AAPS PharmSciTech **2003; 4 (3) Article 41 (http://www.pharmscitech.org).**

Acid-Treated Yeast Cell Wall as a Binder Displaying Function of Disintegrant

Submitted: February 4, 2003; Accepted: July 9, 2003

Tetsuya Ozeki,[1] Hideyo Katsuyama,[1] Yuriko Yasuzawa,[1] Yuuki Takashima,[1] Takahide Kasai,[2] Takahiro Eguchi,[2] Hisaya Kakiuchi,[2] Hiroshi Yuasa,[1] and Hiroaki Okada[1]

[1]Department of Pharmaceutics and Drug Delivery, School of Pharmacy, Tokyo University of Pharmacy and Life Science, Tokyo, Japan

[2]Applied Research Center, Research and Development Division, Kirin Brewery Co, Ltd, Gunma, Japan

ABSTRACT

This investigation examined the application of acid-treated yeast cell wall (AYC) as a binder functioning as a disintegrant. Acetylsalicylic acid (ASA) was granulated with AYC, hydroxypropylcellulose (HPC), polyvinylpyrrolidone (PVP), or pullulan (PUL) and compressed into a tablet in the absence of disintegrant. Particle size and angle of repose of the granules, tensile strength, disintegration time, and water absorption behavior of the tablets and ASA release profiles from the tablets were measured. The surface of AYC-granules was observed with a scanning electron microscope. As was the case with the granules of HPC, PVP, or PUL, D50 of the granules of AYC increased with increasing AYC addition percentage, indicating that it is possible to granulate ASA with AYC. Tablets incorporating HPC, PVP, and PUL failed to disintegrate within 30 minutes at all percentages of binder addition because in the case of the HPC, PVP, or PUL tablets in the dissolution medium, water scarcely penetrated into the inner region of the tablet, causing no disintegration. In the case of the AYC tablets, disintegration was not detected at 3% or less of AYC. When AYC was equal to or greater than 5%, AYC tablets disintegrated in approximately 4 minutes and rapid ASA release from the tablets was observed. These results may have been caused by the following. In the case of the AYC 3% granules, ungranulated aspirin powder remained, but in the case of the AYC 5% granules, ASA powder was granulated and covered with AYC. Water absorption was observed initially; however, a plateau was reached in the case of the AYC 3%-tablet. In contrast, in the cases of the AYC 5% and more tablets, water absorption was greater and increased with time. The angle of repose of the AYC 5% granules was 25.7°, which represented high fluidity. The tablets produced by compressing the granules demonstrated sufficient tensile strength greater than 0.8 MPa. The tablets rapidly disintegrated and rapid ASA release was obtained. AYC functioned as a binder at granulation; additionally, AYC served as a disintegrant in the dissolution of drug from the tablets. These results indicate that AYC affords high utility as a unique pharmaceutical additive possessing contrary functions such as binding and disintegration.

Corresponding Author: Tetsuya Ozeki, Department of Pharmaceutics and Drug Delivery, School of Pharmacy, Tokyo University of Pharmacy and Life Science, Tokyo, Japan. Phone: +81 426-76-4492; Fax: +81 426-76-4492; Email: ozekit@ps.toyaku.ac.jp

KEYWORDS: acid-treated yeast cell wall, pharmaceutical additive, binder, disintegrant, granulation, swelling

INTRODUCTION

Recently, natural materials have been examined as pharmaceutical additives from the perspective of utilization of available resources and safety.[1-4] Previously, a novel preparation for acid-treated yeast cell wall (AYC) via acidification of brewers' yeast cell wall in an attempt to elucidate novel applications regarding its unique functions was reported.[5-8] The chemical components of the yeast cell wall of Sacchromyces cerevisiae, known as brewers' yeast, are mainly polysaccharides such as glucan and mannan and a small percentage of protein.[9,10] A model involving a double layer is currently advocated for the structure of the yeast cell wall comprising mannan-protein complex serving as the upper layer and glucan functioning as the lower layer.[11,12] Although a portion of these components might be lost during the acidification process, the remaining glucan and mannan-protein complex exist in the form of graft chains on the surface of AYC; this complex forms a hydrogel layer in water.

