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Application of acid-treated yeast cell wall (AYC) as a pharmaceutical additive. II: effects of curing on the medicine release from AYC-coated tablets

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Abstract

Acid-treated yeast cell wall (AYC) was newly prepared by acidifying brewers' yeast cell wall. Core tablets containing 3% of acetaminophen (AAP) were coated with the AYC aqueous dispersion containing 5% (w/v) of AYC and 0.35% (w/v) of glycerol. The curing of AYC-coated tablets was performed at various curing periods of time and temperatures. The effects of curing on AAP release from AYC-coated tablets, the weight and thickness of the coated layer of AYC and the water sorption into the AYC-coated tablets were studied. The tensile strength and pore size distribution of the AYC cast film were measured. In the case of 60, 80, or 100°C curing, AAP release from AYC-coated tablets showed a sigmoidal release profile with an initial lag time. The duration of the lag time increased with the increasing curing time and temperature, though the release rate after the lag time hardly changed. At 120°C curing, the release rate after the lag time decreased with the increasing curing time and a sustained release was observed. The weight and thickness of the AYC-coated layer and the water sorption rate into AYC-coated tablets decreased with the increasing curing time and temperature. The tensile strength of the AYC cast film increased with increasing the curing temperature, particularly at 120°C curing. It is considered that the water was evaporated from the AYC-coated layer and the adhesion force between AYC particles increased during curing, making the structure of the AYC-coated layer densely firm. The changes in the duration of lag time and the release rate may be due to changes in the structure of the AYC-coated layer caused by curing. These results show that it is feasible to control the lag time and the release rate of AAP from AYC-coated tablets by varying the curing time and temperature.

Keywords: Acid-treated yeast cell wall (AYC); Curing; Lag time; Release rate; Film structure; Cast film

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1. Introduction

In our previous report, we newly prepared acid-treated yeast cell wall (AYC) by acidifying brewers' yeast cell wall to find a new utilization of its unique functions and found that AYC has a high utility as a novel aqueous coating material for pharmaceuticals. According to our findings, AYC was dispersed as independent hydrogel particles in water unlike other polymers generally used as a solution, and the medicine release from the tablets coated with AYC was hardly affected by pHs of the dissolution fluid or by the storage at room temperature for 120 days. The AYC film showed an extremely small oxygen permeability coefficient corresponding to the value for the aluminum foil laminated with polyethylene and polyethyleneterephtalate and a sufficiently low level of water permeability coefficient to protect the medicine from moisture (Kasai et al., 2000).

Curing techniques involve heat curing, UV irradiation curing and the curing by chemical reaction using catalysts. These curing techniques are applied in electronic, light, chemical, food, medical, dental and pharmaceutical fields (Gursoy and Akbuga, 1986; Okhamafe and York, 1989; Nakamura et al., 1992; Griggs et al., 1994; Deasy and Murtagh, 1996; Hemmer et al., 1996; Tanoue et al., 1998; Ireland and Sherriff, 1998; Aydin et al., 1999; Leroy and de Vuyst, 1999; Meredith, 1999; Mills et al., 1999; Benedio et al., 2000). Heat curing is most widely used for coating in the pharmaceutical field (Bodmeier and Paeratakul, 1994a,b; Miller et al., 1997; Noemi et al., 1997).

For example Bodmeier and Paeratakul (1994a,b) have reported that curing conditions such as curing time and curing temperature affect the drug release from the preparations coated with ethylcellulose pseudolatex (Aquacoat®). They have proposed that the curing process is necessary and useful for a reduction of the amount of a plasticizer added in order to obtain an excellent film structure and a controlled drug release profile.

Miller et al. (1997) reported that in the heat curing of the whey protein film, an increase in curing temperature caused an increase in the largest tensile strength, an decrease in Young modulus and the broken elongation percentage and an improvement in the moisture permeation barrier characteristics.

In this paper, heat curing for AYC-coated tablets was carried out at various curing periods of time and temperatures, and the effects of curing on the medicine release profile and the internal structure of the AYC-coated layer were studied.

2. Materials and methods

2.1. Materials

Brewers' yeast (*Saccharomyces cerevisiae*, Kirin Brewery, Tokyo) after being actually used for manufacturing beer was used as a raw material. Acetaminophen (AAP, Tokyo Kasei Kogyo, Tokyo) was used as a model drug. Hydroxypropylcellulose (HPC-L, viscosity 6.0–10.0 cps, Shin-Etsu Chemical, Tokyo), magnesium stearate (Wako Pure Chemical Industries, Osaka) and glycerol (Wako Pure Chemical Industries, Osaka) were used as a binder, lubricant and plasticizer, respectively. Lactose (DMV Japan, Tokyo) and microcrystalline cellulose (Avicel® PH-301 Asahi Chemical Industry, Tokyo) were used as excipients.

