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# Design of Rapidly Disintegrating Oral Tablets Using Acid-Treated Yeast Cell Wall: A Technical Note

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## INTRODUCTION

Natural materials should be useful as pharmaceutical additives from the perspective of resource utilization and safety.[1-4] Acidified brewers' yeast cell wall (AYC) has been examined with respect to novel applications[5-9] as it can be used as an aqueous coating material for tablets and granules.[5-7] In accordance with these properties of AYC, AYC maintains the baggy structure of the original yeast. In water, AYC is dispersed as independent particles with a surface hydrogel layer. Water is included within the structure unlike other polymers. The release profile of drugs from tablets coated with AYC is sigmoidal with an initial lag time, and drug release is scarcely affected by the pH of the dissolution fluid or by storage at room temperature for 120 days. The lag time and release rate of drug is controllable by varying the curing time and temperature. The surface of granules is smooth at a coating ratio of only 5% AYC, unlike other agents, which generally require approximately 15% to 30% coating against core granule weight, with no aggregation. The oxygen permeability coefficient of AYC film is extremely low and corresponds to the value of aluminum foil laminated with polyethylene and polyethylene terephthalate. In addition, AYC has a low water permeability coefficient, which protects the included drug from moisture. Based on these findings, AYC became commercially available as the coating agent, YeastWrap, for food in April 2000. The adhesion and binding abilities of the AYC hydrogel layer as well as the water absorption and swelling properties of AYC have been examined. Tablets containing at least 5% AYC used as a binder during granulation disintegrate in approximately 4 minutes, indicating that AYC functions as a binder at granulation in addition to being a disintegrant during the dissolution of drugs from the tablets. These results indicate that AYC is a unique pharmaceutical additive possessing opposing functions with respect to binding and disintegration.[8,9]

Pharmaceutical disintegrants are classified broadly by mechanism into the following:

- Swelling types absorb water, so that increasing swelling pressure causes the tablet to disintegrate.
- Wicking types absorb water through pores in tablets by capillary action that enlarges the pores and reduces the binding force between particles.
- Other types disintegrate via both mechanisms.

The present study examines the ability of 4 disintegrants mixed with granules consisting of 5% AYC, used as a binder during granulation, and acetylsalicylic acid (ASA) as a model drug to further decrease disintegration rates.

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## MATERIALS AND METHODS

### *Materials*

The mean diameter (specific surface area diameter) of the model drug ASA (Tsukishima, Tokyo, Japan) was approximately 12.6 μm. The binder was 5% (wt/vol) AYC (YeastWrap, Kirin Brewery, Tokyo, Japan) aqueous dispersion, and magnesium stearate (Wako Pure Chemical Industries, Osaka, Japan) was the lubricant. The viscosity of the aqueous dispersion of 5% AYC measured using a digital cone-plate viscometer (model DV-II+, Brookfield Engineering Laboratories, Middleboro, MA) was 3.32 mPa. Carmellose (NS300, Gotoku Chemical, Tokyo, Japan), croscarmellose

sodium (AcDiSol, Asahi Kasei, Tokyo, Japan), carmellose calcium (ECG505, Gotoku Chemical), and low substituted hydroxypropylcellulose (L-HPC, Shin-Etsu Chemical, Tokyo, Japan) were used as disintegrants, after passage through a sieve with 106 μm pores.

### *Granulation*

ASA was granulated using a fluidized bed granulator (MP-01, Powlex Corp, Osaka, Japan) and top spraying. Operating conditions for granulation were as follows: ASA powder, 500 g; binder concentration, 5% (wt/vol); inlet and outlet air temperatures, 80°C and 45°C, respectively; fluidization air flow rate, 15 to 70 $m^3$/h; spray pressure, 1.5 kgf/$cm^2$; spray air flow rate, 25 L/min; nozzle insert diameter, 0.8 mm; spray rate, 15 g/min; ratio of added binder as solid mass, 5% against ASA weight.

### *Granule Particle Size*

Samples (10 g) were passed through woven wire cloth and perforated metal plate (Tokyo Screen Co, Tokyo, Japan) with 38-, 75-, 106-, 150-, 212-, and 355-μm pores using an electromagnetic vibrating sieving machine (Tsutsui Rikagaku Kikai Co, Tokyo, Japan) for 10 minutes. Particle size distribution was determined by weighing the amount of granules remaining on the sieves. The mean particle diameter ($D_{50}$) was defined as the 50% diameter of the cumulative curve of particle size distribution.