AYC exhibits great utility as a novel aqueous coating material for tablets and granules.[5-7] In accordance with these findings, AYC maintains the shape of the origin yeast, which is characterized by a baggy structure. In water, AYC was dispersed as independent hydrogel particles displaying a hydrogel layer on the surface; moreover, water was included within the structure unlike other polymers generally employed as a solution. Acetaminophen was used as a model drug and the drug release from tablets coated with AYC exhibited a sigmoidal release profile with an initial lag time. Furthermore, drug release was scarcely affected by the pH of the dissolution fluid or by storage at room temperature for 120 days. Control of lag time and release rate of drug was feasible upon variation of curing time and temperature. AYC-coated granules demonstrated smooth surfaces at a coating ratio of only 5%, which generally requires approximately 15% to 30% coating against the core granule weight, with no aggregation. The AYC film revealed an extremely small oxygen permeability coefficient corresponding to the value for aluminum foil laminated with polyethylene and polyethyleneterephtalate as well as a sufficiently low water permeability coefficient, which protects the medicine from moisture. Based on the aforementioned result, AYC was listed on the market as a coating agent for food in April 2000 (YeastWrap, Kirin Brewery Co, Ltd, Tokyo, Japan).

Binder is an additive agent that affords binding power between powder particles.[13,14] Water-soluble synthetic polymers or starches are generally employed in the form of a powder, solution, or slurry.[15-20] Although the binding power between powder particles increases with increasing amounts of binder addition, the disintegrating ability of the granules, or the tablet produced by compressing the granules, decreases. Therefore, in the case of pharmaceutical formulation design, the level of addition of the optimal binder must be carefully determined; the amount of disintegrant must be considered.[21,22]

Generally, an additive agent is selected and prescribed according to function. For example, a binder is added in order to bind between particles, whereas a disintegrant is added in order to disintegrate granules and a tablet rapidly. In the event that 1 additive agent demonstrates 2 or more functions in pharmaceuticals, the type and amount of additive agent and the number of manufacturing processes can be reduced; thus, design of the preparation of high drug content is attained. Dumoulin et al utilized a cross-linked amylose as a binder and as a disintegrant at direct powder compaction.[23] In our previous report, the plate-like calcium hydrogenphosphate dihydrate was granulated with AYC. This finding indicated that AYC possesses dual functions, as a coating agent as well as a binder.

In the present study, adhesion and binding ability of the AYC-hydrogel layer as well as water absorption and swelling properties of AYC were examined. ASA was selected as a model drug because of its high plastic deformability and compressibility. We attempted to apply AYC as a unique pharmaceutical material possessing contrary functions such as binding and disintegration (ie, as a binder functioning as a disintegrant).

MATERIALS AND METHODS

Materials

Acetylsalicylic acid (ASA) (Tsukishima, Co, Tokyo, Japan) served as a model drug. The mean diameter (Feret diameter) of ASA was approximately 52 mm. AYC (YeastWrap), hydroxypropylcellulose (HPC) (HPC-SL, Shin-Etsu Chemical Co, Ltd, Tokyo, Japan), polyvinylpyrrolidone (PVP) (Plasdone, K-29/32, ISP Japan, Ltd, Tokyo, Japan) or pullulan (PUL) (PI20, Hayashibara Co, Ltd, Okayama, Japan) were used as binders. YeastWrap is the AYC aqueous dispersion containing 8.5% (wt/vol) AYC. Magnesium stearate (Wako Pure Chemical Industries, Ltd, Osaka, Japan) was employed as a lubricant. The viscosities of dispersions or solutions of AYC, HPC, PVP, and PUL at 5% (wt/vol), which were measured with a corn-plate viscometer (digital viscometer, model DV-II+, Brookfield Engineering Laboratories Inc, Middleboro, MA), were 3.32, 21.5, 2.50, and 16.3 MPa, respectively. These 5% (wt/vol) dispersions/solutions were used as binders.

