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Changes in Physical Characteristics of Ethylaminobenzoate Tablets during Storage[1)]

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The changes in the physical characteristics of the tablets containing ethylaminobenzoate during storage under drying conditions at different temperatures below the melting point were investigated. Changes in the crushing strength of the tablets, the disintegration properties of the tablets, the penetrating speed of water into the tablets and the pore diameter in the tablets were apparent even below the melting point. These changes tended to become larger at higher storage temperature. Based on a comparison with the results for stored tablets composed of only one component, it is considered that one of the causes of these changes is sintering. It is suggested that these changes are affected by the excipients in the tablets.

Keywords——tablets; storage temperature; physical characteristics; ethylaminobenzoate; lactose; starch; sintering

Drug preparations are exposed to various conditions during distribution and storage after manufacture, prior to use. Clearly, changes in the characteristics of the preparations are undesirable. Many reports exist[2)] on the chemical stability of the medicines in tablets, but little work has been done on the changes in the physical characteristics of tablets during storage, except for the effect of the absorption of moisture on tablets.[3)] In recent years, the prevention of moisture absorption by tablets has been remarkably improved as a result of the progress in packing techniques.[4)] However, most medicines are organic powders and some of them have relatively low melting points. Therefore, it is considered that the physical characteristics of tablets containing these medicines might change depending on the storage conditions, particularly temperature.

In this work, we prepared tablets containing ethylaminobenzoate, which has a relatively low melting point (mp 89—90 °C), and observed the changes in some physical characteristics of the tablets during storage at various temperatures under dry conditions.

Experimental

Materials——(1) Ethylaminobenzoate (JP X). This is abbreviated as Et-PAB. (2) Lactose (JP X). (3) Corn Starch (JP X). This is abbreviated as CS.

All of the above samples were dried at 60 °C over 8 h and passed through the No. 100 sieve (150 μm).

Tabletting——Et-PAB, lactose and CS were weighed out in a weight ratio of 5 : 4 : 1 and mixed. Then, 0.5 g of the mixture was weighed out and compressed in a tabletting machine (F-6, Nichiei Seiko Co., Ltd.) with flat-faced punches (cross-sectional area 1 cm^2). In order to prevent adhesion of the powder, magnesium stearate was distributed on the surfaces of the punches and the die. The compression pressure of the upper punch was about 1000 kg/cm^2.

Storage of Tablets——The tablets were stored in desiccators with silica gel as the drying agent for 50 d at 20 °C, which is the standard temperature of JP X, and at 40 °C, which is nearly the maximum temperature in summer in Japan.[5)]

Measurement of Physical Characteristics of Tablets——The tablets were taken from the desiccators, and allowed to cool for 2 h at room temperature, then various measurements were carried out as follows.

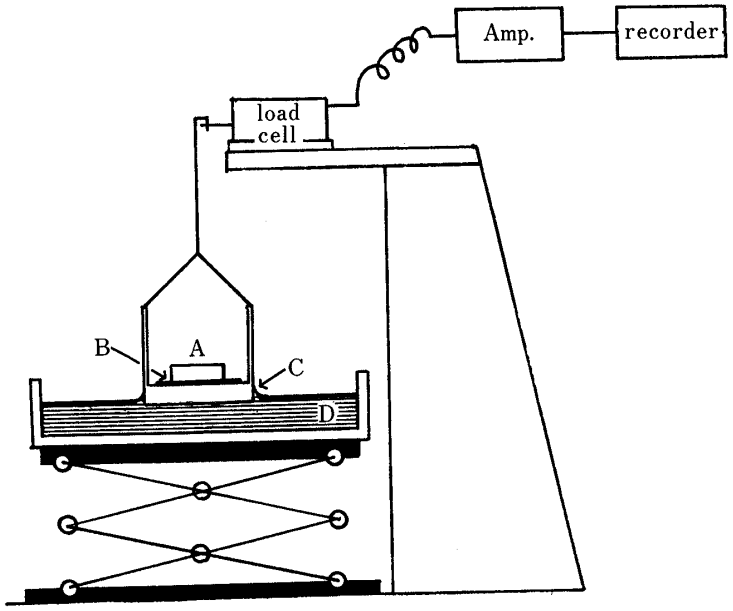

Fig. 1. Diagrammatic Sketch of the Tester Used for Measurement of Penetrating Speed of Water into Tablets

A, tablet; B, filter paper; C, glass filter; D, water.