2.2. Preparation of AYC

AYC was prepared in the same manner as previously reported (Kasai et al., 2000). The intracellular components of intact yeast were solubilized by reaction with intracellular or external enzymes, such as protease and glucanase, and the soluble components were removed. The acidifying reaction was then carried out with 5% (w/v) aqueous dispersion of the residual fraction and 0.5N HCl at 80°C for 20 min. After centrifugation, the precipitates were thoroughly washed with water. The pH of the system was adjusted to 9.0 to remove the bitterness substances originating from hops because the brewers' yeast used in this study was the residue after actually being used for manufacturing beer. The pH was readjusted to 3.8–4.2 and AYC was then obtained after centrifugation and washing with water.

2.3. Preparation of core tablet

The formulation of the core tablet is shown in Table 1. The mixed powder of AAP, lactose and microcrystalline cellulose was granulated with a fluidized bed (MP-01, Powlex, Osaka) using HPC-L aqueous solution as a binder by the top spray method. The granules obtained were mixed with magnesium stearate and compressed with a rotating tableting machine (HT-22P HATA, Tokyo) equipped with a 7 mm diameter and 4.5 mm radius of curvature die.

2.4. Preparation of AYC-coated tablets

The AYC aqueous dispersion containing 5% AYC and 0.35% glycerol was used for coating. The coating of the core tablets by the AYC aqueous dispersion was performed with an improved HCT-MINI (FREUND, Tokyo) at the coating ratio of 15% based on the weight of the core tablet. The improved HCT-MINI is additionally equipped with a spray air flowmeter. The ability of the heater and blower and the pan sealingness have been improved in order to enhance the drying efficiency.

The operating conditions for coating were as follows: core tablets, 250 g; inlet and outlet air temperatures, 100 and 42–45°C, respectively; spray pressure, 1.5 kgf/cm^2; spray rate, 4.5 g/min; spray air volume, 40 l/min; pan revolution, 40 rpm.

2.5. Release study

The release profiles of AAP from the AYC-coated tablet were studied with a dissolution tester (NTR-6100A, Toyama Sangyo, Osaka), according to the paddle method (JP13) using 900 ml of distilled water at 37 ± 0.5°C and a rotating paddle at 100 rpm. The quantity of AAP was determined spectrophotometrically by measuring the absorbance at 242 nm.

The apparent change in the AYC-coated tablet during the release process was observed with an optical microscope (Nikomat, Nikon, Tokyo).

Table 1

Formulation of core tablet (mg)	
AAP	6.0
Lactose	142.0
Microcrystalline cellulose	47.4
HPC	0.6
Magnesium stearate	4.0
Total weight	200.0/tab.

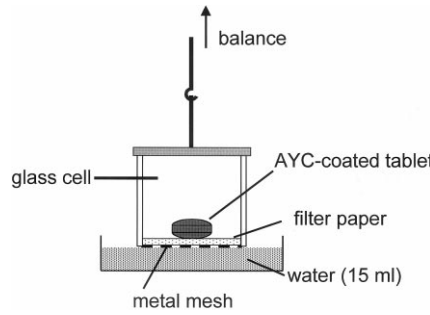

Fig. 1. Schematic diagram of apparatus for measurement of amount of water sorbed into AYC-coated tablet.

2.6. Curing method

The AYC-coated tablets or the AYC cast film were placed on teflon petri dishes. The curing was performed using ovens at various temperatures (60, 80, 100 and 120°C) for various periods of time (0.5, 1.0, 2.0, 6.0 and 24.0 h).

2.7. Measurement of amount of sorbed water into AYC-coated tablet

The amount of the water sorbed into the AYC-coated tablet was measured with a contact angle infiltration rate equipment (PHW, Kyowa Kaimenkagaku, Tokyo) at 25°C as shown in Fig. 1. The AYC-coated tablet was placed on a paper filter set on a metal mesh bottom of a cylindrical glass cell. The water in a glass petri dish was absorbed through the filter paper into the AYC-coated tablet and the change in the weight of the tablet was measured. The area contacted with the filter paper was almost the same for all tablets.