Methods

Granulation

ASA was granulated with a fluidized bed (MP-01, Powlex Corp, Osaka, Japan) by the top spray method. Operating conditions for granulation were as follows: ASA powder, 500 g; concentration of binder, 5% (wt/vol); inlet and outlet air temperatures, 80°C and 45°C, respectively; fluidization air flow rate, 15 to 70 m3/h; spray pressure, 1.5 kgf/cm2; spray air flow rate, 25 L/min; nozzle insert diameter, 0.8 mm; spray rate, 15 g/min; percentage of added binder weight as a solid mass; 1% to 10% against an ASA weight.

Angle of Repose

Angle of repose of the AYC 5% granules, immediately after drying in the fluidized bed, was measured with a Konishi angle of repose testing machine (Konishi Medical &#amp;amp; Surgical Co, Osaka, Japan) in an air-conditioned room. The granules were poured onto a circular plate. The conic sedimentary layer of the granules was generated, and the angle between the base line and the slope of the cone was measured with a fixed protractor.

Particle Size of Granules

Test sieves of woven wire cloth and perforated metal plate (Tokyo screen Co, Ltd, Tokyo, Japan) were used. Sizes of openings were 38, 75, 106, 150, 212, and 355 mm. Samples (10 g) were sieved with an electromagnetic vibrating sieving machine (Tsutsui Rikagaku Kikai Co, Ltd, Tokyo, Japan) by vibrating the sieves for 10 minutes. Particle size distributions were determined by weighing the amount of granules on the sieves. The mean particle diameter (D_{50}) was defined as the 50% diameter at cumulative curve of particle size distribution.

Scanning Electron Microscope Observation

ASA powder, AYC 3% granules and AYC 5% granules were observed under a scanning electron microscope (SEM) (S-2250N, Hitachi Co, Ltd, Tokyo, Japan). The samples were coated with gold with a thickness of 25 nm using a quick carbon coater (SC-701C, Sanyu Electronics Co, Ltd, Tokyo, Japan). Magnifications were 50 and 150 times.

Tableting

ASA powder or the granules were compressed employing a universal testing machine (TCM-5000C, Keiaisha NMB Co, Ltd, Tokyo, Japan) equipped with a 8-mm diameter flat-punch at 100 MPa of compression pressure and 50 mm/min compression speed by the external lubrication method. Tablet weight was 200 mg.

Tensile Strength

Hardness of the tablets was measured with a tablet hardness tester (KHT-20, Kiya Corp, Tokyo, Japan). Tensile strength was calculated employing the following equation:

$$\text{Tensile strength} = 2P/\pi Dt \quad (1)$$

where P, π, D, and t are the hardness of tablet, the ratio of the circumference of a circle to its diameter, the diameter of tablet, and the thickness of tablet, respectively.

Disintegration Time

Disintegration time of tablets was measured with a disintegration tester (NT-20H, Toyama Sangyo Co, Ltd, Osaka, Japan) using distilled water at 37 ± 2°C.

Release Study

The release profiles of ASA from the tablets and the AYC granules were examined with a dissolution tester (NTR-6100A, Toyama Sangyo), in accordance with the paddle method (JP14), involving 900 mL of distilled water at 37 ± 0.5°C and a rotating paddle at 100 rpm functioning as the flow system. Aliquot portions of the solution were obtained for measurement of the absorbance and immediately returned to the test solution. The quantity of ASA released was determined spectrophotometrically via measurement of absorbance at 246 nm. The flow system was used as mentioned above; 1 g of ASA dissolved in 300 mL of water at 25°C. The release study was performed under sink conditions.

Water Absorption into Tablet

The amount of water absorption into the tablet was measured with contact angle infiltration rate equipment (PHW, Kyowa Interface Science Co, Ltd, Tokyo, Japan) at 25°C.[6] One tablet was used for the measurement. Water was absorbed through the filter paper into the tablet; subsequently, the change in the weight of the tablet was determined.

