〔Chem. Pharm. Bull.
26(3) 967—971 (1978)〕

UDC 615.453.6.011.4.014.21 : 548.734

Moisture Sorption and Volume Expansion of Amorphous Lactose Tablets[1]

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(Received June 7, 1977)

Measurements of the moisture sorption and the volume expansion of amorphous lactose tablets, as well as measurements of the formation of crystalline lactose, were carried out under controlled relative humidities. At high relative humidity, it was suggested that the supersaturated solution of lactose was formed on some parts of the surface of amorphous lactose particles and the crystallization occured in an autocatalytic manner, which led to a rapid expansion of tablets. On the other hand, at low relative humidity, it appeared that the hygroscopic swelling owing to the physical adsorption of moisture on the inner surface of tablets occured without crystallization.

Keywords——moisture sorption; volume expansion of tablets; crystallization; X-ray diffraction analysis; a modified sample holder of an X-ray diffractometer; amorphous lactose

In order to prove the hypothesis that hygroscopic swelling of diluents and/or binders contained in a tablet may cause splitting of the sugar coating layer of the tablet, studies on the moisture sorption and volume expansion of model tablets of starch,[3a] cellulose,[3b] anhydrous α- and β-lactose were made previously. In the present paper, the influence of crystallization of an amorphous substance on the volume increase of tablet size has been examined by the use of amorphous lactose which is more or less contained in spray-dried lactose.[4,5] Several workers[6,7] have reported on the moisture uptake by amorphous lactose and the subsequent formation of crystalline lactose. But, no attempt has been made to relate the crystallization process to the tablet expansion.

In measuring the crystallization of the samples with an X-ray diffractometer, it was desired to avoid the change in conditions under which the sample was placed during the experiment, because the rate of crystallization of amorphous lactose was fairly rapid and was affected by humidity of the surrounding atmosphere. Therefore, a new sample holder of an X-ray diffractometer was devised in which the sample could be always exposed to an atmosphere of a given relative humidity (R.H.). This apparatus is supposed to be also useful for researches on formation of hydrates, release of moisture from hydrates, phase transition of polymorphs, and so on.

Experimental

Materials——Amorphous lactose was prepared by spray drying a saturated aqueous solution of lactose monohydrate employing a laboratory spray drier[8] equipped with a centrifugal atomizing wheel. The

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[1] *a*) This paper constitutes the 4th report in the series of Moisture Sorption and Volume Expansion of Tablets; *b*) Proceeding paper: A. Otsuka, T. Wakimoto, and A. Takeda, *Yakugaku Zasshi*, **96**, 351 (1976).

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[3] *a*) A. Otsuka, T. Wakimoto, and A. Takeda, *Yakuzaigaku*, **29**, 85 (1969); *b*) T. Wakimoto, A. Takeda, and A. Otsuka, *ibid.*, **29**, 263 (1970).

[4] R.W. Bell, *Ind. Eng. Chem.*, **22**, 51 (1930).

[5] W.C. Gunsel and L. Lachman, *J. Pharm. Sci.*, **52**, 178 (1963).

[6] B.L. Herrington, *J. Dairy Sci.*, **17**, 501 (1934).

[7] J.H. Bushill, W.B. Wright, C.H.F. Fuller, and A.V. Bell, *J. Sci. Fd Agric.*, **16**, 622 (1965).