2.8. Measurement of weight and thickness of AYC-coated layer

The curing for the core tablet was performed in the same manner as the AYC-coated tablet. The weight and thickness of the core and AYC-coated tablets were measured at the interval of curing mentioned above. The thickness of the core and AYC-coated tablets was measured with a dial thickness gage (Mitsutoyo, Tokyo). The thickness was determined as the distance between the tops of the curvature of a tablet. The weight and thickness of the AYC-coated layer were calculated by subtracting the weight and thickness of the core tablet from those of the AYC-coated tablet, respectively.

2.9. Preparation of AYC cast film

The AYC cast film was prepared with the AYC aqueous dispersion containing 3.0% AYC and 0.21% glycerol. After degassing, the dispersion containing 0.45 g AYC was placed in a teflon petri dish with the diameter of 75 mm and dried at 40°C and 0% RH for 3 days.

The thickness of the AYC cast film was measured with a dial thickness gage (Mitsutoyo, Tokyo).

2.10. Tensile test of cast film

The tensile strength of the AYC cast film cut in the dimension of 20×40 mm was measured with a universal testing machine (TCM-5000C, Minebea Co. Ltd., Japan) with a load cell (U3B1-20K-B, Minebea Co. Ltd., Japan) and a chuck cell (CH-200N, Minebea Co. Ltd., Japan) at 23°C, 50% RH and 10 mm/min cross-head speed. The stress–strain curve was recorded for each sample with an analysis recorder (AR-1200, Yokogawa Electric Co., Tokyo).

The tensile strength of the cast film was calculated by the following equation (Ononokpono and Spring, 1987; Lin et al., 1991; Obara and McGinity, 1994):

$$\text{Tensile strength} = (F/a \cdot b)(1 + (\Delta L/L)) \quad (1)$$

where L, a and b are the length, thickness and width of the cast film before the test, respectively, and ΔL and F are the elongation and the stress at break of the film.

2.11. Observation of surface and cross-section of AYC cast film

A scanning electron microscope (SEM) (S-2250N, Hitachi, Tokyo) was used to observe the surface and cross-section of the AYC cast film. The surface of the AYC cast film was observed after gold coating to observe it at a high magnification. The cross-section of the AYC cast film was observed under a low vacuum condition without gold coating to observe it more naturally.

2.12. Pore size distribution of AYC cast film

The pore size distribution of the AYC cast film was measured using a mercury porosimeter (Autoscan33, Quantachrome. Florida) by the mercury intrusion method. In order to evaluate the pore openings existing in the cross-section and surface of the film separately, the cross-section of the film was covered with Carnauba wax (density, 0.990–0.999 g/cm^3). The pore size distributions of the film with or without wax treatment and the wax solidified after melting were measured.

3. Results and discussion

3.1. Effects of curing temperature and curing time on AAP release profiles from AYC-coated tablets

Fig. 2 shows the effects of the curing temperature and curing time on the AAP release profiles from the AYC-coated tablets. In the case of 60, 80and 100°C curing (A, B or C), AAP release from the AYC-coated tablets showed a sigmoidal release profile with an initial lag time. The duration of the lag time increased with the increasing curing temperature and curing time, though the release rate after the lag time was slightly changed. At 120°C curing (D), the release rate after the lag time decreased with the increasing curing time and a sustained release was observed by curing for more than 6.0 h.

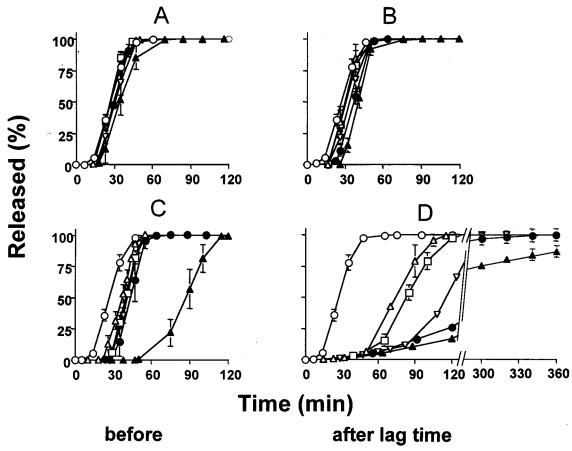

Fig. 2. Effects of curing temperature and curing time on AAP release profile from AYC-coated tablet. Curing temperature (°C): A, 60; B, 80; C, 100; D, 120; ○, without curing. Curing time (h): △, 0.5; □, 1.0; ▽, 2.0; ●, 6.0; ▲, 24.0. Each point represents the mean ± S.D. ($n = 3$).

