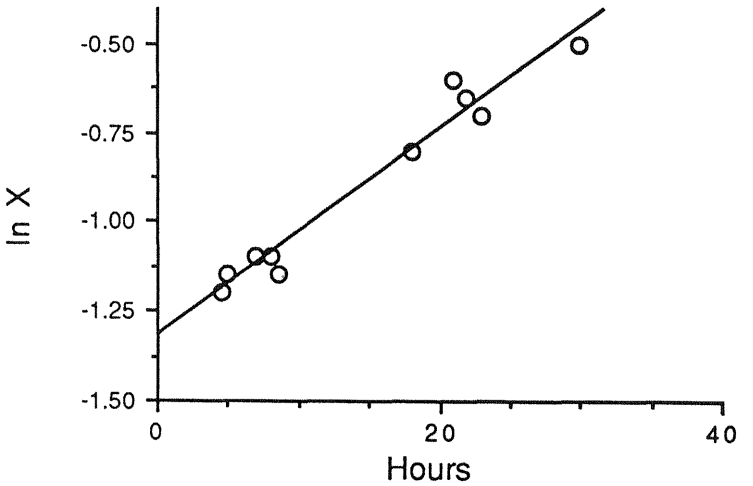


**Fig. 21** Decomposition of tartaric acid plus sodium bicarbonate tablets at 55°C (5 kP force). Least squares fit: $\ln\{X\} = -1.3225 + 0.0291 \cdot t$ ($R = 0.98$). (Graph constructed from data by Usui and Carstensen, 1985.)

The data can be modeled in the fashion shown in the following. $M'$ is the number of moles of sodium bicarbonate left at time $t$, $M'_0$ is the initial number of moles, $S$ is its solubility in water, and $C$ is the concentration in the water present at time $t$. $S_1$ is the solubility of the tartaric acid in water.

According to the reaction scheme the number of moles of water present at time $t$ then is

$$(M'_0 - M' + z)\text{moles} = (M'_0 - M' + z)\ 0.018\ \text{liters} \tag{6.60}$$

The disappearance rate of sodium bicarbonate in solution is given by

$$\frac{-dC}{dt} = k_2 S_1 S \tag{6.61}$$

where $k_2$ is the second-order rate constant. To express this as number of moles decomposed, this figure is multiplied by the volume of water present, i.e., the expression in Eq. (6.60):

$$\frac{dM'}{dt} = -k^*(M'_0 - M' + z) \tag{6.62}$$

where

$$k^* = 0.018 k_2 S_1 S \tag{6.63}$$

Equation (6.62) can now be recast in the form

$$\ln(M'_0 - M' + z) = k^* t + \ln[z] \tag{6.64}$$

or employing $X$, the mole fraction decomposed:

$$\ln\left[X + \frac{z}{M_0}\right] = k^* t + \ln\left[\frac{z}{M_0'}\right] \tag{6.65}$$

Recalling that $z$ is a small number, the term $z/M_0$ is small, and the Eq. (6.65) then simplifies to

$$\ln[X] = k^* t + \ln\left(\frac{z}{M_0'}\right) \tag{6.66}$$

Data are plotted in this fashion in Fig. 21. It is seen that the linearity is quite good. The value of $z$ may be estimated from the intercept and comes to about 0.1 mg per tablet, which is a reasonable figure. This, in essence, shows that the theories suggested by Wright (1983) are correct.

It is obviously of pharmaceutical importance in most situations to slow down the reaction in the solid state and yet maintain the reactivity in the solid state. (An exception to this is when a reaction is purposely carried out during a granulation, for instance.) One way of retarding the reaction rate is to preheat the bicarbonate to 95°C for a certain length of time (White, 1963, Mohrle, 1980). This will react by the scheme

$$2NaHCO_3 \rightarrow Na_2CO_3 + H_2O \tag{6.67}$$

The water formed granulates the mixture and makes it easier to compress. But more importantly, the sodium carbonate formed can form double salts with the bicarbonate. These are dodecahydrates and act as moisture scavengers. They hence stabilize the acid/base mixture in the solid state (if reasonable moisture barriers are provided): any *small* amount of moisture created by a beginning reaction of the type of Eqs. (6.48) or (6.49) will react with a mixture of the carbonate and bicarbonate to form a double salt hydrate.

## 9. INCOMPATIBILITY PREVENTION TECHNIQUES

Frequently, interactions are particle size dependent. This stands to reason, because the finer a powder is, the more contact points there will be in the tablet mass, hence the larger the potential for interaction. Means of overcoming this are as follows.

In double granulation or pocketing techniques, one component is placed in one granulation, the other in another; keeping the granulations coarse will give fewer contact points, hence less interaction. This is a technique often used in vitamin granulations. Here the more famous incompatibilities are usually those involving (a) cyanacobalamine, iron, and ascorbic acid (b) vitamin A, (c) calcium pantothenate, and (d) tocopherol. The first of these cases is one where *pocketing* is used. This can be accomplished by actually coating (rather than just granulating) the iron salt (often ferrous fumarate) in order to separate it from the remaining ingredients. The other cases will be dealt with separately below.

Other means of separating incompatible ingredients is to make a compression-coated tablet. This consists of an inner tablet compressed in a coating granulation. This principle can be extended to a tablet within a tablet within a tablet

(Bicota™, Manisty). The machines used to make them are, however, slow. If a layer separation is necessary (and effective), then it is most often accomplished by triple-layer tablets. It should noted that these techniques are ineffective in the case of reactions that occur via the gas phase. (These types of reactions will be discussed in the following.)

As mentioned, coating is a special case of pocketing. Ferrous fumarate is sometimes coated, but the most famous case of coating is undoubtedly that of vitamin A esters. Prior to this technique, in the early 1950s vitamin A was added, with an antioxidant, to powder blends that were then encapsulated or tableted. The loss of the vitamin was excessive (frequently 50% in 6 months, plus a processing loss). In the early 1950s Hoffmann-La Roche and Pfizer (almost simultaneously) marketed a so-called beadlet. The coating of vitamin A was a bit different from that of other compounds, since the most common ester (acetate) is a liquid. The coating was therefore done by making an emulsion of the vitamin A in a solution of gelatin, spraying this onto an insoluble starch derivative (which rapidly absorbed moisture), and then further drying the beadlet. After drying, the starch derivative could be separate from the vitamin A by sieving. Later, the coated palmitate bead was introduced, and, with normal precautions, oxidation of the vitamin A (except for the droplets on or rather in the surface) was prevented. It follows from this that the finer the beadlet, the less stable will it be (because there will be more surface droplet of vitamin A). 40 mesh is about the coarsest than can be handled in tableting or encapsulation, and this mesh cut offers a good stability. Obviously compression will cause fracture of the beads to some extent and this is the actual stability problem in a dry tablet.