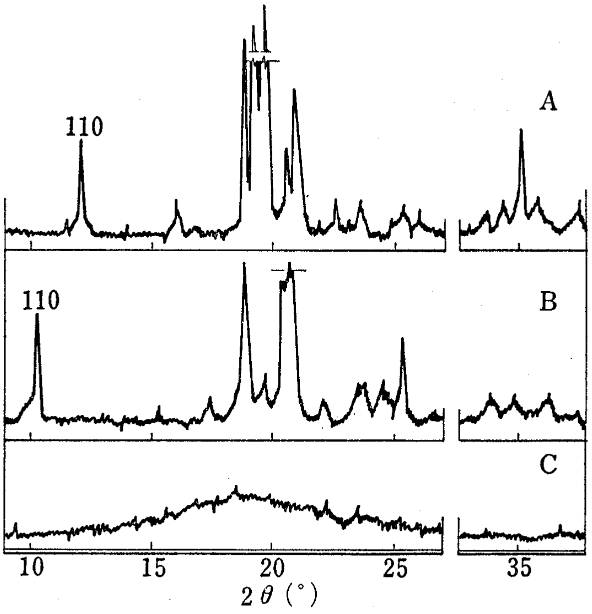

Fig. 1. X-Ray Diffraction Patterns of Crystalline and Amorphous Lactose

A: α-lactose monohydrate, B: anhydrous β-lactose, C: amorphous lactose.

temperature around the nozzle and of the chamber was maintained at 145±5°. The greatest care was taken about the temperature regulation, because the change of temperature greatly affected the formation of amorphous lactose. The mean particle size of the powdered sample determined by scanning electron microscope was 11.4 μm. Fig. 1 shows the X-ray diffraction pattern of amorphous lactose obtained, together with the patterns of α-monohydrate and β-anhydrous.

Tablet Preparation——0.5 g of amorphous lactose was pressed statically under a pressure of 2 ton/cm^2 to make a tablet of 1.6 cm diamter. Tablets made were dried over P_2O_5 at 90° under reduced pressure for 6 hrs and then aged for 30 days over P_2O_5 in a desiccator at room temperature to release the strain.

Measurements of X-Ray Diffraction——A new sample holder was designed for carrying out continuous measurement of X-ray diffraction at an atmosphere of constant R.H. and temperature. A schematic diagram of the holder is shown in Fig. 2. A sample chamber with a copper fin for raising heat conduction is sunk into a thermostatic chamber. The air of a known R.H. is passed through the liquid in the thermostatic chamber and is introduced to the sample chamber. The incidence window of X-ray is covered with Mylar film and sealed sufficiently. For the adjustment of the central axis of the holder to the incident X-ray beam pass, the vertical adjustment mechanism is installed. A commercial X-ray diffractometer (Japan Electron Optics Laboratory Co. Ltd., Tokyo, DX-GE-2F type) was employed to determine the relative crystallinity of the sample. The X-ray source was Cu Kα with Ni filter; voltage 20 kv; current 5 mA; scanning speed 2°/min; time constant 1 sec; divergence slit 1 mm; Soller silt 4.8 mm; scattering slit 0.2 mm;