(1) Dimensions: The thickness and the diameter of the tablets were measured with a dial gauge.

(2) Crushing Strength: The crushing strength of the tablets in the direction of the diameter was measured with our own tester.[6]

(3) Disintegration Time: The disintegration time was measured with a JPX disintegration tester by the JPX method. Pure water was used as the disintegration medium.

(4) Dissolution Test: The dissolution test was carried out by the JPX No. 1 method (rotating basket method; rotating speed 150 rpm). Pure water was used as the dissolution medium. At every sampling time, 1 ml of solution was taken, and the quantity of dissolved Et-PAB was determined by measuring the absorbance at 284 nm.

(5) Measurement of Penetrating Speed of Water into Tablets: An apparatus made by us (shown in Fig. 1) was used.

A glass filter (C) was positioned so that the surface of the water was about half way up the thickness of the filter. Then the filter paper (B) was gently placed on the glass filter. When the water surface was calm, one tablet was put softly on the filter paper, and then the weight of water which penetrated into the tablet was measured with a load cell (120T-50B, Kyowa Dengyo Co., Ltd.) and recorded. The effect of the variation of buoyancy accompanying the slight drop of the water line was corrected on the basis of a blank test.

A plot of the weight of water penetrating the tablet against time was found to be essentially linear until the tablet was saturated with water. Therefore, the penetrating speed of water into tablets can be obtained from the slope of this straight line.

(6) Measurement of Pore Size in Tablets: The pore diameter was measured by means of a mercury porosimeter (motor-driven, 15000 psi, AMINCO). The contact angle of mercury on the tablet was regarded as 130°.[7]

Results and Discussion

Change in the Weight of Tablets

The change in the weight of tablets during storage is shown in Fig. 2. Slight weight loss was recognized in the tablets at 1—3 d after storage. This loss can be regarded as being due to the loss of moisture absorbed in the process of tabletting. However, in the later storage period, little change in weight was found. Thus, it is considered that the change of moisture content in the tablets during storage is negligible.

Change in the Dimensions of Tablets

The change in the thickness of the tablets during storage is shown in Fig. 3. At 1 d after tabletting, an increase in thickness by 0.3—0.4% (regarded as delayed elastic recovery) was

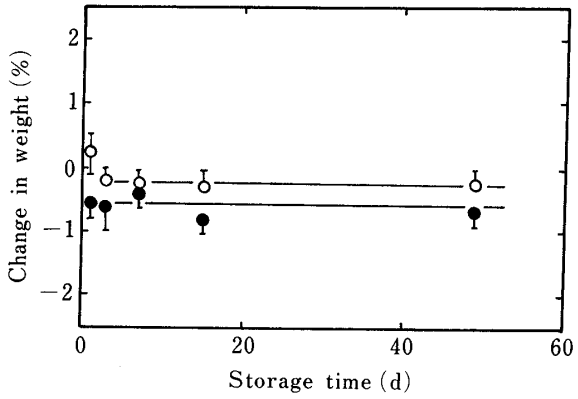

Fig. 2. Relationship between Change in Tablet Weight and Storage Time

Storage temperature: ○, 20 °C; ●, 40 °C.

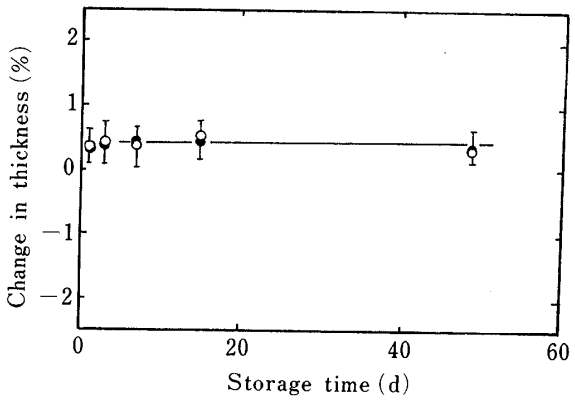

Fig. 3. Relationship between Change in Tablet Thickness and Storage Time

Storage temperature: ○, 20 °C; ●, 40 °C.