RESULTS AND DISCUSSION

Mean Particle Diameter of Granules

Figure 1 exhibits the mean particle diameter (D_{50}) of the granules granulated with various binders. As was the case with the granules of HPC, PVP, and PUL, D_{50} of the granules of AYC increased with increasing AYC addition percentage, indicating that it is possible to granulate ASA with AYC, following calcium hydrogenphosphate dihydrate as discussed in our previous report.[8] The increase in the D_{50} of the AYC granules with increasing AYC addition percentage was smaller

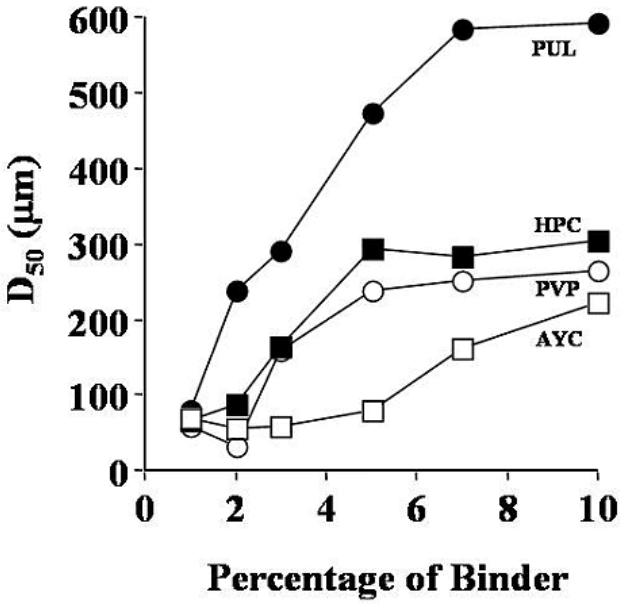

Figure 1. Mean particle diameter (D_{50}) of granules prepared with various binders.

than that of other binders. HPC, PVP, or PUL binders were employed as a solution; moreover, after drying, solid bridges of the polymers between particles generated the binding force, and granulation proceeded. In contrast, the binding force of the AYC binder originated within the tangling of hydrogel layers of the AYC particles after drying. So, the binding force of the AYC may be smaller in comparison with other polymers. However, this result suggests that the phenomenon of hardening into a lump, which prohibits the granulation procedure, cannot occur readily in granulation by AYC.

Tensile Strength of Tablets

Tablets were produced via compression of granules granulated with various binders; subsequently, tensile strength, disintegration time of tablets, and ASA release profiles from the tablets were measured. The study was performed at 1%, 2%, 3%, 5%, 7%, and 10% binder. **Figure 2** presents the tensile strength of the tablets produced by compression of the granules by the external lubrication method in the absence of disintegrant. In the case of tablets prepared by compression of the granules granulated with HPC, PVP, or PUL, tensile strength increased with increasing percentage of binder. This phenomenon may be caused by the adhesion (tacking) force of the polymers and the plastic deformation of the polymers in addition to the plastic deformation of ASA.[24,25] On the other hand, tensile strength of the tablets prepared by compression of the granules granulated with AYC slightly decreased with increasing percentage of AYC. This observation may be attributable to the fact that the adhesion force between dried AYC, which covered the ASA particles at compression, is smaller and the compressibility of AYC is poor. At all AYC percentages, however, tensile strength was greater than 0.8 MPa, which corresponded to approximately 5.2 kgf for hardness. When the hardness of a commercial tablet is 3 kgf or greater, it is satisfactory at practical use. These results indicate that it is feasible to prepare tablets displaying sufficient tensile strength produced by compression of the granules granulated employing AYC aqueous dispersion as a binder.