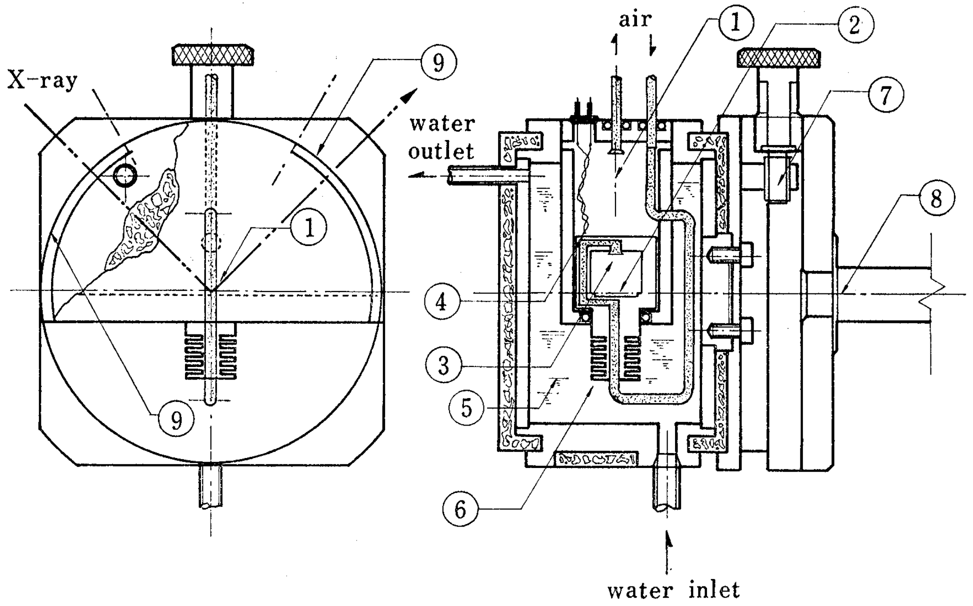

Fig. 2. Sample Holder Used for X-Ray Diffraction Analysis

① sample chamber, ② sample, ③ blowoff of humidity controlled air, ④ thermister thermometer, ⑤ thermostatic chamber, ⑥ copper fin, ⑦ holder vertical adjustment mechanism, ⑧ central axis, ⑨ Mylar film.

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8) H. Takenaka, Y. Kawashima, and T. Yoneyama, *Chem. Pharm. Bull.* (Tokyo), **19**, 1234 (1971).

receiving slit 1 mm. A modification was made on the goniometer to scan between 2θ: 9° and 17° repeatedly, and the heights of the selected peaks (2θ: 12.4° for α-monohydrate and 10.5° for β-anhydrous) were read at regular time intervals. The peak from a brass block at 2θ: 42.1° was used as a standard for the adjustment of the instrument. No regard was given to the shift of the sample surface due to the expansion of sample during processing.

Fig. 3 shows the apparatus for preparing the air stream to be introduced to the sample chamber. Humidity-controlling is carried out by passing the air through scrubbing bottles that contain sulfuric acid solutions of the appropriate concentration to give desired R.H. The air rate used is 180 ml/min. Circulating water is sent from the main constant temperature bath into the sample holder to keep its temperature at 30°.

Measurements of the Expansion of Tablets——Changes in thickness and diameter of tablets with time were measured using an electron micrometer (Anritsu Electric Co., K-402-B and K-301 Rigid Stand type) in the chamber kept at 30°. Further details of the apparatus were described in the previous paper.[3a)]

Measurements of the Amount of Sorbed Moisture——Change in weight by sorption of moisture with time was measured in the same chamber as used for the measurements of expansion using a direct reading balance.

Examination with Scanning Electron Microscope——Some of the samples were examined with scanning electron microscope (Japan Electron Optics Laboratory Co. Ltd., Tokyo, JSM-S1 type) before and after moisture sorption.

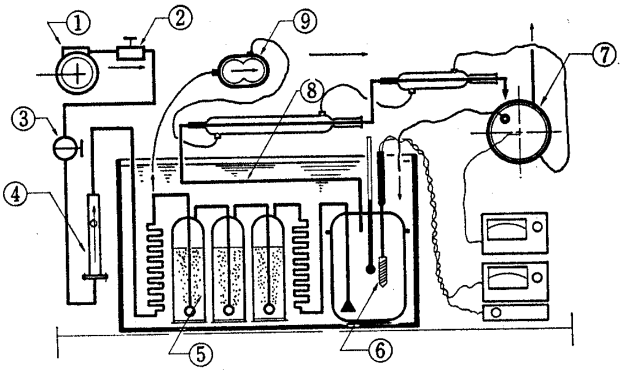

Fig. 3. Schematic Diagram of Apparatus for Preparing the Air Stream Kept at a Given Humidity

① rotary compressor, ② pressure regulator, ③ needle valve, ④ flowmeter, ⑤ sulfuric acid solution, ⑥ LiCl hygrometer, ⑦ sample holder, ⑧ constant temperature bath, ⑨ circulating pump.