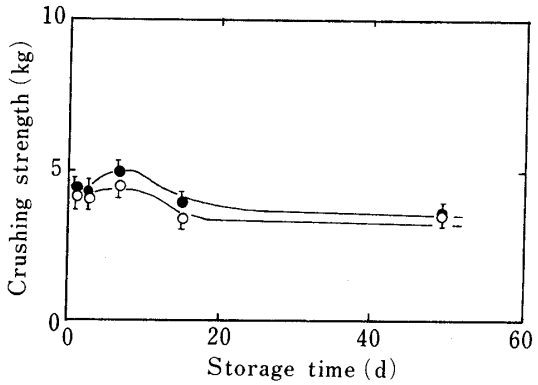

Fig. 4. Relationship between Crushing Strength of Tablets and Storage Time

Storage temperature: ○, 20 °C; ●, 40 °C.

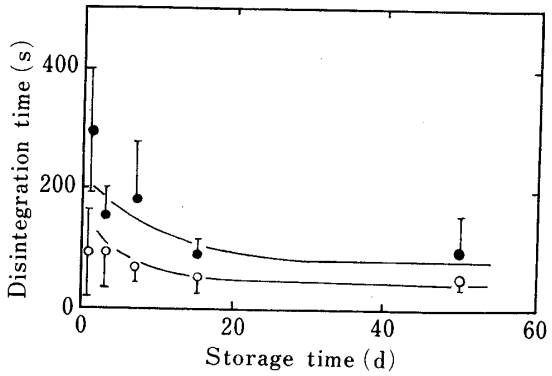

Fig. 5. Relationship between Disintegration Time of Tablets and Storage Time

Storage temperature: ○, 20 °C; ●, 40 °C.

recognized, but little change in thickness occurred during further storage. Similarly, an early increase of 0.1% in the diameter of the tablets was recognized, but little further change occurred during storage.

Change in the Crushing Strength of Tablets

The change in the crushing strength of the tablets during storage is shown in Fig. 4. The crushing strength of the tablets was maximum after about 7 d of storage, decreased from 7 d to 15 d and tended to remain constant after 15 d. The value of the maximum crushing strength at 40 °C was larger than at 20 °C.

Change in the Disintegration Time

The results of measurement of the disintegration time of the tablets are shown in Fig. 5. The tablets stored at 40 °C had a longer disintegration time than those stored at 20 °C. A longer disintegration time was observed in the tablets stored for a relatively short period (1—7 d) than in the tablets stored for a long time (15—50 d). This tendency was marked at 40 °C. It is considered that this change approximately corresponds to the change in the crushing strength shown in Fig. 4. Thus, the tablets stored at 40 °C which have a greater value of crushing strength also show a larger disintegration time than those stored at 20 °C. Furthermore, when the crushing strength decreases during prolonged storage, the disintegration time becomes shorter.

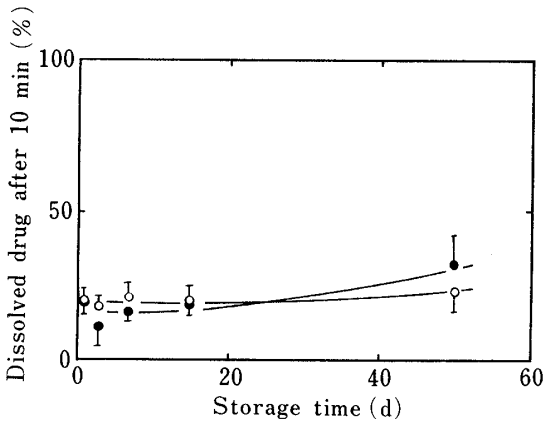

Fig. 6. Relationship between Percentage of Dissolved Drug after 10 min and Storage Time
Storage temperature: ○, 20 °C; ●, 40 °C.

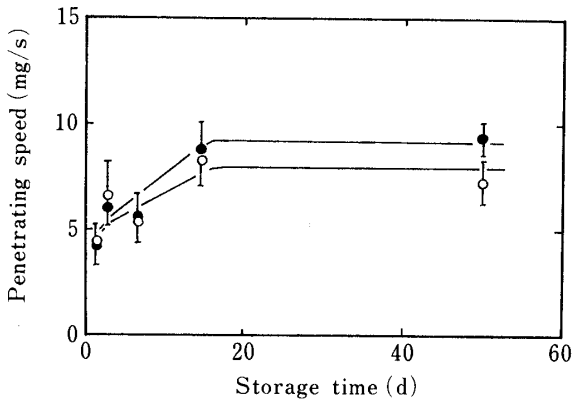

Fig. 7. Relationship between Penetrating Speed of Water into Tablets and Storage Time
Storage temperature: ○, 20 °C; ●, 40 °C.