The apparent change of the AYC-coated tablet during the release process is shown in Fig. 3. A is the tablet cured at 60°C for 24 h and B is the tablet cured at 120°C for 24 h. In the case of A, the apparent change of the tablet was hardly observed during the lag time. After the lag time, however, the AYC-coated layer was broken as shown in the central photograph, and then the core tablet was disintegrated as shown in the right photograph. The same manner was observed in the cases of no curing, 80°C curing and 100°C curing. AAP release started with the collapse of the AYC-coated layer, causing a sigmoidal release. In the case of B, the collapse of the AYC-coated layer was not observed during the whole release process. This result indicates that AAP release occurred through the AYC-coated layer, causing a sustained release.

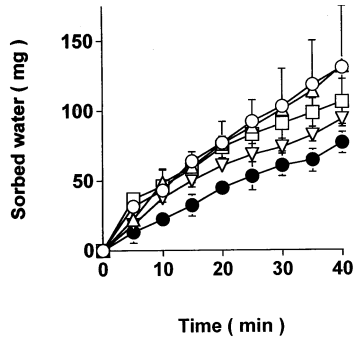

Fig. 4. Effect of curing temperature on water sorption into AYC-coated tablet. (24 h curing). ○, without curing. Curing temperature (°C): △, 60; □, 80; ▽, 100; ●, 120. Each point represents the mean ± S.D. ($n = 3$).

3.2. Effects of curing on water sorption behavior into AYC-coated tablets and percentages of weight change and thickness change of AYC-coated layer

The effect of curing temperature on the water sorption behavior into the AYC-coated tablet is shown in Fig. 4. The curing time was 24 h. The water sorption rate was smaller at a higher curing

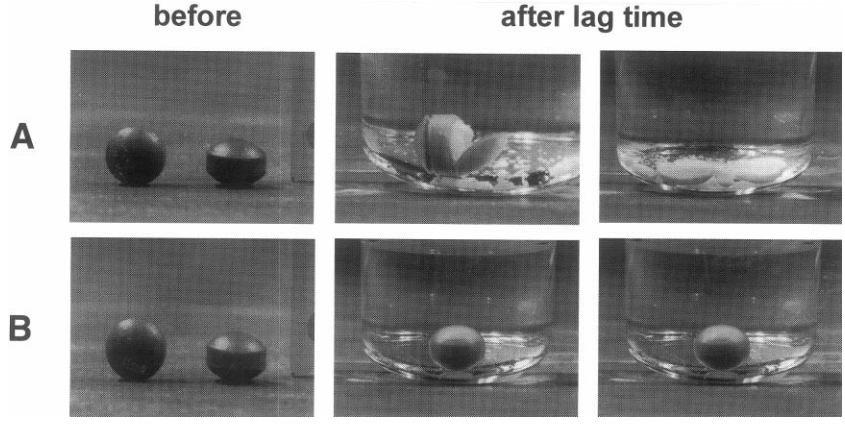

Fig. 3. Apparent change of AYC-coated tablet during release process. A: 60°C, 24 h curing. B: 120°C, 24 h curing.

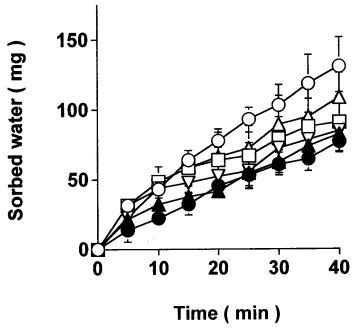

Fig. 5. Effect of curing time on water sorption into AYC-coated tablet. (120°C curing). ○, without curing. Curing time (h): △, 0.5; □, 1.0; ▽, 2.0; ●, 6.0; ▲, 24.0. Each point represents the mean ± S.D. ($n = 3$).

temperature. Similar results were obtained in the cases of other curing times (data not shown). The effect of curing time on the water sorption behavior is shown in Fig. 5. The curing temperature was 120°C. The water sorption rate was smaller at a longer curing time. Similar results were obtained in the cases of other curing temperatures (data not shown).