### *Tablet Formation*

The mixture of the 5% AYC granules and disintegrants was compressed into 200-mg tablets by external lubrication using a universal testing machine (TCM-5000C, Keiaisha NMB Co, Tokyo, Japan) equipped with an 8-mm diameter flat-punch at 75 to 200 MPa compression pressure and 50 mm/min compression speed.

### *Hardness*

The tablet crushing load, which is the force required to break a tablet into halves by compression in the diametral direction, was measured with a hardness tester (KHT-20, Kiya Corp, Tokyo, Japan). The plunger was driven down at a speed of 20 mm/min.

### *Disintegration Time*

Tablet disintegration time was measured using a JP14 disintegration tester (NT-20H, Toyama Sangyo Co, Osaka, Japan). The rigid basket-rack assembly supporting 6 cylindrical glass tubes with 21.5-mm internal diameter was swung in distilled water at 37 ± 2°C at 30 times/min. The opening of the mesh at the bottom of the glass tube was 2 mm. Only 1 tablet at a time was tested, and it was considered disintegrated when completely dispersed fragments were obtained.

### *Water Absorption by Tablet*

The amount of water absorbed by individual tablets was measured using contact angle infiltration rate equipment (PHW, Kyowa Interface Science Co, Tokyo, Japan) at 25°C.[6] Water was absorbed through filter paper into the tablet, and then the change in weight of the tablet was determined.

### *Oral Disintegration Time of Tablet*

The time required for the tablets to completely disintegrate without water—until the rough feel had disappeared—in the mouths of 5 healthy adult volunteers was measured. After testing, the content was immediately removed from the mouth, and the mouth was thoroughly rinsed with water.

## RESULTS AND DISCUSSION

### *AYC Tablets Including Various Disintegrants*

The $D_{50}$ value of ASA granulated with 5% AYC was approximately 80 μm. The mixture of the granules and 10% disintegrant was compressed into tablets at 100 MPa by external lubrication. NS300 (carboxymethylcellulose) is hydrophilic but has low swelling ability. NS300 plays a role in absorbing water into tablets and is called wicking type. AcDiSol (sodium salt of cross-linked carboxymethylcellulose) has a high swelling ability and may disintegrate tablets by mainly swelling pressure. AcDiSol is classified into swelling type. ECG505 (calcium salt of carboxymethylcellulose) and L-HPC (low substituted hydroxypropylcellulose) disintegrate tablets via both actions. **Figure 1** shows the hardness and disintegration time of the tablets. The hardness of commercial tablets must be at least 3 kgf to be practical, and all tablets met this criterion. However, the disintegration time obviously differed depending on the disintegrant. Tablets containing wicking type NS300 rapidly disintegrated. **Figure 2** shows an inverse relationship between the water uptake rate and the disintegration time of tablets containing various disintegrants, that is, a more rapid water uptake rate decreased the disintegration time. It is speculated that this was caused by NS300 transporting water by capillary attraction to the inside of the tablet, where it was absorbed by AYC, which subsequently swelled. These actions could weaken the binding force between ASA parti-

cles, leading to rapid disintegration of the tablet. These results suggest that the disintegration rates of tablets can be decreased by using wicking-type disintegrants. Therefore, NS300 was used as the disintegrant and the influence of the amount added to tablets on disintegration was examined.

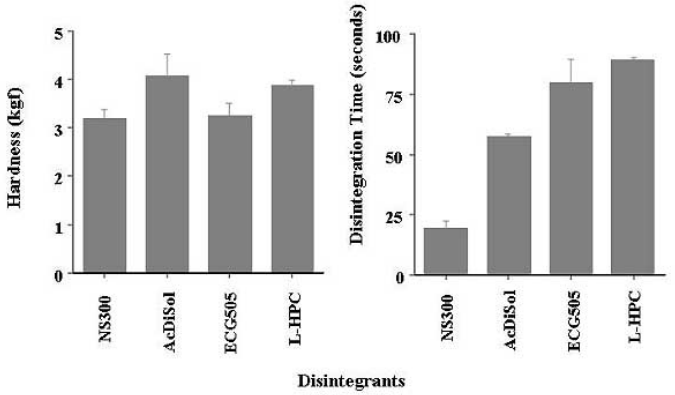


**Figure 1.** Hardness and disintegration time of tablets containing various disintegrants. Each point represents mean ± SD (n = 3).

