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Note

Predicting polymorphic transformation curves using a logistic equation

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Abstract

The commonly used solid-state reaction models (for example—Prout–Tompkins, Avrami–Erofe'ev) describe the polymorphic transformation data only over a certain range, α from 10% to 90%. Predictions based on a fit to a fraction of the data are inadequate because we ignore the early induction phase of the reaction, which is important for predictive purposes. A four-parameter logistic equation describes the data over the entire curve for polymorphic transformation at high temperatures. We use the parameters of the logistic equation to predict the transformation curves. The predicted curves agree with the experimental data.

Keywords: Polymorphic transformation; Logistic equation; Prediction

We begin analyzing data from a solid-state reaction study by plotting the % transformed, α, versus time, t (Fig. 1). The curves of α versus t are usually S-shaped (Byrn et al., 1999). The commonly used solid-state reaction models (for example—Prout–Tompkins, Avrami–Erofe'ev) describe the polymorphic transformation data only over a certain range, α from 10% to 90% (Zhou et al., 2003). Predictions based on a fit to a fraction of the data are inadequate because we ignore the early induction phase of the reaction, which is important for predictive purposes. The motivation in applying the logistic equation to polymorphic transformation is to describe, and predict the data over the entire curve.

The logistic equation assumes that transformation occurs exponentially until an upper limit of the polymorph is reached, at which point the transformation slows and eventually saturates, producing the characteristic S-shape curve (Stone, 1980). A logistic equation describes the data but does not commit to a specific mechanism. The logistic equation is useful in modeling population ecology (Verhulst, 1845; Pearl and Reed, 1920; Leach, 1981; Kingsland, 1995), chemical reactions (Reed and Berkson, 1929), bioassays (Berkson, 1944), radioimmunoassays (Healy, 1972), and dose–response curves (De Lean et al., 1978; Foreman and Johansen, 2003).

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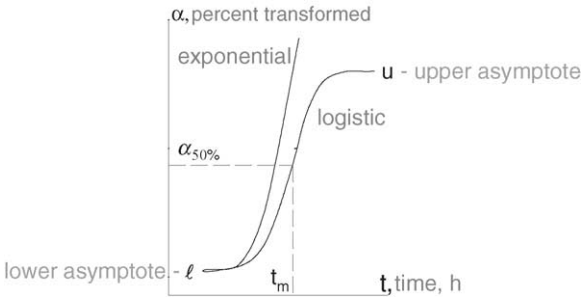

Fig. 1. Comparing the exponential and logistic curve.

In the simple exponential model, the transformation rate dm/dt is proportional to the product

$$\frac{\mathrm{d}m}{\mathrm{d}t} = km \tag{1}$$

m is the amount untransformed, and k is the rate of transformation

In the logistic equation (Reed and Berkson, 1929) the transformation rate dm/dt is proportional to the untransformed and the transformed product.

$$\frac{\mathrm{d}m}{\mathrm{d}t} = km\left[1 - \frac{m}{b}\right] \tag{2}$$

b is the upper limit or upper asymptote, and $(1 - m/b)$ is the fraction of transformed product.

Solving the differential Eq. (2) by separating the variables and integrating gives:

$$m = \frac{b}{1 + \mathrm{e}^{-kt-c}} \tag{3}$$

c is the location parameter that shifts the curve horizontally, and t is the time.

An extension of Eq. (3) is the four-parameter logistic equation (Healy, 1972; De Lean et al., 1978) that increases the flexibility for fitting the data over the entire curve by adding parameters. This is expressed as

$$\alpha = \ell + \frac{u}{1 + (t/t_m)^d} \tag{4}$$

α: % transformed; ℓ : lower asymptote value for α; u: upper asymptote value for α; t: time, hours; t_m: time at which α is 50% (see Jacobs (1997) for not using 50% α as the inflection point); d: slope factor that decides the steepness of the curve.

Table 1
Parameter estimates for the four-parameter logistic function for 180–220 °C data

T (°C)	ℓ	u	t_m	d
180	0.5	98	10.5	−2.2
190	0.0	98	4.10	−2.1
200	1.8	98	1.79	−2.0
210	2.6	98	0.85	−1.9
220	6.0	98	0.57	−1.9

ℓ: Lower asymptote value for % transformed; u: upper asymptote value for % transformed; t_m: time in hours for 50% transformation, estimated from the logistic equation; d: slope factor that decides the steepness of the curve; mean ± 95%PI for 'd' is 2.0 ± 0.3.

