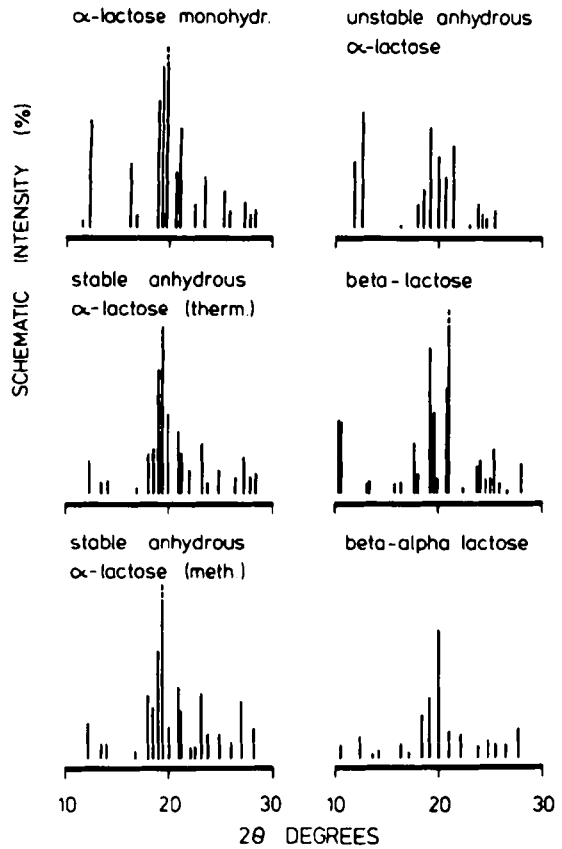

Figure 2—*Representation of the X-ray diffraction patterns of the different forms of lactose*[2].

transition starting at ~140°C, when scanned with a heating rate of 10°C/min, corresponding to dehydration of the product. All three α-lactoses exhibit a melting endotherm beginning at ~210°C. The melting endotherm of unstable α-lactose is, however, preceded, as reported earlier by Itoh *et al.* (3), by an endo- and exothermic peak at ~170°C and 180°C, respectively. This indication of thermal alteration was elucidated in our study by X-ray diffraction analysis and by determination of the β-content performed on samples which were heated to different temperatures as mentioned in Table I. The results show a conversion at ~180°C of unstable α-lactose into a product with a crystallographic structure different from both hydrous and anhydrous α-lactose and from β-lactose.

X-ray diffraction analysis showed the conversion product to agree with lactose crystals, which were prepared by Buma (8) by crystallization from methanol. Buma concluded from specific gravity measurements and sedimentation analysis that the "crystalline lactose obtained from methanol did not consist of α-lactose crystals and β-lactose crystals, as was reported by [Lim and Nickerson (9)], but of crystals consisting of α- and β-lactose." Analysis of the X-ray diffraction patterns (Fig 2) of α-lactose monohydrate, stable anhydrous α-lactose produced by thermal dehydration, stable anhydrous α-lactose obtained by methanol desiccation, unstable anhydrous α-lactose, β-lactose, and the conversion product mentioned before, indicate in our opinion that the last product can best be characterized as a crystalline β/α-lactose compound, having a β:α ratio of ~1:1. From these results it may be concluded, that the first endotherm at ~170°C as shown by the DSC-curves of unstable anhydrous α-lactose (Fig. 1), is the result of the melting of the unstable anhydrous α-lactose, whereas the second endotherm at ~210°C corresponds with the melting point of the crystalline β/α-lactose compound, which crystallized at ~180°C.

These results and the observation of endo- and exothermic transitions at ~160°C and 180°C, respectively, in the DSC-curves of α-lactose monohydrate gave rise to a detailed examination of the thermal treatment of this product. X-ray diffraction analysis performed on samples that were heated at a rate of 2°C/min (instead of the usual 10°C/min) showed at 160°C the occurrence of unstable next to stable anhydrous α-lactose (see Table I). As expected, the crystalline β/α-compound was consequently detected at 200°C. This implies that α-lactose monohydrate loses its water upon heating and changes into both stable and unstable anhydrous α-lactose, the latter being converted into the crystalline β/α-lactose compound at temperatures >180°C. Besides, it is interesting to note that the α-lactoses show a significant conversion into β-lactose upon melting at a temperature of ~220°C.