The percentage of weight decrease of the AYC-coated layer during the curing process is shown in Fig. 6. At all curing temperatures, the weight of the AYC-coated layer decreased with the increasing curing time. A remarkable decrease in the weight percentage of the AYC-coated layer was observed at 120°C, which is higher than the boiling point of water. The percentage of thickness decrease of the AYC-coated layer during the curing process is shown in Fig. 7. At all curing

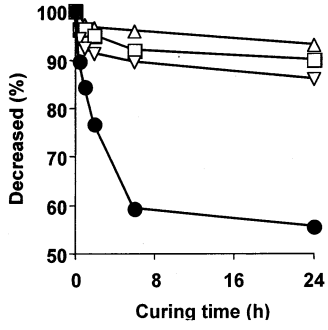

Fig. 6. Effects of curing temperature and curing time on percentage of weight decrease of AYC-coated layer. Curing temperature (°C): △, 60; □, 80; ▽, 100; ●, 120.

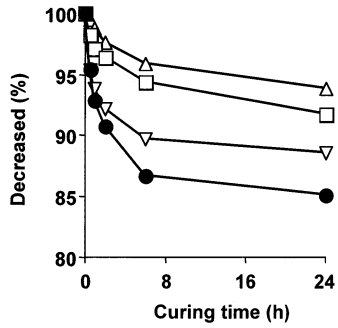

Fig. 7. Effects of curing temperature and curing time on percentage of thickness decrease of AYC-coated layer. Curing temperature (°C): △, 60; □, 80; ▽, 100; ●, 120.

temperatures, the thickness of the AYC-coated layer decreased with the increasing curing time. The degree of decrease was larger at a higher curing temperature.

Fig. 8 shows the relationship between the percentages of weight decrease and thickness decrease of the AYC-coated layer. A linear relationship was observed between these factors. Particularly, at 120°C curing, the percentage weight decrease was larger compared with that at other curing temperatures at the same percentage thickness decrease.

Fig. 9 shows the relationship between the percentage thickness decrease of the AYC-coated layer and the water sorption rate into the AYC-coated tablet. The water sorption rate decreased with the increasing thickness decrease percentage at all curing temperatures. Further, the water sorption rate was smaller at a higher curing temperature.

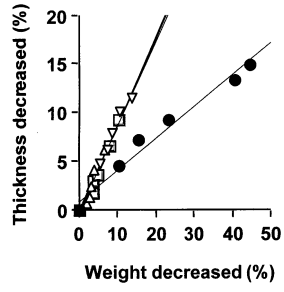

Fig. 8. Relationship between percentages of weight decrease and thickness decrease of AYC-coated layer. Curing temperature (°C): △, 60; □, 80; ▽, 100; ●, 120.

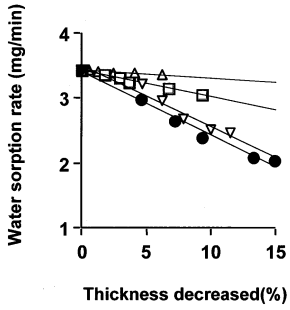

Fig. 9. Relationship between percentage of thickness decrease of AYC-coated layer and water sorption rate into AYC-coated tablet. Curing temperature (°C): △, 60; □, 80; ▽, 100; ●, 120.

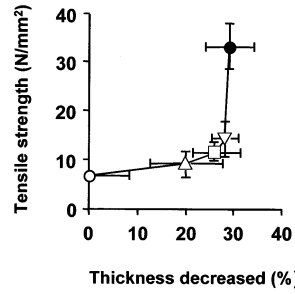

Fig. 10. Relationship between percentage of thickness decrease and tensile strength of AYC cast film cured for 24.0 h. ○, without curing. Curing temperature (°C): △, 60; □, 80; ▽, 100; ●, 120. Each point represents the mean ± S.D. ($n = 3$).

These results suggest that water in the AYC-coated layer was evaporated by curing and the thickness of the AYC-coated layer decreased, causing a decrease in the water sorption rate. Thus, the lag time was increased. Further, the water sorption rate at the same thickness of the AYC-coated layer was smaller at a higher curing temperature, and the weight decrease percentage at 120°C curing was larger compared with that at other curing temperatures. These results indicate that the structure of the AYC-coated layer varied depending on the curing temperature.

Therefore, the AYC cast film was prepared and the tensile test, SEM observation and the pore size distribution measurement were performed to study the effects of curing on the film structure.

3.3. Effect of curing on structure of AYC cast film

Fig. 10 shows the relationship between the thickness decrease percentage and the tensile strength of the AYC cast film at various curing temperatures. The tensile strength increased with the increasing percentage thickness decrease. At higher than 100°C, although the percentage of thickness decrease was small, the tensile strength was drastically increased and a markedly large tensile strength was observed at 120°C curing.