If moisture is present in the tablet, then the gelatin will soften and become more oxygen-permeable, and the stability will suffer. It is therefore always best to perform moisture stress tests in stability programs. At a point in development where enough tablets are available the following is done: four times the regular sample is taken, and this sample is subdivided into four equal portions, A, B, C, and D. A is placed on stability as is. B is exposed to water vapor in a desiccator, and removed and placed on stability when it has gained 0.5% in weight. (The tablets can be placed on Petri dished and weighed periodically.) The procedure is repeated with C to 1% and D to 2%. The information gained is valuable, because it aids in decisions of the following kind: (a) Should a desiccator bag be used? (b) What should the moisture specification on the product be? (c) If there is no effect of moisture, there would be less of a problem selecting plastic bottles for the product.

## 10. pH OF THE MICROENVIRONMENT

In the strictest sense, the term pH is not defined in a solid system. For it to have meaning, there must be some water mediation; tocopheryl acetate and calcium pantothenate are cases in point. The former is sensitive to high pH, the former to low pH. Calcium pantothenate is frequently admixed with magnesium oxide and granulated separately from the remaining ingredients. In this manner an alkaline microenvironment is created, which ascertains the stability of the vitamin.

In the case of tocopheryl acetate, the hydrolysis is accelerated by hydroxyl ions. Again it is noted that the reaction must be associated with some dissolution step in small amounts of water. The produced tocopherol is much less stable, and hence the hydrolysis and the presence of water are contraindicated. This is a particular

case where the use of alkaline excipients (e.g. hydroxyapatite) can be deleterious at higher temperatures. In the absence of (or at low levels of) moisture the reaction may not proceed. It is also characteristic that often, higher temperatures are not indicative of what will happen at room temperature.

If it is desired to control the pH of the microenvironment then citric, tartaric, and fumaric acids are the acids of choice. They are, however, all corrosive, and their pharmaceutical handling is far from ideal. In the case of alkali, sodium bicarbonate, sodium carbonate, and magnesium and calcium oxides are common. They are not as corrosive as the acids mentioned, but they are abrasive, and they, too, are not the most ideal substances to handle in a tablet or a capsule.

For certain compounds it is necessary to control the microenvironment in even more drastic fashion. Gu et al. (1990) report on drug excipient incompatibility studies of moexipril hydrochloride and demonstrate that (even "wet") adjustment of the microenvironmental pH (i.e., adding small amounts of water to a mixture of the drug with sodium bicarbonate or sodium carbonate) did not sufficiently stabilize the mix. But when the mixture *was wet granulated*, and when *stoichiometric amounts of alkali were used*, then stabilization resulted. This essentially means that in the solid state *the sodium salt is stable* as opposed to the acid. It might be argued that in such a situation the sodium salt should be manufactured and used as such. It might be argued that it should be claimed as the active ingredient (equivalent to a certain amount of free acid, or in the case of amphoteric substances, the acid addition salt), but often the salt is very soluble and hygroscopic (e.g., potassium clavulanate) and hence difficult to produce. The situation is referred to in the Federal Register as a *derivative drug*.

## 11. INTERACTIONS INVOLVING A LIQUID PHASE

At times an active ingredient or a decomposition product in a solid dosage form is a liquid, and this may interact with other ingredients in the dosage form. A typical example is the work by Troup and Mitchner (1964) dealing with aspirin and phenylephrine. The authors showed that the decomposition of phenylephrine was linearly related to the formation of salicylic acid. They showed that the decomposition of phenylephrine was an acetylation. This can be thought of in many ways. There has to be some moisture present to allow for the hydrolysis of aspirin. If the salicylic acid is formed by interaction of aspirin with traces of water, then the acetic acid formed may react with the phenylephrine ($R(OH)_3$), again liberating water, so that the moisture does not play a part quantitatively in the overall reaction; in other words,

$$C_6H_4(OCOCH_3) + H_2O \rightarrow C_6H_4(OH)COOH + CH_3COOH \tag{6.68}$$

$$CH_3COOH + 1/3\,R(OH)_3 \rightarrow 1/3\,R(OCOCH_3)_3 + H_2O \tag{6.69}$$

---

$$C_6H_4(OCOCH_3) + 1/3\,R(OH)_3 \rightarrow 1/3\,R(OCOCH_3)_3 \tag{6.70}$$

An alternate explanation would be that phenylephrine interacted directly with aspirin in an anhydrous solid state to transacetylate, which is not probable. The

question is whether the acetic acid (which has a sizable vapor pressure) interacts with the phenylephrine as a gas with a solid reaction (to be covered shortly) or as a liquid with a solid reaction.

There are other examples of the interaction of acetic acid with active ingredients, e.g., the work by Jacobs et al. (1966), in which acetylation of codeine in aspirin/codeine combinations was demonstrated. Again, whether the acetylation is achieved by acetic acid in the vapor phase or in the liquid state or (more unlikely) whether it is a direct solid to solid interaction, is not resolved at the present time. If it were the latter, then Jander kinetics should actually apply. But it is difficult to distinguish this and pseudo-first-order reactions. If it is an interaction in the liquid state, then it probably occurs by the phenylephrine dissolving in the acetic acid formed.

In more general terms, it is assumed that there are two drugs, A and D. A decomposes (e.g., by hydrolysis) to form a liquid decomposition product *C*. The reactions then are

$$A + H_2O \rightarrow B + C \qquad \text{(rate constant } k\text{)} \tag{6.71a}$$

$$D + C \rightarrow \text{decomposition} \qquad \text{(rate constant } k'\text{)} \tag{6.71b}$$

*C* is the species that is liquid. In this case a saturated solution (S moles/mole) of D in *C* is formed, and it is assumed that dissolution is fast. Let A be the number of moles of drug #1 present at time *t*, let *C* be the number of moles of acetic acid, and let M denote the molarity of the liquid decomposition product (e.g., for acetic acid at 25°C the density is 1.05 g/mL, so that, since its molecular weight is 60, *M* would be $1005/60 = 16.75$). The rate at which D disappears is the question. It is assumed that the disappearance rate of A is pseudo–first order, i.e.,

$$A = A_0 \exp(-kt) \tag{6.72}$$

The disappearance rate of D depends on how much C is present, so the equation for *C* must first be established and solved. C is created at a rate of $kA$, but it is consumed by D. The rate of the latter step is given by a second-order reaction term. The concentration of D is *S*, and the concentration of C is *M*. The amount of C at time *t* is *C*, so that (in terms of moles)

$$\frac{dC}{dt} = kA - k'SCM \tag{6.73}$$

Inserting Eq. (6.73), and using and denoting

$$k'SM = a \tag{6.74}$$

where *a* is constant, the following equation is arrived at:

$$\frac{dC}{dt} = kA_0 \exp(-kt) - aC \tag{6.75}$$

Laplace transformation, using **L** notation, gives

$$s\mathbf{L} - 0 = \frac{kA_0}{\mathrm{s}+\mathrm{k}} - a\mathbf{L} \tag{6.76}$$

or

$$\mathbf{L} = \frac{kA_0}{a-\mathrm{k}}\left[\frac{1}{\mathrm{s}+\mathrm{k}} - \frac{1}{\mathrm{s}+a}\right] \tag{6.77}$$

so by taking anti-Laplacians,

$$C = \frac{kA_0}{k'SM - k}\{\exp(-kt) - \exp(-k'SMt)\} \tag{6.78}$$

It follows that the decomposition rate of D is given by

$$\frac{dD}{dt} = k'SCM = aC \tag{6.79}$$

i.e., by integrating Eq. (6.79) and multiplying by $a$, we obtain

$$D = \frac{kaA_0}{k'SM - k}\left[\frac{\exp(-k'SMt)}{k'SM} - \frac{\exp(-kt)}{k}\right] \tag{6.80}$$