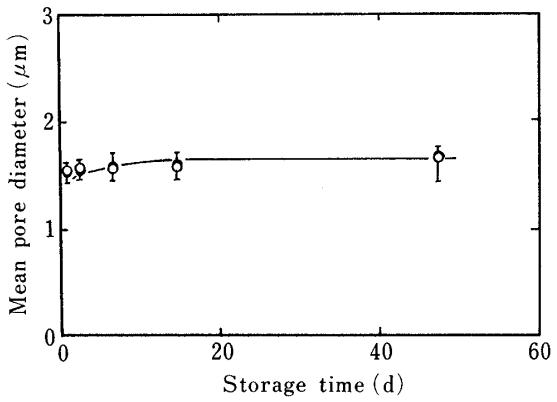

Fig. 8. Relationship between Mean Pore Diameter of Tablets and Storage Time
Storage temperature: ○, 20 °C; ●, 40 °C.

Change in Et-PAB Dissolution from Tablets

Figure 6 shows the relationship between the percentage of Et-PAB dissolved in the first 10 min of the test and the storage time. No clear difference in rate of dissolution was observed between tablets stored at the two storage temperatures. Little change occurred with increase in the storage time.

Change in the Penetrating Speed of Water into Tablets

Figure 7 shows the relationship between the penetrating speed of water into the tablets and the storage time. The penetrating speed increased with the storage time, but in the later period of storage little change was seen. In the case of prolonged storage (exceeding 15 d), the tablets stored at 40 °C had a slightly smaller penetrating speed than those stored at 20 °C. Thus, it can be presumed that in the tablets stored at relatively high temperature for a long time, a change in the internal structure of the tablets occurs which permits the easy penetration of water. As shown in Fig. 5, it is considered that the shortening of the disintegration time is associated with this change. However, the change in the dissolution speed did not seem to be related to the other factors. It is considered that the dissolution speed is lower than the disintegration speed, since Et-PAB is slightly soluble in water. The changes in the crushing strength, the disintegration time and the penetration speed occur together, mainly at storage time of less than 15 d, and a relatively stable state exists after the first 15 d of storage.

Change in the Pore Diameter in Tablets

The relationship between the mean pore diameter (obtained from the distribution curve

of the pore diameter) and the storage time is shown in Fig. 8. The mean pore diameter of the tablets stored at 40 °C was slightly larger than that at 20 °C at long storage times. The mean pore diameter increased slightly with increase of the storage time. However, since the change is small, it is considered that some other change mainly occurs in the tablets, but the details are not clear.

The above experiments indicated it is shown that some of the physical characteristics of the tablets did change. However, the tablets consist of three materials (these tablets are called "multi-component tablets" hereafter), and it is not clear which material is responsible for these changes. Thus, in order to clarify the situation, we prepared tablets containing a single material and carried out the following experiments. (These tablets are called "single component tablets" hereafter). The procedures before tabletting and the storage conditions were the same as before, except that mixing was not carried out. Since dried CS cannot be formed into tablets, the drying process was excluded for CS. As Et-PAB is not wetted by water, the disintegration test and the measurement of the penetration of water were not carried out.

Change in the Weight of Single Component Tablets

Figure 9 shows the change in the weight of the single component tablets during the storage. Both Et-PAB tablets and lactose tablets show small changes in weight (less than 0.1%); therefore it is considered that the change in moisture content of both the tablets was minimal. Probably because of the elimination of the drying process, a reduction of weight by 6—7% at 40 °C or 4—6% at 20 °C was observed for CS, but the reduction of weight at longer storage times was small. Therefore it is considered that the change in the weight of the multi-component tablets was due to the loss of moisture absorbed during the tabletting process.

Change in the Thickness of Single Component Tablets

Figure 10 shows the relationship between the change in the thickness of the single