We use the four-parameter logistic Eq. (4) to describe the polymorphic transformation curves at high temperatures. We assume a simple solid-state transformation where the less stable polymorph is transformed to a more stable polymorph at a certain temperature; the newly formed crystals acts catalytically for the same transformation producing more of the stable polymorph.

We studied the kinetics of transformations using crystals of a compound in development. The more stable crystalline form (Form I) is monotropically related to a less stable crystalline form (Form II), which crystallizes from a suitable solvent system and is kinetically stable under ambient conditions. At high heating rates (e.g., 100 °C/min), a Form II melt is seen at 266 °C with recrystallization of Form I from the melt. At lower heating rates, the exothermic solid-state conversion is completed before the Form II melt occurs. Form I melts at 282 °C.

We used variable temperature X-ray powder diffraction (VT-XRPD) to follow the kinetics of transformation under isothermal conditions. The studies were completed using a Scintag XDS 2000 diffractometer (Thermo Electron Corp., Inc. Cupertino, CA.) with a Cu Kα (λ = 1.540562 Å) source equipped with a Scintag high and low temperature attachment. Quantitative analysis was done using the area of the peak at 9.2° 2Θ in the pattern of Form 1.

Table 1 displays the values of ℓ, u, t_m, and d for the four-parameter logistic fit to the 180–220 °C data. Fig. 2 is a trellis display (Menon and Nerella, 2001) of the experimental data, the curve fit using the four-parameter logistic equation, and the residuals. The upper asymptote is constrained at 98% (read from the 200 °C to 220 °C data) for all temperatures. The

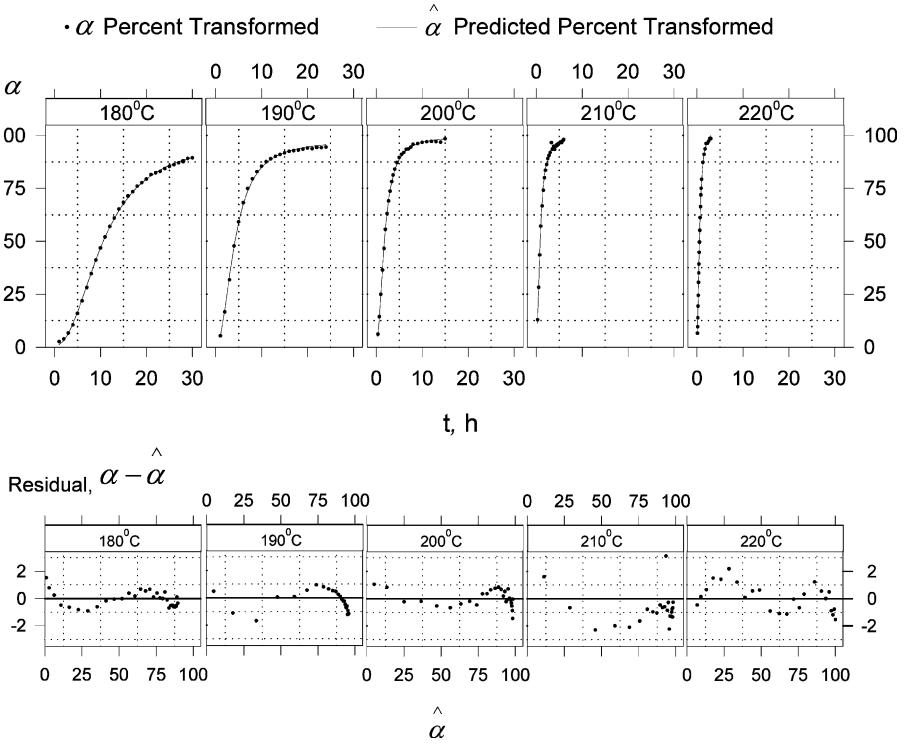

Fig. 2. Polymorphic transformation data, logistic curve fit, and residuals for 180–220 °C.

residuals show systematic deviations but lie within ±3%. We did not try other model estimations and refinement.