An example of this is shown in Fig. 22 using $A = 50$, $k = 0.2$, and $k'SM = 0.1$. A different situation arises when an insoluble component interacts with a drug in solution (or vice versa). An example of this is the interaction between microcrystalline cellulose (R′CHOHR″) and substituted furoic acids (RCOOH) (Carstensen and Kothari, 1983). The furoic acids decompose when heated by themselves, into a liquid decomposition product and carbon dioxide. In the presence of microcrystalline cellulose, however, the mixture forms carbon monoxide:

$$\mathrm{RCOOH} + \mathrm{R'CHOHR''} \rightarrow \mathrm{Q} + \mathrm{Q'} + \mathrm{CO} \tag{6.81}$$

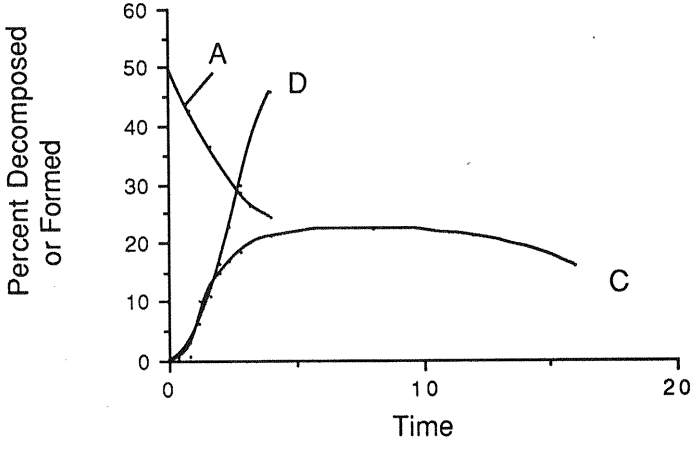


**Fig. 22** Stability profile using $A = 50$, $k = 0.2$, and $a = 1$.

Q is a liquid that will dissolve furoic acid to the extent of its solubility and will spread over the microcrystalline cellulose. There will be a number of contact points, $N$, at which interaction can take place (essentially the "wetted" part of the microcrystalline cellulose). There will be a reaction probability, $a$, associated with each contact point. The reaction accelerates because the larger the extent it has reacted, the more liquid there will be to dissolve the furoic acid hence the more contact points. At a given point in time there will be overcrowding, since dissolved molecules will be next to contact points that have already reacted. Hence there is also a termination probability, $b$. But unlike the Prout–Tompkins model, this is finite at time zero.

It might be argued that the external surface of the microcrystalline cellulose would be insufficient to account for the total decomposition. There are however, two types of surface present in microcrystalline cellulose: nitrogen adsorption gives low surface areas (the external area), whereas for instance water isotherms give surface areas 100 times as large (Hollenbeck, 1978, Marshall et al., 1972, Zografi and Kontny, 1986).

By the decomposition at a contact point, it is assumed that the decomposition, creating one liquid decomposition molecule, will dislodge (dissolve) $S$ molecules of furoic acid at the contact point. If the initial number of contact points is $N_0$ then

$$\frac{dN}{dt} = [-b + a(S-1)]N = qN \tag{6.82}$$

where $q = -b + a(S-1)$. The factor arises from the fact that when molecules react, $aS$ new contact points are created and one (the one at which the reaction took place) is lost.

It follows then from integrating Eq. (6.82) (which can be done, since $a$ and $b$ are assumed constant), that

$$N = N_0 \exp(qt) \tag{6.83}$$

Since, at a given time $t$, the rate of decomposition is proportional to the number of contact points, then, $L$ being the number of intact alkoxyfuroic acid molecules,

$$\frac{dL}{dt} = -gN \tag{6.84}$$

where $g$ is a constant. From the definition of $L$ it follows that the mole fraction, $x$, decomposed is given by

$$x = \frac{L_0 - L}{L_0} \tag{6.85}$$

or

$$\frac{dx}{dt} = -\frac{g}{L_0}\frac{dL}{dt} \tag{6.86}$$

Equation (6.84) inserted in this gives

$$\frac{dx}{dt} = \frac{1}{L_0} gN \tag{6.87}$$

Substituting Eq. (6.83) into this gives

$$\frac{dx}{dt} = \frac{gN_0}{L_0} \exp(qt) \tag{6.88}$$

This integrates to

$$x = \frac{gN_0}{L_0 q}[e^{qt} - 1] = A[e^{qt} - 1] \tag{6.89}$$

where the term $A = gN_0/L_0 q$ has been introduced for convenience. Equation (6.89) is equivalent to

$$\ln[1 + Ax] = qt \tag{6.90}$$

Fig. 23 shows data treated in this fashion.

## 12. CASES OF INTERACTION OF A LIQUID WITH A POORLY SOLUBLE DRUG

There are cases where there are liquids in a solid dosage form. An example is panthenol in a multivitamin tablet. Here it is customary to adsorb the liquid onto a solid carrier, and in the case of panthenol, magnesium trisilicate is used. At elevated temperatures (and at room temperature under compression as well) the panthenol will ooze out of the carrier and come into intimate contact with other solids. If interaction potentials exist, then separation techniques such as triple-layer

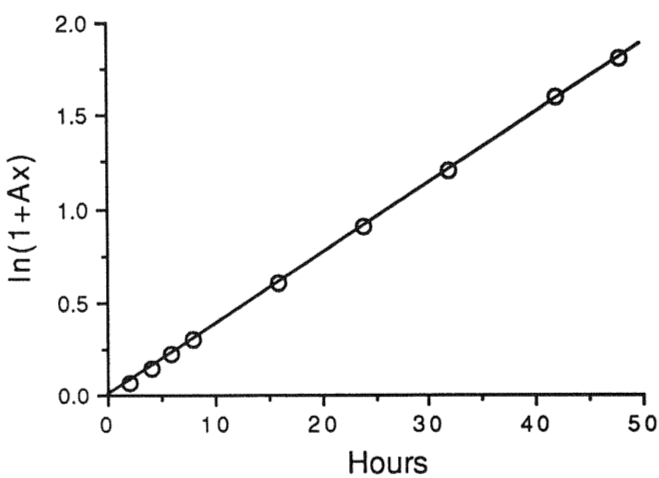


**Fig. 23** Furoic acid data treated according to Eq. (6.90). (Graph constructed from data by Carstensen and Kothari, 1983.)

tablets (or compression coated tablets) are resorted to. In this case, the liquid will still ooze into the layer containing its interactant, but the process will be diffusion controlled. It can be shown (Jost, 1962) that the average concentration, $C$, of the liquid in the neighboring layer, with which it is in contact, is given by

$$\frac{C - C_f}{C_0 - C_f} = Qe^{-kt} \tag{6.91}$$

where $C_f$ is the concentration at infinite time. The term on the right-hand side is actually the leading term of an infinite series.

