ple-dosing regime which might limit the application of the method in patient studies.

Bauer and Gibaldi (7) have proposed an alternative method for performing moment-analysis calculations on multiple-dosing data. It should be noted that their Eq. 7 is equivalent to Eq. 6 in this presentation. The Bauer and Gibaldi method requires the use of calculated concentrations to calculate area under the curve, while this presently proposed method employs only the data observed at multiple-dosing steady state. This raises the possibility of being able to determine whether pharmacokinetic changes, as observed in mean retention times or, perhaps, steady-state volumes of distribution, could have been induced during multiple dosing.

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M. Pfeffer
Bristol-Myers Company
Pharmaceutical Research and Development Division
Syracuse, NY 13221-4755

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Alterations of α-Lactose During Differential Scanning Calorimetry

Keyphrases □ α-Lactose—alterations, differential scanning calorimetry

To the Editor:

Lactose is a natural disaccharide widely used as a diluent in tablet formations. As a solid it is known to occur either in one of four crystalline forms or in an amorphous state. α-Lactose monohydrate is obtained by crystallization from a super-saturated solution at temperatures <93.5°C, whereas β-lactose crystals are obtained at temperatures >93.5°C (1). During crystallization of β-lactose, no water is incorporated in the crystal lattice. The crystals of β-lactose exist in a nonhygroscopic anhydrous form only, in contrast with α-lactose, which occurs both as monohydrate and as anhydrous α-lactose. Thermal dehydration, or desiccation of the hydrate crystals with suitable liquids, converts α-lactose monohydrate into its anhydrous form. A very hygroscopic product, generally called unstable anhydrous α-lactose, is formed when α-lactose hydrate crystals are heated, mostly *in vacuo*, at temperatures of 100–130°C (2–4). Thermal treatment in a moist atmosphere at temperatures over ~110°C, or desiccation with suitable liquids, such as dry methanol, may result in a nonhygroscopic product, generally called stable anhydrous α-lactose (2, 4).

The different types of lactose are increasingly studied by thermal analysis. Berlin *et al.* (5) determined the heat of desorption of water from α-lactose monohydrate by differential scanning calorimetry. Itoh *et al.* (3, 6) used differential thermal analysis in studying the characteristics of α-lactose hydrate and of β-lactose, next to IR absorption and X-ray powder diffraction techniques. Differential scanning calorimetry has been applied by Ross (7) for the direct measurement of the amount of α- and β-lactose in whey powders.

This communication reports the occurrence of changes in the solid state during differential scanning calorimetry of α-lactoses. Figure 1 illustrates the DSC-curves of α-lactose monohydrate and of stable and unstable anhydrous α-lactose, respectively, as recorded by means of a thermal analyzer[1]. The DSC-curve of α-lactose monohydrate shows an endothermic

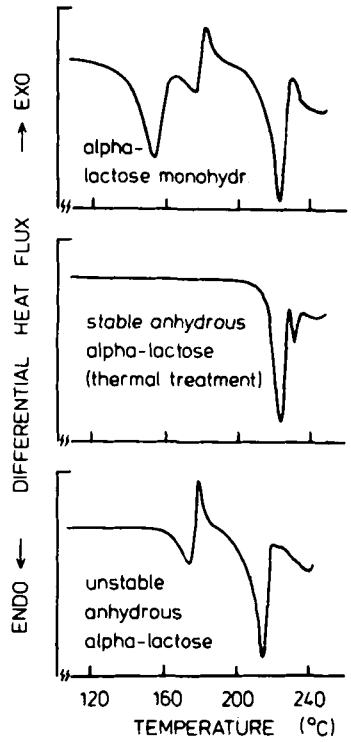

Figure 1—*DSC-curves of α-lactose monohydrate, stable anhydrous α-lactose, and unstable anhydrous α-lactose, respectively, recorded at a heating rate of 10°C/min.*

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

	Temperature, °C						
	20	120	160	180	200	210	220
β-content (%)							
α-Lactose monohydrate	4	5	19	21	23	—	44
Stable anhydrous α-lactose	20	20	—	20	22	34	56
Unstable anhydrous α-lactose	18	—	18	42	—	54	—
Solid State							
α-Lactose monohydrate	AM	SA+(UA)		—	SA+(BA)		
Stable anhydrous α-lactose	SA			SA			
Unstable anhydrous α-lactose	UA				BA		

[a] AM = α-lactose monohydrate; SA = stable anhydrous α-lactose; UA = unstable anhydrous α-lactose; BA = β/α-lactose compound crystal; (UA) and (BA) refer to a heating rate of 2°C/min.

[1] Dupont Model 990 with DSC-cell 910.

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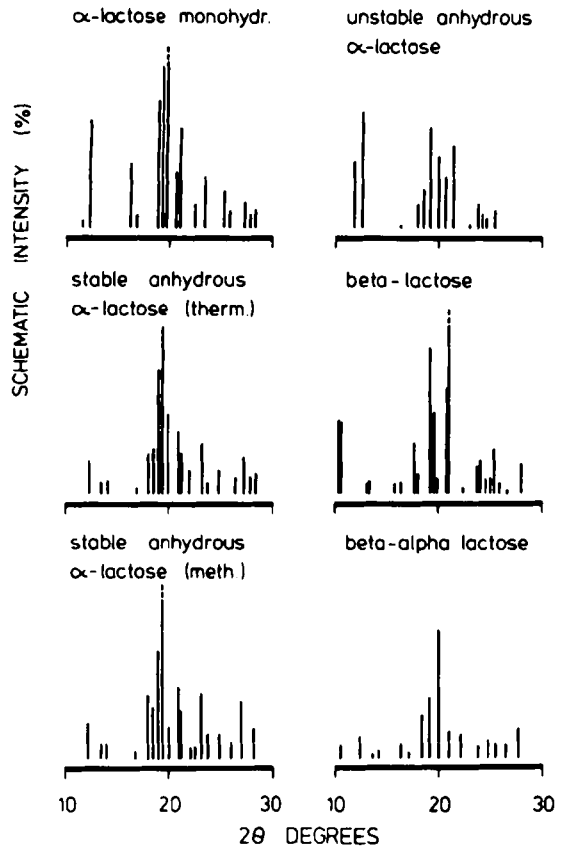

Figure 2—*Representation of the X-ray diffraction patterns of the different forms of lactose*[2].

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.

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C. F. Lerk[x]
A. C. Andreae
A. H. de Boer
Laboratory for Pharmaceutical Technology and Dispensing
State University of Groningen
Ant. Deusinglaan 2, 9713 AW Groningen
The Netherlands
P. de Hoog
K. Kussendrager
J. van Leverink
D.M.V.
P.O. Box 13, 5460 BA Veghel
The Netherlands

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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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