Since y_{max}/y_{min} for t_m is >3 Box et al. (1978) recommend a variance stabilizing transformation of the response. A log transformation makes the t_m data symmetric. Table 2 shows t_m varies inversely as T. We use the relation $\ln t_m$ versus $1/\sqrt{T}$ (Table 2) to extrapolate 't_m' to 160 °C and 170 °C. Using $1/\sqrt{T}$ gives us the lowest predicted sum of square residuals. For predicting the transformation curves at 160 °C and 170 °C, 'ℓ' is set at 1.5% (lower asymptote or y-intercept that can vary between 0 and 2%), 'u' at 98% (upper asymptote read from the 200 °C to 220 °C data), and 'd' at 2 (mean of 180–220 °C, Table 1). For 160 °C and 170 °C we collected the polymorphic transformation data for 40 h. The % transformed for 160 °C and 170 °C in 40 h was 30% and 70%, respectively. Fig. 3 shows the residuals for 160 °C were within 2%, and the residuals for 170 °C increase to 8% with predicted % transformed. There is scatter in the % transformed at 170 °C for the later time points as the transition slows down and settles towards an asymptote (Fig. 3). The scatter probably reflects variability in measuring the area of the peak selected for quantitative analysis. The variability in the area measurement may not influence the

Table 2
Predicting t_m for 160 °C and 170 °C $\ln t_m = 416 \times 1/\sqrt{T} - 28.74$

T (°C)	t_m	$\hat{t}_m$	$t_m - \hat{t}_m$
Extrapolated			
160	NM	63.3	–
170	21.9	23.7	−1.80
180	10.5	9.65	0.85
190	4.10	4.22	−0.12
200	1.79	1.97	−0.18
210	0.85	0.97	−0.12
220	0.57	0.50	0.07

T: Temperature in °C; t_m: time in hours for 50% transformation, estimated from the logistic equation; $\hat{t}_m$: predicted time for 50% transformation from the $\ln t_m = 1/\sqrt{T}$; $t_m - \hat{t}_m$: residuals; NM: not measured.

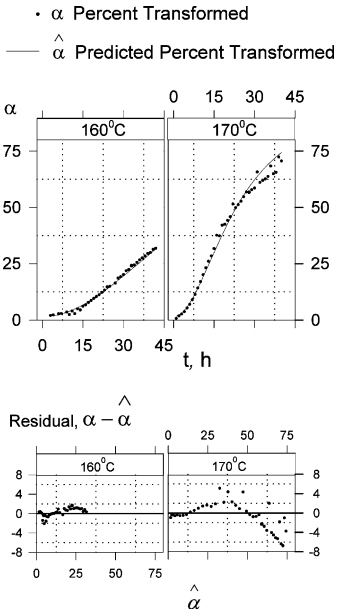

Fig. 3. Observed and predicted polymorphic transformation curves for 160 °C and 170 °C.

crystal growth phase. We did not confirm our theory. The 12 h induction phase at 160 °C suggests that polymorphic transformation will be slow under ambient conditions. After storing the compound for seven years under ambient conditions the polymorphic transformation is undetectable by the powder diffraction technique.

A four-parameter logistic equation predicts the data over the entire curve for polymorphic transformation at high temperatures. The predicted curves agree with the experimental data. The usefulness and limits of the four-parameter logistic equation to polymorphic transformation will be confirmed when repeated for different data sets, and at different temperature ranges.

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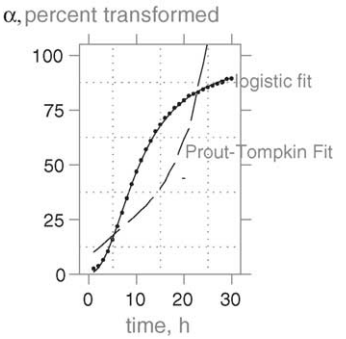


Fig. 4. Comparing the Logistic fit to the Prout–Tompkins fit for 180 °C.