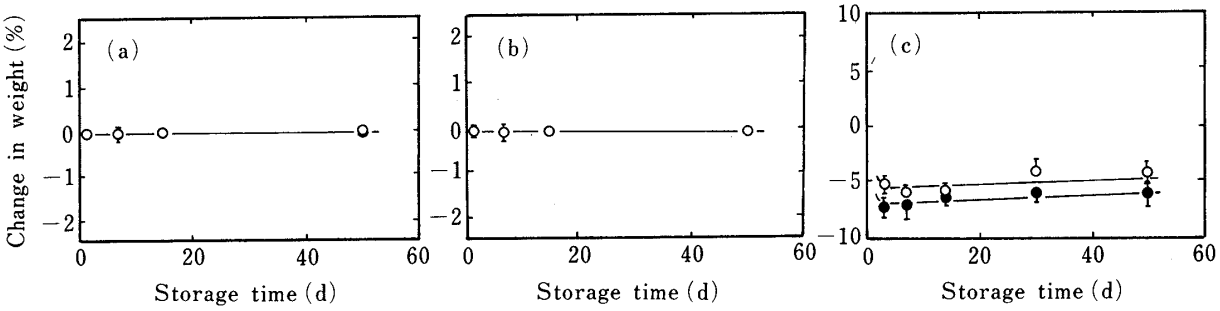

Fig. 9. Relationship between Change in Tablet Weight and Storage Time

Storage temperature: ○, 20 °C; ●, 40 °C. (a), ethylaminobenzoate (ET-PAB); (b), lactose; (c), cornstarch (CS).

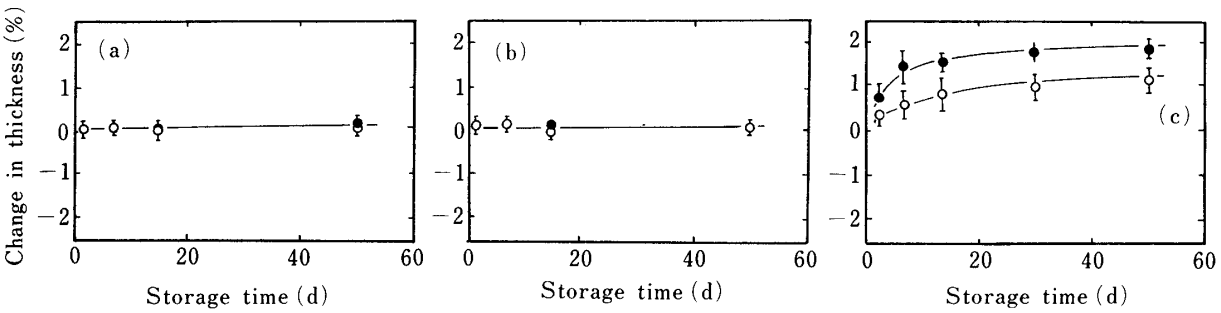

Fig. 10. Relationship between Change in Tablet Thickness and Storage Time

Storage temperature: ○, 20 °C; ●, 40 °C. (a), ET-PAB; (b), lactose; (c), CS.

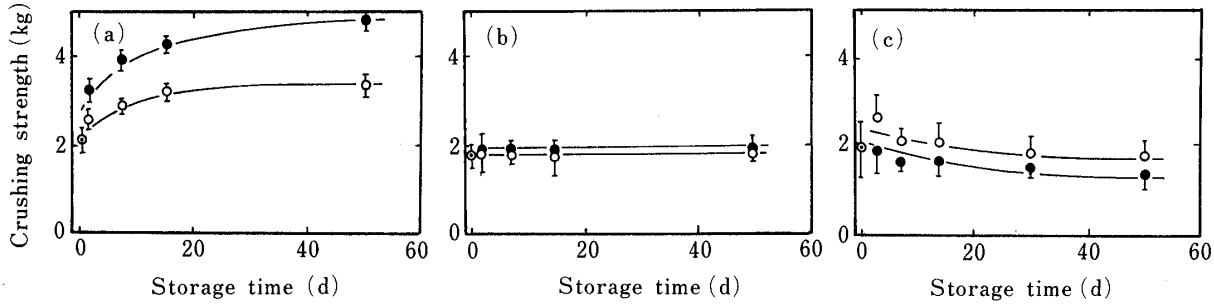

Fig. 11. Relationship between Crushing Strength of Tablets and Storage Time
Storage temperature :○, 20 °C; ●, 40 °C. (a), ET-PAB; (b), lactose; (c) CS.