## 13. REACTIONS VIA THE GAS PHASE

Sometimes the vapor pressure of a drug is sufficiently high that it may interact with other substances via the vapor phase. An example is ibuprofen (B). This is a Lewis acid, and it can interact with Lewis bases. Usual measures, such as e.g. triple-layer tablets, do not work in this case, since the interactant will be present in the gas phase.

If the reaction with another drug (D) is

$$\mathrm{D} + \mathrm{B} \rightarrow \text{decomposition} \tag{6.92}$$

then the initial reaction rate is given by

$$\frac{d\{D\}}{dt} = -kP_B[\mathrm{D}]A \tag{6.93}$$

where $\{D\}$ is the surface density of D molecules (number of molecules per $cm^2$) at time $t$, and $A$ is the surface area. As long as there is no penetration into the crystals, the reaction will therefore be a first-order reaction, since Eq. (6.93) integrates to

$$\ln[C] = -kAP_B t + \ln[C_0] \tag{6.94}$$

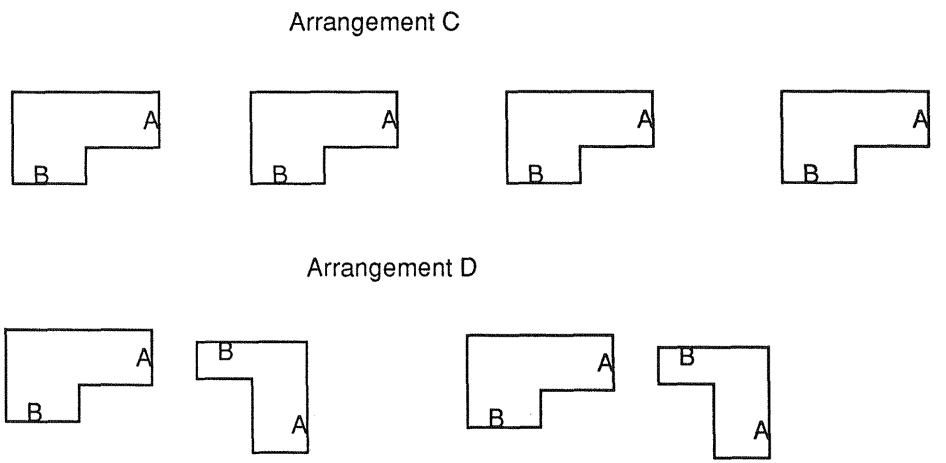


**Fig. 24** Schematic of an example of molecular arrangement possibilities in a crystalline solid. If groups A and B can interact, then the situation in the upper arrangement is less prone to reaction, since A and B are at a greater distance.

where $C_0$ is the initial concentration. This will be true if only the surface of the solid interactant is affected. The extent of decomposition will be slight, because (unless the drug is extremely finely subdivided) only a small fraction of the molecules are on the surface. If, however, the ibuprofen penetrates the crystal, then Jander kinetics should prevail. A similar situation may be at work in the aspirin incompatibilities mentioned earlier.

## 14. AMORPHATES

As mentioned earlier, solids can occur either in crystalline form or as particulate amorphates. The chemical stability of the solid in crystalline form will differ from the same entity in amorphous form. In most cases the crystalline form, under the same conditions, will be more stable than the comparable amorphate.

The most interest and the largest body of work of amorphates is in the field of macromolecules. These usually possess a glass transition temperature*, $T_g$, and the states are referred to as "glassy" below† and "rubbery" above $T_g$.

Only a few articles have appeared on the subject of chemical stability of amorphates. In general, a compound is more stable in the crystalline state than in an amorphous state, but exceptions exist (Sukenik et al., 1975; O'Donnel and Whittaker, 1992; Stacey et al., 1959). There *are* cases that have been reported (Lemmon et al., 1958) where the crystalline state is less soluble than the molecule in solution, but they are rare.

In general, in a crystalline state, molecules are to a great extent fixed in position. In cases where the situation exists where a group from one molecule reacts with another group in a neighbor, the situation as shown in Fig. 24 arises.

Pothisiri and Carstensen (1975) have shown that in a situation such as the case of substituted benzoic acids the decomposition is between two groups in the same molecule.

Suppose parts A and B of the molecule depicted in Fig. 24 react. In such a case arrangement C would give better stability than arrangement D, because A would be further away from B in the former arrangement. Arrangement D can be more adverse than a random orientation as well, and if that is the case, then the amorphous form would be more stable than the crystalline (arrangement D). This is the exception rather than the rule.

In the presence of moisture, conversions from amorphous to crystalline modifications are promoted (Carstensen and Van Scoik, 1990; Van Scoik and Carstensen, 1990), and the material developed in the following all refers to anhydrous conditions.

In the work by Carstensen and Morris (1993), amorphous indomethacin was produced by melting a crystalline form of it to above melting (162°C) and recooling it to below 162°C. Amorphates made in this manner are morphologically stable down to 120°C‡ so that their chemical stability can be monitored. At a range of temperatures below this temperature, crystallization occurs too rapidly to allow for assessment of chemical stability. Amorphous samples were placed at several con-

---

* More than one glass transition temperature may exist.

† The highest $T_g$ in the case of multiple glass transition temperatures.

‡ If the temperatures are lowered rapidly, then stable amorphates can be formed at room temperature, but kinetics cannot be followed easily because of the slow reaction rate at room temperature.

stant temperature stations (145, 150, 155, 165, 175, and 185°C) and assayed from time to time. The content of intact indomethacin was assessed by using the USP method of analysis.

The decomposition curves of amorphous indomethacin and a melt of indomethacin at different temperatures is shown in Figs. 25 and 26. It is noted that the pattern is strictly first-order. Of the few reports in the literature dealing with the chemical stability of compounds in the amorphous state, amorphous cephalosporins (Pfeiffer et al., 1976; Oberholtzer and Brenner, 1979; Pikal et al., 1977) also adhere to a first-order pattern. One purpose of the following writing

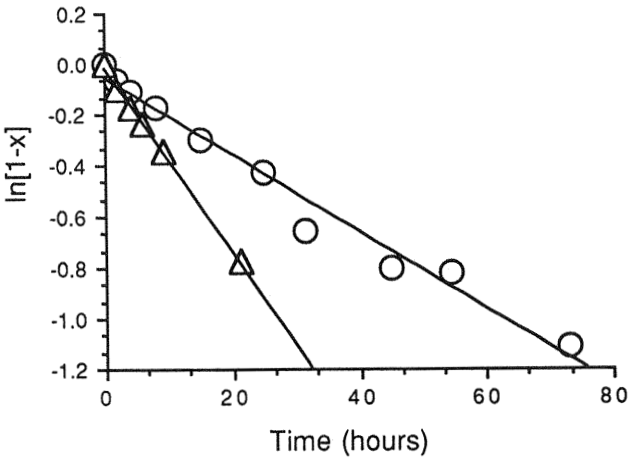


**Fig. 25** Decomposition curves of solid, amorphous indomethacin at two of the three temperatures tested. ○: 145°C ($k = 0.015$ h$^{-1}$); △: 155°C ($k = 0.036$ h$^{-1}$).