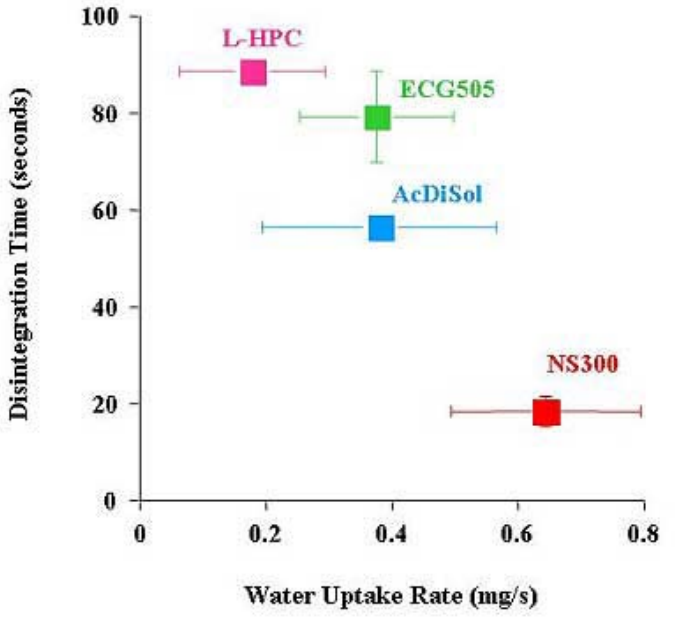


**Figure 2.** Relationship between water uptake rate and disintegration time of tablets containing various disintegrants. Each point represents mean ± SD (n = 3).

## *Effect of NS300 Content in Tablets*

**Figure 3** shows the effect of NS300 content in tablets on the hardness and disintegration time of tablets formed at a compression pressure of 100 MPa. The hardness of tablets remained above 3 kgf in the presence of up to 10% NS300 but decreased at higher concentrations. The disintegration time significantly decreased to less than 20 seconds with increasing NS300 content and remained essentially the same at ratios above 10%. Therefore, 10% NS300 was considered optimal from the viewpoints of prompt disintegration and moderate hardness. There are reports concerning the rapidly disintegrating oral tablets (15-40 seconds) produced by either wet compression or direct compression.[10-13] Considering these values, 20 seconds may be of sufficient value.

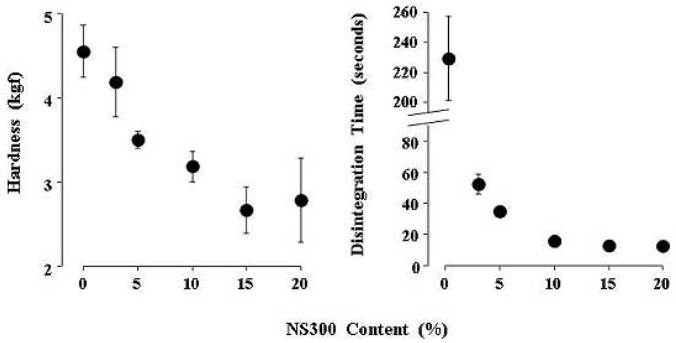


**Figure 3.** Hardness and disintegration time of tablets containing various proportions of NS300 disintegrant. Each point represents mean ± SD (n = 3).

## *Effect of Compression Pressure*

**Figure 4** shows the effect of compression pressure on the disintegration time of tablets containing 10% NS300. The hardness increased to over 3 kgf as compression pressure increased up to and beyond 100 MPa. Tablets rapidly disintegrated at pressures up to 100 MPa but significantly slowed at pressures above 100 MPa. Therefore, 100 MPa is judged as the optimal compression pressure from the viewpoint of practical hardness and rapid disintegration.

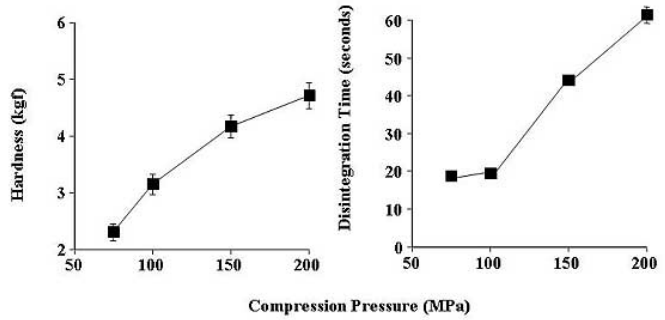


**Figure 4.** Hardness and disintegration time of tablets containing 10% NS300 disintegrant at various compression pressures. Each point represents mean ± SD (n = 3).

## *Oral Disintegration of Tablets*

The disintegration time of tablets containing 10% NS300 compressed at 100 MPa in the mouths of 5 healthy adult volunteers was measured. Complete disintegration was

achieved at 20.2, 20.5, 19.9, 16.6, and 23.1 seconds, respectively (average and SD, 20.1 and 2.3 seconds).

These results showed that these features afford high utility as an oral drug delivery system.

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