Fig. 11 shows the SEM photographs of the surface and cross-section of the AYC cast film at 120°C curing. The surface of the film was hardly changed by curing. Before curing, the AYC cast film included sufficient moisture and had a smooth cross-section. With the increasing curing time, the thickness decreased and the internal structure became densely stratified.

Fig. 12 shows the pore size distributions of the AYC cast film after curing at 120°C for 24.0 h with or without wax treatment and that of the wax solidified after melting. The film without wax treatment had large pores of about 10–200 μm and small pores of about 0.03 μm or less. The film with the cross-section covered with wax had only pores of about 0.2 μm or less and the pore volume at about 0.03 μm or less was large. The wax had pores of about 0.2 μm or less and the pore volume at about 0.03 μm or less was small. These results suggest that pore openings of about 0.03 μm or less might exist on the surface, and pore openings of about 10–200 μm caused by the stratified structure might exist in the cross-section of the cast film after curing.

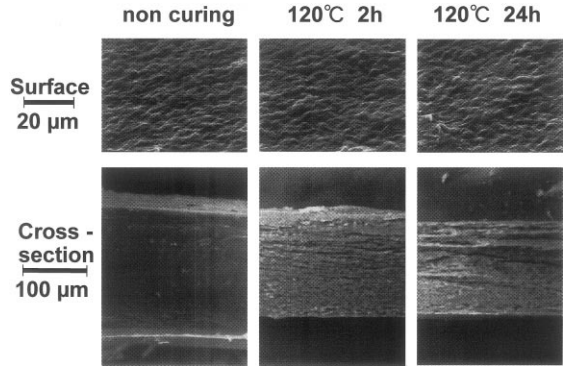

Fig. 11. SEM photographs of AYC cast film.

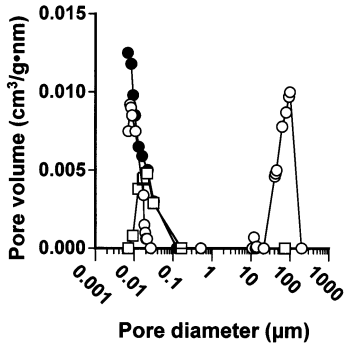

Fig. 12. Pore size distributions of AYC cast film with or without wax treatment and wax. ○, AYC cast film without wax treatment; ●, AYC cast film with wax treatment; □, wax.

The chemical components of the yeast cell wall of *S. cerevisiae*, known as a brewers' yeast, are mainly polysaccharide such as glucan and mannan and a little protein (Northcote and Horne, 1952; Fleet and Manners, 1976). A model of double layer is advocated for the structure of the yeast cell wall composed of mannan–protein complex as the upper layer and of glucan as the lower layer (Lampen, 1968; Kidby and Davies, 1970). Although a part of these components might be lost during the acidifying process, the remained glucan and mannan–protein complex exist as graft chains on the surface of AYC and will be hydrogel layer in the water. As we previously reported, AYC keeps the shape of origin yeast and has the baggy structure (Kasai et al., 2000). In the water, AYC disperses as a hydrogel particle including the water inside the structure. Therefore, the coating layer just after the coating operation is composed of the AYC having hydrogel layer on the surface and including sufficient moisture. By heat curing, the water existed inter and inside the AYC particles was evaporated and the contact area between the hydrogel layers of AYC was increased and the mutual tangling of the hydrogel layers was progressed, causing the decrease in the thickness and the dense structure of the AYC-coated layer.

The structure of the AYC layer changed due to the differences in the water evaporation rate depending on the curing temperature, and the permeation rate of the dissolution fluid into the AYC-coated layer varied, causing changes in the duration of lag time. At 120°C curing, the water evaporation rate from the AYC layer was very large and the adhesion among the AYC particles was promoted, causing a large tensile strength of the AYC layer. Thus, the AYC-coated layer did not disintegrate during the release process and a sustained release was observed.

4. Conclusion

The above results suggest that it is possible to control the duration of lag time and the release rate of AAP from the AYC-coated tablets by varying the curing temperature and curing time. It is considered that the water was evaporated from the AYC-coated layer and the adhesion force among the AYC particles was increased during curing. The structure of the AYC layer became densely firm and the permeation rate of the dissolution fluid decreased. The changes in the duration of lag time and the release rate may be due to the changes in the structure of the AYC-coated layer caused by curing.

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