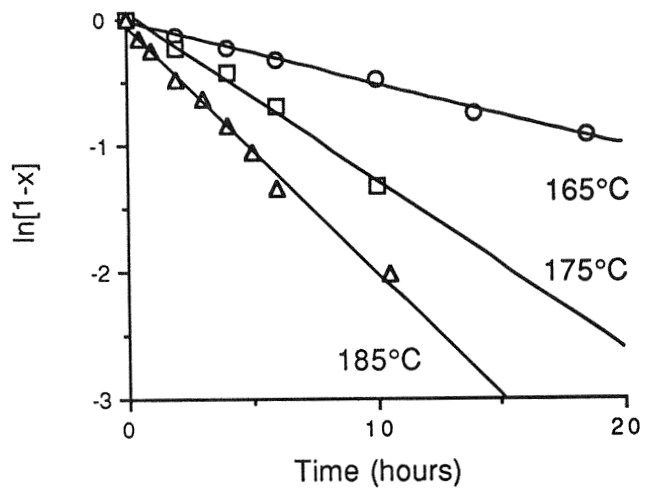


**Fig. 26** Decomposition data of indomethacin in a molten state. Circles 165°C (rate constant 0.05 h$^{-1}$); squares: 175°C (rate constant 0.13 h$^{-1}$); triangles: 185°C (rate constant 0.19 h$^{-1}$).

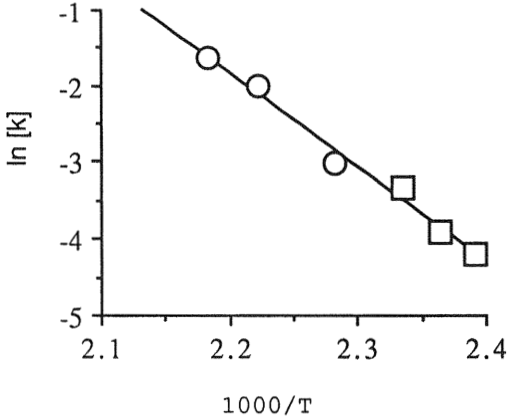


**Fig. 27** Arrhenius plot of data from Fig. 24 and Fig. 25. Squares are melt and circles are amorphate. The least squares fit is $\ln[k] = 25.218 - (12{,}300/T)$.

is to seek an explanation for this pseudo-first-order (or indeed, truly first-order) pattern. The explanation must lie, in some manner, with the fact that in the rubbery state, the molecules can arrange in a random fashion, in a somewhat frozen (or much slowed) manner of that of the melt above the traditional melting point.

The results obtained from the melt are shown in Fig. 26, and against a first-order plot results. If an Arrhenius plot is drawn of the data from both Fig. 25 and 26, then Fig. 27 results.

It is seen that the Arrhenius plot of the amorphate continues into the Arrhenius plot of the melt. An attempt to explain this is made in the following.

If the substance in Fig. 24 were a crystalline solid, then the potential energy between molecules would be inversely proportional to a power function of their distance (the lattice constant) (Carstensen and Morris, 1993), i.e., would be akin to a Lennard-Jones potential (Lennard-Jones, 1931). However, in the amorphous state, if the decomposition is an intermolecular (rather than an intramolecular) reaction, then a group A in molecule I interacts with group B in the neighboring molecule II. The energy of the molecular pair will be dependent on the distance between the group A in one of the pair and group B in the other. These distances would be assumed to be randomly distributed, and a certain fraction $N_{>i}/N_0$ of the molecular pairs would be at or above a critical energy, $E_i$, necessary for reaction between A and B. The fraction of molecules that have this energy, $E_i$, is given by the Boltzmann distribution (Moelwyn-Hughes, 1961):

$$\frac{N_i}{N} = \frac{\exp(-E_i/RT)}{\sum_{k=0}^{k=\infty} \exp(-E_k/RT)} \tag{6.95}$$

where $N$ is the total number of molecules and where the summation is over all energy levels. The fraction of molecules having energies in excess of $E_{>i}$ is then $N_{>i}$, given by

$$\frac{N_{>i}}{N} = \frac{\sum_{k=i}^{k=\infty} \exp(-E_k/RT)}{\sum_{k=0}^{k=\infty} \exp(-E_k/RT)} \tag{6.96}$$

There are several ways of approaching these summations, e.g., by considering the energy differences small and integrating. A discrete approach is to assume that the energy difference, $\Delta E$, between adjoining energy states is constant. In this case Eq. (6.96) can be written:

$$\frac{N_{>i}}{N} = \frac{e^{-E_i/RT} + e^{-(E_i+\Delta E)/RT} + \ldots}{e^{-E_0/RT} + e^{-(E_0+\Delta E)/RT} + \ldots}$$
$$= \frac{e^{-E_i/RT}[1 + e^{-\Delta E/RT} + e^{-2\Delta E/RT} + \ldots]}{e^{-E_0/RT}[1 + e^{-\Delta E/RT} + e^{-2\Delta E/RT} + \ldots]} \tag{6.97}$$

i.e.,

$$\frac{N_{>i}}{N} = \frac{e^{-E_i/RT}}{e^{-E_0/RT}} = e^{-(E_i-E_0)/RT} \tag{6.98}$$

Alternatively, if the difference between energy levels is large compared to the ground state energy, one can simply approximate the series in the numerator and denominator of these equations with their leading terms. This leads to the same result:

$$\frac{N_{>i}}{N} = \frac{\sum \exp(-E_i/RT)}{\sum \exp(-E_0/RT)} = \exp\left[\frac{-(E_i - E_0)}{RT}\right] \tag{6.99}$$

If, in a time element $dt$, a fraction of the molecules ($dN/N$) reaching $E_i$ (or higher) react, then, denoting this fraction $q$,

$$\left(\frac{1}{N}\right)\frac{dN}{dt} = q\left[\frac{N_{>i}}{N}\right] = q\exp\left[\frac{-(E_i - E_0)}{RT}\right] = -k_1 \tag{6.100}$$

where $k_1$ (by definition in differential form) is a first-order rate constant, i.e., by integrating Eq. (6.100) and imposing $N = N_0$ at time $t = 0$,