In conclusion, thermal treatment of α-lactoses involves changes in β-content and in crystal structure.

(1) T. A. Nickerson, "Fundamentals of Dairy Chemistry," 2nd ed. AVI-Publishing Co. Inc., Westport, Conn., p. 300.
(2) T. J. Buma and G. A. Wiegers, *Neth. Milk Dairy J.*, **21**, 208 (1967).
(3) T. Itoh, M. Satoh, and S. Adachi, *J. Dairy Sci.*, **60**, 1230 (1977).
(4) P. F. Sharp, U.S. Patent 2,319,562 (1943).
(5) E. Berlin, P. G. Kliman, B. A. Anderson, and M. J. Pallansch, *Thermochim. Acta*, **2**, 143 (1971).
(6) T. Itoh, M. Katoh, and S. Adachi, *J. Dairy Res.*, **45**, 363 (1978).
(7) K. D. Ross, *J. Dairy Sci.*, **61**, 255 (1978).
(8) T. J. Buma, *Neth. Milk Dairy J.*, **32**, 258 (1978).
(9) S. G. Lim and T. A. Nickerson, *J. Dairy Sci.*, **56**, 843 (1973).

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Received July 11, 1983.
Accepted for publication March 21, 1984.

Transitions of Lactoses by Mechanical and Thermal Treatment

Keyphrases □ α-Lactose—mechanical and thermal treatment, transition

To the Editor:

Comminution techniques, such as crushing and grinding, are frequently used to prepare samples for the determination

[2] Philips Defractometer CuK radiation was used.

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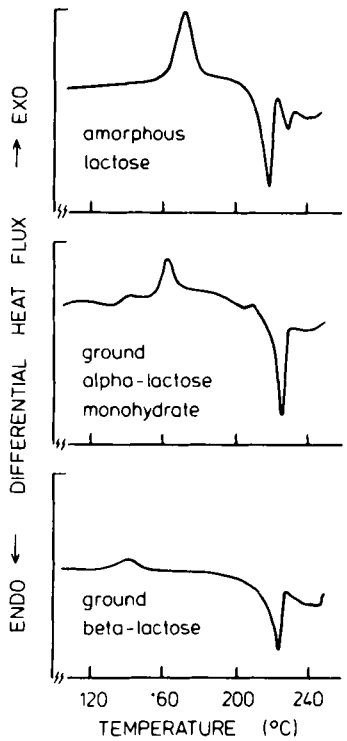

Figure 1—*DSC-curves of amorphous lactose, intensively ground α-lactose monohydrate, and intensively ground β-lactose, respectively, recorded at a heating rate of 10°C/min.*

Table I—Changes in β-Content (GLC-Determination) and in the Solid State (X-ray Diffraction Analysis). During Thermal Treatment (DSC-cell 910; Heating Rate 10°C/min)[a]

	Temperature, °C	
	20	180
β-content (%)		
Amorphous lactose	54	50
Ground α-lactose monohydrate	2	42
Ground β-lactose	82	79
Solid State		
Amorphous lactose	(—)	BA
Ground α-lactose monohydrate	(—)	BA
Ground β-lactose	(—)	B

[a] B = β-lactose; BA = β/α-lactose compound crystal; (—) = amorphous lactose (no or only a few very weak diffraction lines could be detected.

of the physicochemical properties of solid materials. Size reduction is, however, a very active process, supplying energy to a particle during fragmentation. It is well known that mechanical treatment of minerals can result in activation and changes in surface properties, in polymorphic transitions and alterations in physical properties of the bulk phase, in uncrystallization, as well as in mechanochemical solid-state reactions (1).

Hüttenrauch, in his series on molecular pharmaceutics, studied the mechanical activation of drugs and excipients and showed uncrystallization of α-lactose monohydrate during milling (2). We reported earlier (3) changes in the β-content and in the solid state of α-lactose monohydrate, stable anhydrous α-lactose, and unstable anhydrous α-lactose, respectively, by thermal treatment. Continuing this study, amorphous lactose and intensively ground samples of α-lactose monohydrate and β-lactose, respectively, were examined for their thermal characteristics. Figure 1 illustrates the Differential Scanning Calorimetry (DSC)-curves of these preparations, obtained at a heating rate of 10°C/min, using a thermal analyzer[1].