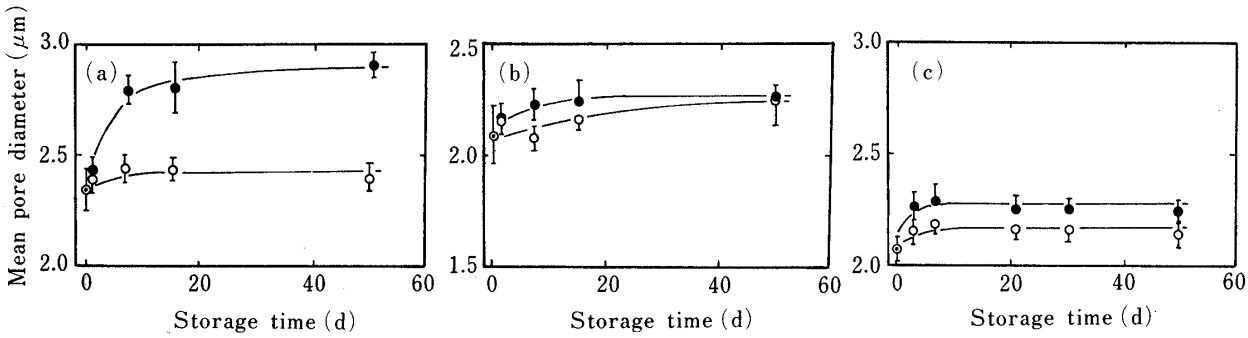

Fig. 12. Relationship between Mean Pore Diameter of Tablets and Storage Time
Storage temperature: ○, 20 °C; ●, 40 °C. (a), ET-PAB; (b), lactose; (c), CS.

component tablets and the storage time. A slight change in thickness (about 0.1%) was recognized in Et-PAB tablets and lactose tablets, but it was smaller than in the multi-component tablets. In CS tablets, an increase in thickness (0.6—2%) was recognized after storage for 7 d. Thus, it is considered that the change in the thickness of the multi-component tablets is due to the expansion of CS.

Change in the Crushing Strength of Single Component Tablets

Figure 11 shows the change in the crushing strength of the single component tablets during storage. The crushing strength of Et-PAB tablets rapidly increased with storage time after tabletting and then approached a constant value. At a high storage temperature, the increase in strength was large. In lactose tablets little change in the crushing strength was recognized at any storage temperature. The crushing strength of CS tablets tended to decrease. The mode of the change of all the single component tablets was different from that of the multi-component tablets. In the case of multi-component tablets, it is presumed that the increase in the crushing strength at the initial stage of storage is ascribable to Et-PAB and that the decrease in the crushing strength at later storage times is ascribable to CS.

Change in the Mean Pore Diameter of Single Component Tablets

In Fig. 12 the relationship between the mean pore diameter and the storage time is shown. There is a tendency for the mean pore diameter to increase with increasing storage time. This tendency is marked in the cases of CS and Et-PAB at 40 °C. It is considered that the main factor which may alter the internal structure (such as the pore diameter) of a porous material below the melting point is the expansion, shrinkage or deformation of the constituent particles or of voids. In this experiment, large changes in the pore diameter appeared in Et-PAB and CS. In the case of CS, it is considered that the change in the pore diameter was mainly due to deformation recovery, because this material shows a large change in dimensions

and does not melt when heated. In the case of Et-PAB, it is considered that the change in the pore diameter was due to some factor other than expansion or deformation, because this material has a relatively low melting point and is recognized to show little change in dimensions. It seems reasonable to assume that the cause of this change was sintering, as proposed by Danjo *et al.* based on storage experiments with loosely packed powder.[8]

Kuczynski presented various sintering mechanism[9]; however, as little change in dimension was recognized in Et-PAB, it is considered that a mechanism such as surface diffusion or evaporation–condensation may be predominant. Whatever the mechanism may be, it is considered that the increase in the crushing strength with the passage of time in Et-PAB tablets is due to bonding of the contact points or an increase in the contact area of the particles. In the multi-component tablets, the crushing strength initially increased and then decreased. This change was different from the simple changes in the single component tablets. It is considered that at the initial stage of storage, the crushing strength increased because particle bonding by sintering is higher, but deformation recovery proceeds at the same time, leading to a decrease in the crushing strength at longer storage times. On the other hand, the change in pore diameter is small in the multi-component tablets. It can be presumed that, because the mixture of lactose and CS dose not readily undergo sintering, the probability that lactose and CS particles contact Et-PAB particles becomes larger, and hence a macroscopic change (such as in the pore diameter) is difficult.

Conclusion

In tablets containing Et-PAB, the physical characteristics of the tablets such as the crushing strength, the disintegration time, the penetrating speed of water and the pore diameter varied during storage even at temperatures below the melting point. These changes were greater at higher storage temperature. Deformation recovery and sintering are considered to be the major causes of these changes. It is suggested that these changes are dependent on the nature and proportions of the constituents of the tablets.

References and Notes

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