$$\ln\left[\frac{N}{N_0}\right] = -k_1 t \tag{6.101}$$

i.e., first-order, where the rate constant is given by

$$k_1 = q\exp\left[\frac{-(E_i - E_0)}{RT}\right] \tag{6.102}$$

or its logarithmic equivalent,

$$\ln[k_1] = \ln[q] - \frac{E_a}{RT} \tag{6.103}$$

i.e., an Arrhenius equation where the activation energy is given by

$$E_a = E_i - E_0 \tag{6.104}$$

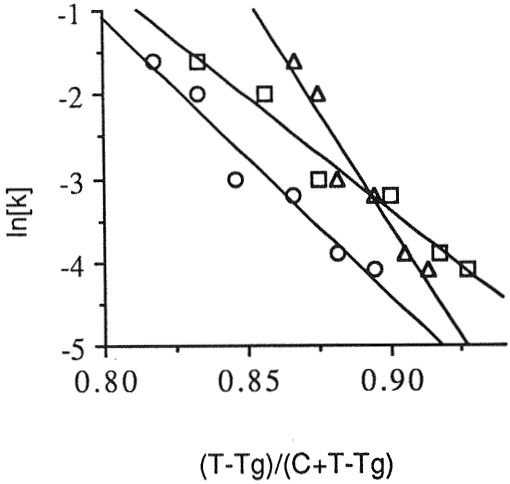


**Fig. 28** Data from Fig. 26 plotted by the inverse function of the WLF equation. *Triangles:* $T_g = 80°$, $C_2 = 10$: $\ln[k] = 25.40 - 33.117\{T - T_g\}/\{C + (T - T_g)\}$; $R = 0.977$. *Circles:* $T_g = 100°$, $C_2 = 6$: $\ln[k] = 45.48 - 54.47\{T - T_g\}/\{C + (T - T_g)\}$; $R = 0.97$. *Squares:* $T_g = 120°$, $C_2 = 5$: $\{T - T_g\}/\{C + (T - T_g)\} = -0.771 \ln[k] + 0.0289$; $R = 0.982$.

The data in Figs. 24 and 25 demonstrate the correctness of Eq. (6.100), i.e., the expectancy of a first-order decomposition, and Fig. 27 demonstrates the correctness of Eq. (6.102).

There have been proposals (Moelwyn-Huges, 1961, Franks, 1989) that the stability of a compound near its $T_g$ is best described in terms of the Williams-Landel-Ferry equation (Williams et al, 1955):

$$\ln[R] = \ln[R_g] + \left[\frac{c_1\{T - T_g\}}{\{C_2 + (T - T_g)\}}\right] \tag{6.105}$$

where $C_2$ and $c_1$ are constants. It is far from certain that this equation would apply to chemical reactions, but Fig. 28 shows its application to the data in Fig. 27. Several different values of $C$ and $T_g$ will give reasonable fits, as seen. It would seem intuitive that if the Arrhenius equation fits, then there would be values of $C_2$ that would make the WLF equation fit as well.

Schmitt et al. (1999) described the crystallization of amorphous lactose above the glass transition temperature to follow the Johnson–Mehl–Avrami (Johnson and Mehl, 1939; Avrami, 1939) equations:

$$[-\ln(1 - \alpha)]^{1/n} = k(t - t_i) \tag{6.106}$$

Pikal et al. (1977) employed solution calorimetry to determine the amorphous content of cephalothin sodium, cefazolin sodium, cefamandole naphtate, and cefamandole sodium. Since the amorphous forms are more energetic, they have a higher heat of solution, and the percent amorphate can be obtained if the heat of solution of amorphate and crystalline forms separately is known.

Lo (1976) showed that ampicillin trihydrate dehydrated to amorphous ampicillin, which had much poorer stability than the trihydrate. Upon storage the decomposition appears biphasic.

## 15. PSEUDO-POLYMORPHIC TRANSFORMATIONS

Dehydration, as mentioned above, may result in amorphous anhydrates, but it may also result in another crystalline phase (e.g., a lower hydrate or a crystalline anhydrate). These are, properly speaking, *pseudo-polymorphic transformations.* There are several steps in dehydration of a hydrate, and they can be summarized in the following manner, where S denotes solid, D denotes drug, V denotes vapor, and L denotes liquid (Han and Suryanarayanan, 1997).

$$D \cdot xH_2O \rightarrow D_S + xH_2O_L \qquad \text{(enthalpy of dehydration} = \Delta H_D)$$
$$D_S + xH_2O_L \rightarrow D_S + xH_2O_V \qquad \text{(enthalpy of vaporization} = \Delta H_V)$$

---

$$D \cdot xH_2O \rightarrow D_S + xH_2O_V \qquad \text{(enthalpy of transition} = \Delta H_T)$$

i.e.,

$$\Delta H_T = \Delta H_V + \Delta H_S \tag{6.107}$$

so that different results can be obtained in DSC experiments depending on whether a crimped or open pan is used.

Bray et al. (1999) have shown such a diagram for [2(S)-[p-toluenesulfonyl amino]-3-[ [ [5,6.7.8-tetrahydro-4-oxo-5-{5-[2-(piperidin-4-yl)ethyl]-4-H-pyrazolo[1, 5-a][1,4]diazepin-2-yl]carbonyl]amino]-propionic acid.

Suihko et al. (1997) have employed DSC to show that dehydration of theophylline monohydrate is a two-step process.

## 16. POLYMORPHIC TRANSFORMATIONS

Polymorphic transformation rates have become of importance of late, and an example is a recent article by Agbada and York (1994) dealing with the dehydration kinetics of theophylline. The article by Ng (1975) is similarly instructive in the sense that it reviews all the equations that have been developed for polymorphic transformation kinetics.

In most cases the transformation kinetics are S-shaped curves, and before any model is imposed on the data, the following model should be considered. (This is comparable to the model proposed by Carstensen and Van Scoik, 1990). If the phenomenon that governs the transformation is essentially the nucleation lag time, then the curves may be considered as representing either a normal or a log-normal error curve, and the mean would be the mean (or geometric mean) nucleation time. What this states is that each particle, in a sense, acts as its own entity, that there is a nucleation time (with an error or a variance attached to it) and that the particle will endure the nucleation time and then decompose, individually, very rapidly.

**Table 8** Data (Fig. 16) from Which Fig. 29 Was Generated

| | Fraction remaining | | Standard normal deviate | |
|---|---|---|---|---|
| Time (h) | A | B | $Z_A$ | $Z_B$ |
| 0 | 1.00 | 1.00 | | |
| 0.2 | 0.698 | | 0.50 | |
| 0.25 | | 0.72 | | 0.58 |
| 0.3 | 0.33 | | −0.43 | |
| 0.5 | 0.17 | 0.42 | −0.92 | −0.2 |
| 0.7 | 0.08 | 0.28 | −1.5 | −0.58 |
| 1.0 | | 0.11 | | −1.18 |
| 1.25 | | 0.08 | | −1.4 |

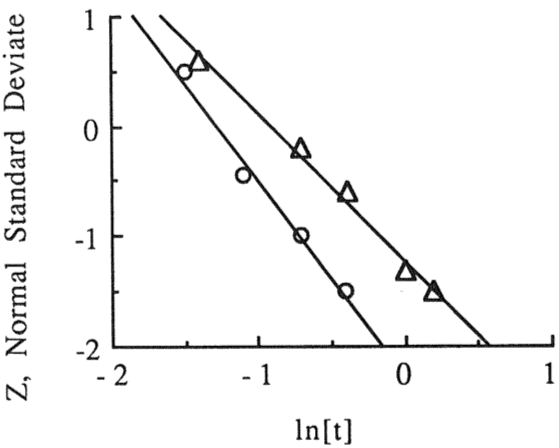


**Fig. 29** Data from Fig. 16 treated as log-normally distributed in time.

The data from Fig. 16 are shown in tabular form in Table 8. These data are plotted log-normally in Fig. 29, and it is seen that there is excellent linearity. The model is much simpler and much more reasonable in the case of polymorphic transformations than other models relying on farfetched mechanistic assumptions.