The DSC-curve of the amorphous lactose, prepared by spray-drying, shows an exothermic transition at ~160°C and an endotherm at ~210°C. An analogous pattern was recorded for intensively ground α-lactose monohydrate. Its DSC-curve shows, in contrast to that of nonground α-lactose monohydrate, hardly a dehydration endotherm, but an exotherm at ~160°C. Intensively ground β-lactose exhibited an exotherm as well, but at a slightly lower temperature (≃140°C).

To elucidate the indication of thermal transition during the dynamic process of DSC, X-ray diffraction patterns were made of samples, both prior to and after thermal treatment by heating to ~180°C followed by immediate cooling to room temperature. As expected, the nonthermally treated but intensively ground samples showed no, or at least very weak, diffraction lines (Table I). This indicates that comminution had resulted in uncrystallization of both α-lactose monohydrate and β-lactose. The uncrystallized products crystallized on heating. X-ray diffraction analyses of samples of amorphous lactose and of intensively ground α-lactose hydrate, respectively, both proved to correspond with a crystalline β/α-lactose compound, when heated to 180°C with subsequent cooling to room temperatures.

Uncrystallized β-lactose was, however, found to crystallize into β-lactose on thermal treatment. This difference in thermal behavior between samples of intensively ground α-lactose monohydrate and β-lactose, respectively, is supported by the observation of an increase in β-content for ground α-lactose monohydrate from 2 to 42% and hardly any change in β-content for uncrystallized β-lactose on thermal treatment (Table I).

To investigate more thoroughly the formation of the crystalline β/α-lactose compound from amorphous lactose, six batches of amorphous lactose, differing in ratio from ~3:7 to ~8:2 and prepared by freeze- or spray-drying, were heated to different temperatures and subsequently cooled to room

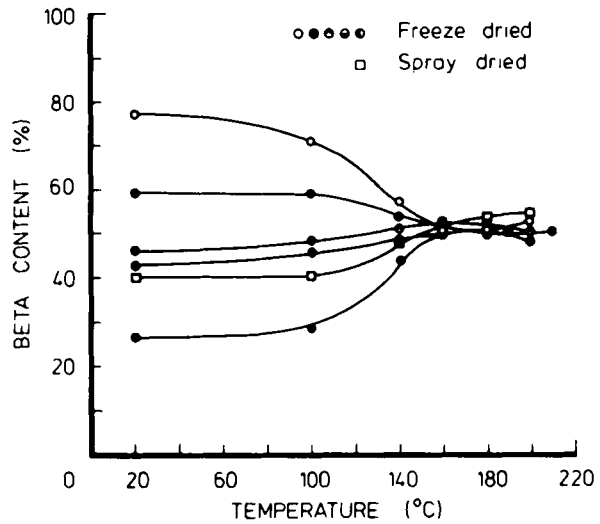

Figure 2—*Change in β-content of different amorphous lactose products with temperature[2] heating rate 10°C/min.*

[1] DuPont Model 990 with DSC-cell 910.
[2] Mettler TA 2000.

temperature. Determination of the β-content of the products showed that all preparations had a final β:α ratio of ~1:1 (see Fig. 2). X-ray diffractograms of the samples that were heated to ~200°C proved to correspond to a crystalline β/α-lactose compound.

In conclusion, α-lactose monohydrate is found to lose its water of crystallization and like β-lactose, changes into an amorphous state on intensive grinding. Thermal treatment of both amorphous lactose and uncrystallized α-lactose monohydrate results in crystallization of a crystalline β/α-lactose compound. This is in contrast to uncrystallized β-lactose, which crystallizes into β-lactose.

(1) I. J. Lim, S. Nadiv, and D. J. M. Grodzian, *Miner. Sci. Eng.*, **7**, 313 (1975).

(2) R. Hüttenrauch, *Acta Pharm. Technol.*, suppl. **6**, 55 (1978).

(3) C. F. Lerk, A. C. Andreae, A. H. de Boer, P. de Hoog, K. Kussendrager, and J. van Leverink, *J. Pharm. Sci.*, in press.