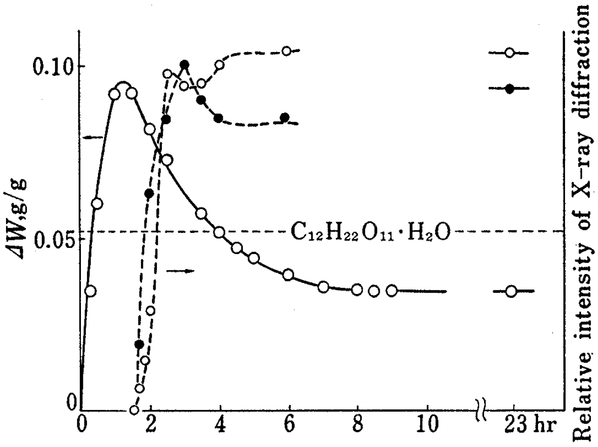

Fig. 4. Change in Moisture Content and Cristallinity with Time for Amorphous Lactose Powder at Relative Humidity of 78% at 30°

—○—: moisture content, g/g dry solid,
---●---: height of peak at 2θ=12.4°,
---○---: height of peak at 2θ=10.5°.

Results and Discussion

The change in moisture content and crystallinity of amorphous lactose powder with time at 78% R.H. were shown in Fig. 4. Full line indicates the amount of sorbed moisture and broken lines indicate the height of two peaks at 2θ: 12.4° and 10.5°. The rate of moisture sorption was relatively rapid and the amount sorbed reached the maximum after about one hr. Thereafter it began to decrease and an equilibrium state was attained after about 7 hr. On the other hand, the peaks in the X-ray diffraction patterns emerged when the amount of sorbed moisture became to decrease. The heights of which rise rapidly and equilibrium was reached within a few hrs. Similar phenomena were found in amorphous sucrose powder by Palmer, Dye and Black.[9)] These observations suggest following mechanism: in the beginning of the moisture sorption, moisture was sorbed on the surface of amorphous lactose particles. As the amount of sorbed water increases, supersaturated solution was formed on some parts of the surface, which led to the formation of nuclei and the growth of crystals from the

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[9)] K.J. Palmer, W.B. Dye, and D. Black, *Agri. Food Chem.*, 4, 77 (1956).

nuclei. As the crystallization proceeds, the release of the sorbed water occurs. This is due to a decrease in surface area with a transformation of amorphous lactose to a crystalline state. Then, this liberated water promotes the formation of supersaturated solution of lactose and accelerates the crystallization autocatalytically.

The X-ray diffraction pattern of the final product indicated that the lactose was present as a mixture of α-monohydrate and β-anhydrous even after 45 hr. This observation was in consistent with the fact that the moisture content at the equilibrium state was lower than the value when the product was assumed to be monohydrate only. It was reported in previous paper[1b)] that β-anhydrous was less hydroscopic at below 90% R.H.

Fig. 5 shows the results of the amorphous lactose tablet under the same condition (at 30°, 78% R.H.). The amount of sorbed moisture and the increase in volume of the tablet are shown in left vertical-axis, and the relative intensity of X-ray diffraction in right axis. The patterns of moisture sorption and of X-ray diffraction were qualitatively similar to those in the powdered sample. However, both the rate of moisture sorption and the rate of crystallization were extremely slow, compared with the powder. This may be due to the contraction of capillary space between particles owing to the applied pressure during tablets preparation processes. At the early stage of moisture sorption, slow expansion of tablet was

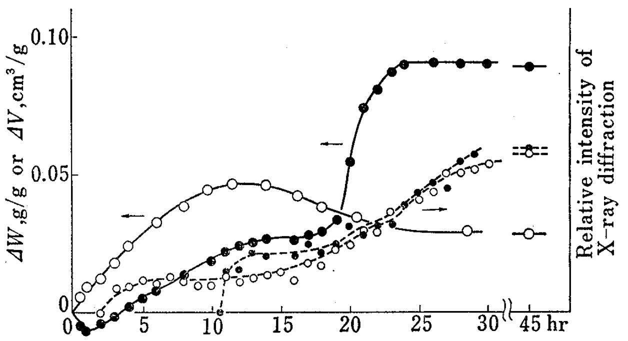

Fig. 5. Change in Moisture Content, Volume and Crystallinity of Amorphous Lactose Tablet with Time at Relative Humidity of 78% at 30°

—○—: moisture content, g/g dry solid,
—●—: volume expansion, cm^3/g dry solid,
---•---: height of peak at $2\theta=12.4°$,
---○---: height of peak at $2\theta=10.5°$.