Appendix

Deriving the Prout and Tompkins (1944) from the logistic function

$$m = \frac{b}{1 + e^{-kt-c}} \tag{3}$$

assuming $\frac{m}{b} = \alpha$

$$\alpha = \frac{1}{1 + e^{-kt-c}}$$

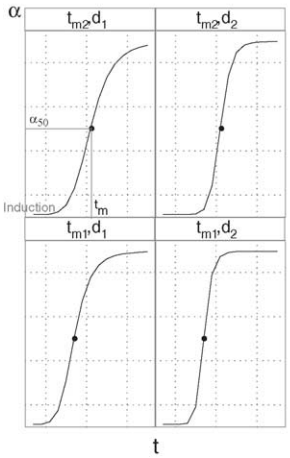
$$1 - \alpha = 1 - \frac{1}{1 + e^{-kt-c}} = \frac{1 + e^{-kt-c}}{1 + e^{-kt-c}} = \frac{e^{-kt-c}}{1 + e^{-kt-c}}$$

$$\frac{\alpha}{1-\alpha} = \frac{1/(1 + e^{-kt-c})}{e^{-kt-c}/(1 + e^{-kt-c})} = \frac{1}{e^{-kt-\beta}} = e^{+kt+c}$$

$$ln\left(\frac{\alpha}{1-\alpha}\right) = kt + c \ldots$$

× (same from as Prout–Tompkins)

Fig. 4 compares the logistic fit to the Prout–Tompkins fit for entire experimental data at 180 °C. The Prout–Tompkins does not describe the experimental data compared to the four-parameter logistic fit.



$$\alpha = 1.5 + \frac{98}{1 + \left(\frac{t}{t_m}\right)^d}$$

α: percent transformed
t: time
t_m: time at which α is 50% (t_{m1} = 6, t_{m2} = 8)
d:slope factor that decides the steepness of the curve (d_1 = -6, d_2 = -12).

Fig. 5. Effect of 't_m' and 'd' on the induction phase and shape of the S-curve.

Fig. 5 shows that 't_m' and 'd' affects the induction phase and the shape of the S-curve. In the figure, 'd' decreases going from left to right (−6 to −12), and 't_m' increases going from bottom to top (6–8). Increasing in t_m and d prolongs the induction phase.

References

Berkson, J., 1944. Application of the logistic function to bioassay. JASA 39, 357–365.

Byrn, S., Pfeiffer, R.R., Stowell, J.G., 1999. Solid-State Chemistry of Drugs, second ed. SSCI Inc., IN, pp. 443–452.

Box, G.E.P., Hunter, W.G., Hunter, J.S., 1978. Statistics for Experimenters. Wiley and Sons, NY, p. 234.

De Lean, A., Munson, P.J., Rodbard, D., 1978. Simultaneous analysis of families of sigmoidal curves: application to bioassay, radioligand assay, and physiological dose–response curves. Am. J. Physiol. 235, E97–E102.

Foreman, J.C., Johansen, T., 2003. Textbook of Receptor Pharmacology, second ed. CRC press, NY.

Healy, M.J.R., 1972. Statistical analysis of radioimmunoassay method. Biochem. J. 130, 207–210.

Jacobs, P.W.M., 1997. Formation and growth of nuclei and the growth of interfaces in the chemical decomposition of solids, new insights. J. Phys. Chem. B 101, 10086–10093.

Kingsland, S., 1995. Modeling Nature. In: Episodes in the History of Population Ecology, second ed. University of Chicago Press, Chicago, pp. 64–98.

Leach, D., 1981. Re-evaluation of the logistic curve for human populations. JRSS, Series A 144, 94–103.

Menon, A., Nerella, N., 2001. Effective graphical displays. Pharm. Dev. Technol. 6, 477–484.

Pearl, R., Reed, J.L., 1920. On the rate of growth of the population of the United States since 1790 and its mathematical representation. Proc. Natl. Acad. Sci. U.S.A. 6, 275–288.

Prout, E.G., Tompkins, F.C., 1944. The thermal decomposition of potassium permanganate. Trans. Faraday Soc. 40, 488–498.

Reed, J.L., Berkson, J., 1929. The application of the logistic function to experimental data. J. Phys. Chem. 33, 760–799.

Stone, R., 1980. Sigmoids. Bull. App. Stat. 7, 59–119.

Verhulst, P.-F., 1845. Recherches mathématiques sur la loi d'accroissement de la population. Nouv. mém. de l'Académie Royale des Sci. et Belles-Lettres de Bruxelles. 18, 3–38.

Zhou, D., Schmitt, E.A., Zhang, G.G., Devalina, L., Vyzovkin, S., Wight, C.A., Grant, D.J., 2003. Crystallization kinetics of amorphous nifedipine studied by model fitting and model-free approaches. J. Pharm. Sci. 92, 1779–1792.