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Received July 11, 1983.
Accepted for publication March 21, 1984.

Concentration Ratio Method to Determine the Rate Constant for the Special Case when $k_a = k_e$

Keyphrases □ Pharmacokinetics—one-compartment open model, concentration ratio method to determine rate constant

To the Editor:

In a one-compartment open model with first-order absorption and elimination processes, the plasma concentrations (C_p) of a drug at any time, t, after its extravascular administration are generally described by:

$$C_p = \frac{FDk_a(e^{-k_e t} - e^{-k_a t})}{Vd(k_a - k_e)} \qquad \text{(Eq. 1)}$$

where F is the fraction of dose (D) absorbed, k_a and k_e are absorption and elimination rate constants, respectively, and Vd is the apparent volume of distribution. In the special case where k_a is equal to k_e, Eq. 1 becomes mathematically indeterminable, and the general equation (Eq. 2) describing the $C_p t$ profile can be explicitly obtained by setting $k_a = k_e = k$ and using the standard integration technique:

$$C_p = \frac{FDkte^{-kt}}{Vd} \qquad \text{(Eq. 2)}$$

It was proposed recently by Chan and Miller (1) that the $C_p t$ data of this special case could be described by Eq. 1 using the nonlinear regression program NONLIN (2) provided there was at least a small difference between k_a and k_e. This analysis will yield similar values for k_a and k_e which will, in essence, identify equality between k_a and k_e. This approach, applied successfully by the authors to one data set containing 5% random noise, seemed superior to the one proposed by Bialer (3). The shortcomings of the latter were recently discussed by Barzegar-Jalali and Toomanian (4).

In this study, a simple plasma concentration ratio method is proposed to determine the rate constant k using plasma concentrations at any two consecutive times, t_{n-1} and t_n (as defined by Eq. 2):

$$C_p^{n-1} = \frac{FDkt_{n-1}e^{-kt_{n-1}}}{Vd} \qquad \text{(Eq. 3)}$$

and

$$C_p^{n} = \frac{FDkt_{n}e^{-kt_{n}}}{Vd} \qquad \text{(Eq. 4)}$$

Dividing Eq. 4 by Eq. 3, taking the natural logarithm of the resulting expression, and solving for k yields the following relationship:

$$k = \frac{\ln(t_n/t_{n-1}) - \ln(C_p^n/C_p^{n-1})}{(t_n - t_{n-1})} \qquad \text{(Eq. 5)}$$

Where k represents the estimated rate constant between the time interval t_{n-1} to t_n. Since a datum set will usually contain several plasma concentrations, k can be estimated for each time interval and averaged to obtain an overall estimate of k:

$$k = \frac{1}{n-1}\sum_{i=2}^{n}\frac{\ln(t_n/t_{n-1}) - \ln(C_p^n/C_p^{n-1})}{(t_n - t_{n-1})} \qquad \text{(Eq. 6)}$$

It is apparent from Eq. 5 that the proposed method does not require blood sampling at close intervals. Also, the proposed method is applicable to the entire time course of a drug and even to those cases where sampling schedule is limited and regression analysis of the $C_p t$ data according to Eq. 1 is not practical.

The concentration ratio method was compared against the approach of Chan and Miller (1) as well as the theoretical method (Eq. 2). Plasma concentrations with only rounding error were calculated at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, and 16 h using Eq. 2 with $FD/Vd = 10.0$ and $k = 0.5$. Twelve additional datum sets were generated by adding normally distributed random error with an RSD of ±10%. Each set was analyzed by curve-fitting the data to Eqs. 1 and 2 using the NONLIN program as well as by the present concentration ratio method. The curve-fitting of the data to Eqs. 1 and 2 was performed using the reciprocal of plasma concentration as a weighting function. The results are compared in Table I.

The nonlinear regression analysis of the $C_p t$ data according to Eq. 1 identified equality[1] of k_a and k_e in several cases (cases 1, 6–12, Table I). The estimated k_e values by Eq. 1 were smaller (>10%) than that estimated by Eq. 2 in 4 of 14 cases. The mean k_e value estimated by Eq. 1, 0.458, was 8% smaller

[1] Equality was identified when $k_a \pm SD$ overlapped $k_e \pm SD$.

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