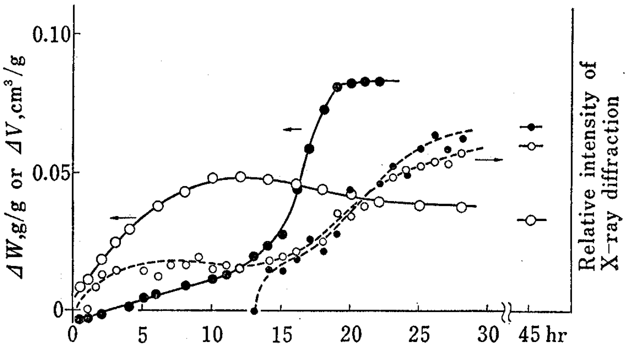

Fig. 6. Change in Moisture Content, Volume and Crystallinity of Amorphous Lactose Tablet with Time at Relative Humidity of 94% at 30°

—○—: moisture content, g/g dry solid,
—●—: volume expansion, cm^3/g dry solid,
---•---: height of peak at $2\theta=12.4°$,
---○---: height of peak at $2\theta=10.5°$.

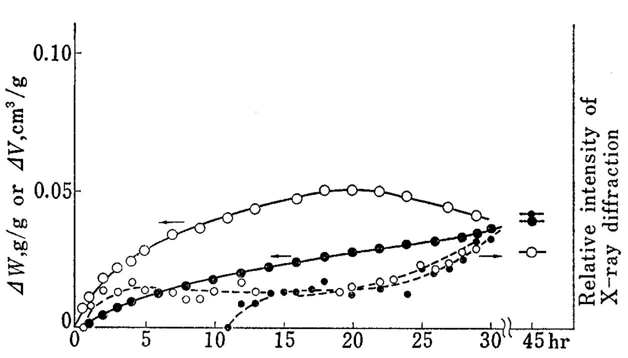

Fig. 7. Change in Moisture Content, Volume and Crystallinity of Amorphous Lactose Tablet with Time at Relative Humidity of 49% at 30°

—○—: moisture content, g/g dry solid,
—●—: volume expansion, cm^3/g dry solid,
---•---: height of peak at $2\theta=12.4°$,
---○---: height of peak at $2\theta=10.5°$.

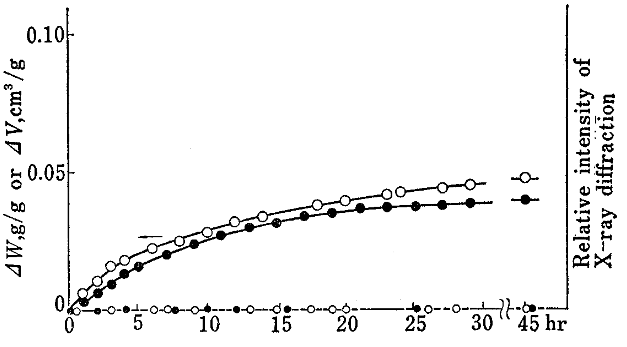

Fig. 8. Change in Moisture Content, Volume and Crystallinity of Amorphous Lactose Tablet with Time at Relative Humidity of 35.5% at 30°

—○—: moisture content, g/g dry solid,
—●—: volume expansion, cm^3/g dry solid,
---•---: height of peak at $2\theta=12.4°$,
---○---: height of peak at $2\theta=10.5°$.

observed. Subsequently, a rapid increase in volume occured corresponding to the decrease in moisture content and the increase in crystallinity, and the equilibrium was reached within a few hrs.