The reason for the log-normal relationship is not difficult to understand. Solids are usually log-normally distributed. If the nucleation time is inversely proportional to size, then it too would be log-normally distributed.

Dehydration, at times, results in a morphic transformation. For instance, Lo (1976) showed that the transformation of crystalline ampicillin trihydrate to amorphous penicillin was primarily first order, it either was first order or followed a contracting cylinder model ($(1-x)^{1/2}$ being proportional to time).

### 16.1. Pseudo-Polymorphic Transformations. Dehydration Kinetics of Hydrates

A special case of polymorphism is pseudo-polymorphism which deals with hydrates. Anydrates and hydrates often crystallize in different crystal systems, but the mol-

ecule in solution is the same. In the solid state there is a difference in that water molecules form part of the matrix.

Dehydration kinetics of hydrates has had the attention of the pharmaceutical scientist for a while. As far back as 1967, Shefter and Kmack (1967) studied the dehydration of theophylline hydrate and found it to be first order. However, this is not the normal order of dehydration.

Byrn (1982) has developed a generalized kinetic theory for isothermal reaction in solids, and theophylline has been used as a model for several studies of this kind (Lin and Byrn, 1979; Suzuki et al., 1989; Agbada and York, 1994). In the recent work by Dudu et al. (1995), microcalorimetric methods were used and show a two-step process to take place. The predominant model used for this type of kinetics is the Avrami–Erofeev treatment leading to the equation

$$[-\ln(1-x)]^{0.25} = kt \tag{6.108}$$

and good adherence of the data for each step was found. This points to microcalorimetry as being a potent tool in the investigation of such projects.

There are vacuum/electrobalances on the market now, which have the capability of increasing the relative humidity and keeping the "new" relative humidity constant until the weight gain of a sample in the balance assembly has gained less than a preset quantity of water. When an anhydrate is placed in a vacuum in such a balance assembly and the relative humidity gradually raised, then the "up" and "down" portions of the curve will often have the profile shown in Fig. 30.

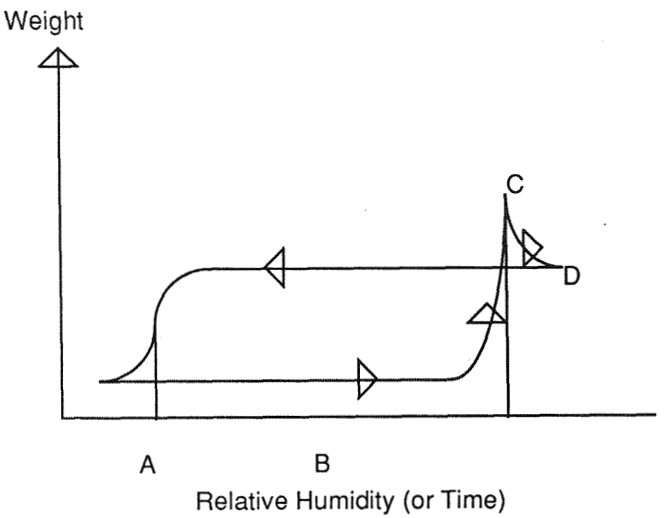


**Fig. 30** A represents the relative humidity over the crystalline hydrate, and at this point hydration should actually occur. But a metastable situation usually occurs, so if the amorphate is exposed to higher humidities, then it is not until at B that it changes, and in this case it forms a (supersaturated) solution, which at C precipitates out as the crystalline hydrate D. The desorption isotherm then results in a constant composition until a lower humidity, where the hydrate starts dehydrating into the amorphous anhydrate.

It is to be expected that the weight of the anhydrate will not increase until the relative humidity of the salt pair is reached. If one only considers the part ABC, then this is logical.

It is noted that the abscissa is time as well as relative humidity, since this latter is changed as a function of time. The curve often goes beyond the weight of the anhydrate, and it is hypothesized that what actually happens is that the relative humidity at which the increase occurs is that of the saturated solution of the anhydrate. This is a metastable solution and will start precipitating out in time (point C) until the weight levels off at the theoretical weight of the hydrate. On the "down" curve, this hydrate then remains until the relative humidity of the salt pair is reached, and then it drops off.

So, if an experiment is carried out as shown in Fig. 30, it is not certain that the relative humidity at A is the equilibrium relative humidity of the hydrate/anhydrate salt pair, because as in a conventional isotherm, the "water channel" could act in the same fashion as a pore, and the "breakthrough" vacuum might be an indication of the effect of the Kelvin equation.

Only a few unreported studies have been carried out of this kind (Pudipeddi, 1995; Dali, 1995; Shlyankevich, 1995), but the method, in the sense of the preceding paragraph, could be of importance in assessing diameters of water channels and of interfacial tension between water and the organic and inorganic matrix molecule (via the Kelvin equation).

## 17. PHOTOLYSIS IN THE SOLID STATE

Not much systematic work has been reported on photolysis of solids. Lachman et al. (1961) pointed out that, most often, a solid tablet will decompose by photolytic decomposition only in the surface area, so that if one broke a "discolored," exposed tablet the color would be unaffected in the interior.

However, Kaminski et al. (1979) reported on a case where a combination of moisture and light caused an interaction between a dye and a drug that permeated the entire tablet.

Tønnesen et al. (1997) have reported on the photoreactivity of mefloquine hydrochloride in the solid state.

## REFERENCES

Adler, M., Lee, G. (1999). J. Pharm. Sci. 88:199.
Agbada, C. O., York, P. (1994). Int. J. Pharm. 106:33.
Anderson, N. R., Banker, G. S., Peck, G. E. (1982). J. Pharm. Soc. 71:7.
Avrami, M. (1939). J. Chem. Phys. 7:1103.
Bawn, C. (1955). "Chemistry of the Solid State," p. 254, Academic Press, New York.
Bray, M. L., Jahansouz, H., Kaufman, M. J. (1999). Pharm. Devl. Techn. 4:81.
Byrn, S. R. (1982). Solid State Chemistry of Drugs. New York: Academic Press, pp. 59–70.
Carstensen, J. T., Kothari, R. (1983). J. Pharm. Sci. 72:1149.
Carstensen, J. T., Morris, T. (1993). J. Pharm. Sci. 82:657.
Carstensen, J. T., Musa M. N. (1972). J. Pharm. Sci. 61:273, 1112.
Carstensen, J. T., Pothisiri, P. (1975). J. Pharm. Sci. 64:37.
Carstensen, J. T., VanScoik, K. (1990). Pharm. Res. 7:1278.
Carstensen, J. T., Aron, E., Spera, D., Vance, J. J. (1966). J. Pharm. Sci. 55:561.