Fig. 6 shows the results at 94% R.H., which were similar to those for 78% R.H., except that the abrupt change in each set of measurement commenced at a earlier time.

Fig. 7 shows the results at 49% R.H. The shape of the curves of both the moisture content and X-ray diffraction intensity suggested the formation of crystalline lactose. However, the volume of tablet increased monotonously and an abrupt change in expansion was not observed. From these results, it is suggested that a considerable amount of amorphous lactose still remained after 45 hr.

The results at 35.5% R.H. are shown in Fig. 8. In this condition, a monotonous increase in both the moisture sorption and the tablet volume with time was observed. On the other hand, crystallization was not detected by the X-ray diffraction analysis throughout the experiment. It appears probable that the amount of moisture sorbed was not sufficient for making the supersaturated solution of lactose. Accordingly, the expansion of amorphous lactose tablet under low R.H. was considered to be the hygroscopic swelling without crystallization owing to the physical adsorption of moisture on the inner surfaces of tablets. These results closely resemble those for model tablets of high polymers such as starch[3a)] and cellulose.[3b)]

The scanning electron micrographs of the amorphous lactose powder and the tablet before and after moisture sorption were shown in Fig. 9. These micrographs may support the results described above.

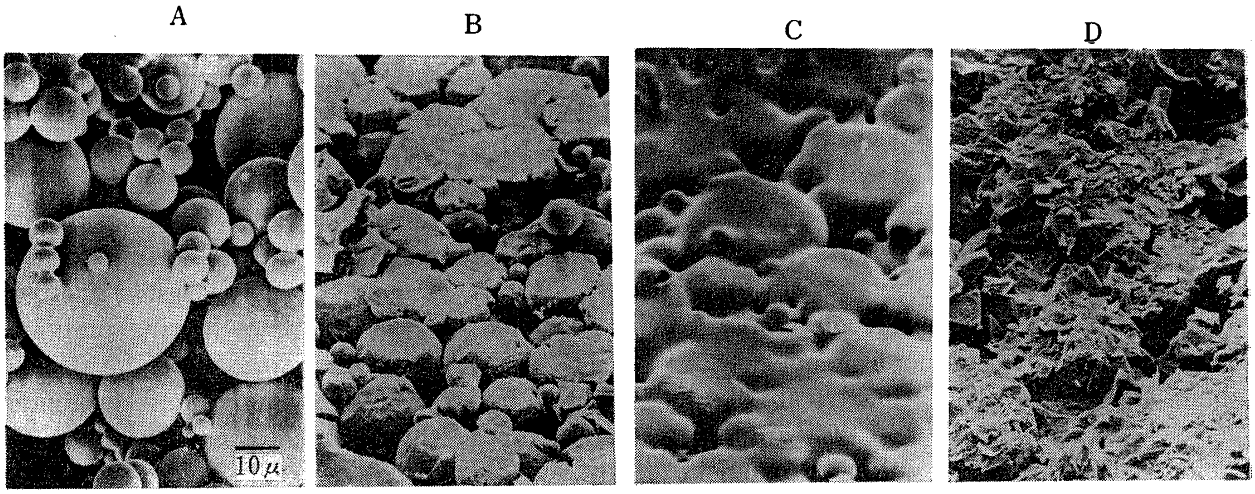

Fig. 9. Scanning Electron Micrographs of the Amorphous Lactose Powder and of the Surface of the Tablet before and after Moisture Sorption

A: amorphous lactose powder before moisture sorption, B: amorphous lactose tablet surface before moisture sorption, C: tablet surface after standing for 45 hr at relative humidity of 35.5% at 30°, D: tablet surface after standing for 17 hrs at relative humidity of 94% at 30°.

Acknowledgement The authors are grateful to Prof. Hideo Takenaka and Dr. Yoshiaki Kawashima for permission to use a spray drier at Gifu College of Pharmacy.