Dali, M.V. (1995). Personal communication.
Dudu, S. P., Das, N. G., Kelly, T. P., Sokoloski, T. D. (1995). Int. J. Pharmaceutics 114:247.
Fini, A., Fazio, G., Alvarez-Fuentes, J., Fernández-Hervás, J. T., Holgado, M. A. (1999). Int. J. Pharm. 181:11.
Franks, F. (1989). Process Biochem 24:3–8.
Goldstein, M., Flanagan, T. (1964). J. Chem. Ed. 41:276.
Gu, L., Strickley, R. G., Chi, L.-H., Chowhan, Z. T. (1990). Pharm. Res. 7:379.
Han, J., Suryanarayanan, R. (1997). Int. J. Pharm. 157:209.
Hollenbeck, R. G., Peck, G. E., Kildsig, D. O. (1978). J. Pharm Sci. 67:1599.
Jacobs, A., Dilatusch, A., Weinstein, S., Windheuser, J. (1966). J. Pharm. Sci. 53:893.
Jander, W. (1927). Z. Anorg. Chem. 163:1
Johnson, W. A., Mehl, R. F. (1939). Trans. Am. Inst. Min. Eng. 135:416.
Jost, H. (1962). Diffusion. New York: Academic Press, p. 45.
Kaminski, E. E., Cohn, R. M., McGuire, J. L., Carstensen, J. T. (1979). J. Pharm. Sci. 68:368.
Kissinger, H. E. (1956). J. Res. Nat. Bur. Std. 57:217.
Kittel, C. (1956). Introduction to Solid State Physics. 2d ed. New York: John Wiley.
Kornblum, S., Sciarrone, B. (1964). J. Pharm. Sci. 53:935.
Lachman, L., Weinstein, S., Swartz, C., Urbanyi, T., Cooper, J. (1961). J. Pharm. Sci. 50:141.
Lemmon, R. M., Gordon, P. K., Parsons, M. A., Mazetti, F. (1958). JACS 80:2730.
Lennard-Jones, J. E. (1931). Proc. Phys. Soc. (London) 43:461.
Leung, S. S., Padden B. E., Munson, E. J., Grant, D. J. W. (1998a). J. Pharm Sci. 87:501.
Leung, S. S., Padden B. E. Munson, E. J., Grant, D. J. W. (1998b). J. Pharm. Sci. 87:509.
Lin, C. T., Byrn, S. R. (1979). Mol. Cryst. Liq. Cryst. 50:99.
Lo, P. K. A. (1976). A study of the solid state stability of ampicillin. Ph.D. thesis, University of New York at Buffalo.
Maron, S. M., Prutton, C. F. (1965). Principles of Physical Chemistry, MacMillan, London, p. 322
Marshall, K., Sixsmith, D., Stanley-Wood, N. G. (1972). J. Pharm. Pharmacol. 24:138.
Moelwyn-Hughes, E. A. (1961). Physical Chemistry 2d rev. ed. New York: Pergamon Press, p. 31.
Mohrle, R. (1980). In: Lieberman, H. A., Lachman, L., eds. Pharmaceutical Dosage Forms: Tablets. Vol. 1, New York: Marcel Dekker. p. 24.
Nelson, E., Eppich, D., Carstensen, J. T. (1974). J. Pharm. Sci. 63:755.
Ng, W. L. (1975). Aust. J. Chem. 28:1169.
Oberholtzer, E. R., Brenner, G. S. (1979). J. Pharm. Sci. 68:863.
O'Donnel, J. H., Whittaker, A. K. (1992). J. M. S.-Pure Appl. Chem. A29:1–10.
Oksanen, C. A., Zografi, G. (1993). Pharm. Res. 10:791.
Olsen, B. A., Perry, F. M., Snorek, S. V., Lewellen, P. L. (1997). Pharm. Dev. Tech. 2:303.
Otsuka, M., Teraoka, R., Matsuda, Y. (1991). Pharm. Res. 8:1066.
Otsuka, M., Onoe, M., Matsuda, Y. (1993). Pharm. Res. 10:577.
Otsuka, M., Ofsua, T., Yoshihisa, M. (1999). Drug Dev. Ind. Pharm. 25:197.
Pfeiffer, R. R., Engel, G. L., Coleman, D. (1976). Antimicrobial Agents Chemotherapy 9:848.
Pikal, M. J., Lukes, A. L., Lang, J. E., Gaines, K. (1976). J Pharm. Sci. 67:767.
Pikal, M. J., Lukes, A. L., Jang, J. E. (1977). J. Pharm. Sci. 66:1312.
Pothisiri, P., Carstensen J. T. (1975). J. Pharm. Sci. 64:1931.
Prout, E., Tompkins, F. (1944). Trans. Faraday Soc. 40:448.
Pudipeddi, M. (1995). Personal communication.
Roy. M. L., Pikal, M. J., Rickard, E. C., Maloney, A. M. (1990). International Symposium on Product Biological Freeze-Drying and Formulation, Bethesda, USA. In Develop. Biol. Standard. 74:323–340 (Karger, Basel, 1991).
Shefter, E, Lo, A., Ramalingam, S. (1974). Drug Dev. Comm. 1(1):29.
Schmitt, E. A., Law, D., Zhang, G. G. Z. (1999). J. Pharm. Sci. 88:291.

Shefter, E., Kmack, G. (1967). J. Pharm. Sci. 56:1028.
Shlyankevich, A. (1995). Personnel communication.
Stacey, F. W., Sauer J. C., McKusick, B. C. (1959). JACS 81:987.
Suihko, E., Ketolainen, J., Poso, A., Ahlgren, M., Gynther, J., Paronen, P. (1997). Int. J. Pharm. 158:47.
Sukenik, C. N., Bonopace, J. A., Mandel, N. S., Bergman, R. C., Lau, P.-Y., Wood, G. (1975). JACS 97:5290.
Suzuki, E., Shimomura, K., Sekiguchiki, I. (1989). Chem. Pharm. Bull. 37:493.
Tønnesen, H. H., Skrede, G., Martinsen, B. K. (1997). Drug Stability 1:249.
Troup, A., Mitchner, H. (1964). J. Pharm. Sci. 53:375.
Tzannis, S. T., Prestrelski S. J. (1999). J. Pharm. Sci. 88:351.
Usui, F. (1984). Master's thesis, University of Wisconsin, School of Pharmacy, Madison, WI 53706.
Usui, F., Carstensen, J. T. (1985). J. Pharm. Sci. 74:1293.
VanScoik, K., Carstensen, J. T. (1990). Int J. Pharmaceutics 58:185.
White, B. (1963). U. S. (Patent) 3 105 1792.
Williams, M. L., Landel, R. F., Ferry, J. D. (1955). JACS 77:3701.
Wright, J. L., Carstensen, J. T. (1986). J. Pharm. Sci. 75:546.
Zografi, G., Kontny, M. (1986). Pharm. Res. 3:187.