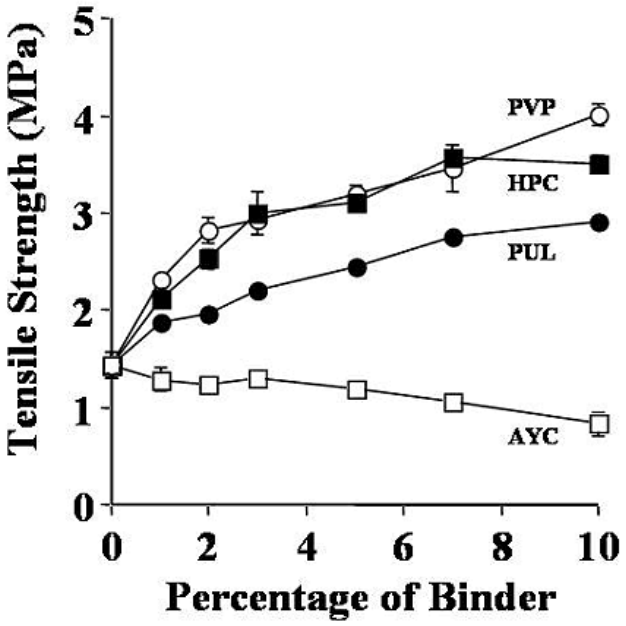

Figure 2. Tensile strength of tablets prepared via compression of granules granulated with various binders. Each point represents the mean ± SD (n = 5).

Disintegration Time of Tablets and ASA Release

Tablets including HPC, PVP, or PUL failed to disintegrate within 30 minutes, which is the disintegration time specified by JP14 at all addition percentages of binders. In the case of AYC tablets, disintegration was not observed at AYC contents of 3% or less. On addition of AYC at concentrations of 5% or greater, the AYC tablets disintegrated within approximately 4 minutes.

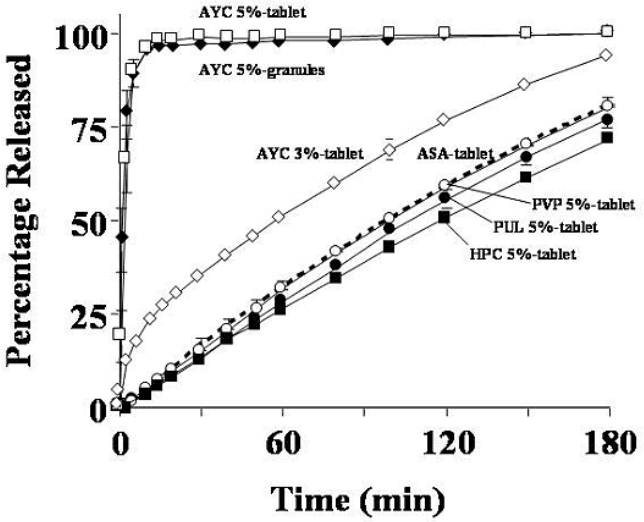

Figure 3. Release profiles of ASA from granules and tablets prepared via compression of granules granulated with various binders. Each point represents the mean ± SD (n = 3).

Figure 3 illustrates the ASA release profiles from tablets prepared via directly compressing ASA powder, AYC 3% and AYC 5% tablets, HPC, PVP, or PUL 5% tablets, and AYC 5% granules. The ASA release profiles from the directly compressed tablet and HPC , PVP, or PUL tablets were nearly identical. These tablets did not disintegrate in 180 minutes during the dissolution test; furthermore, ASA was gradually released from the surface of the tablets. In the case of AYC 3% tablets, an initial rapid release occurred; however, the release rate after that point was similar to that of the directly compressed tablet and HPC, PVP, or PUL tablets. In the case of AYC 5% tablets, extremely rapid ASA release was observed, which was similar to the behavior of the AYC 5% granules. This phenomenon may be attributable to the rapid disintegration of the tablet into granules.

When the angle of repose of granules is 40° or less, it is generally considered that the fluidity is sufficient for use in the manufacture of tablets. The angle of repose of the AYC 5% granules was 25.7°, which represented high fluidity. The tablets produced by compressing the granules demonstrated sufficient tensile strength greater than 0.8 MPa. The tablets rapidly disintegrated, and rapid ASA release was obtained. These results indicate that the granules granulated with AYC are useful as granules for tableting.

The results from D_{50} testing of the granules, tensile strength and disintegration of the tablet, and drug release from the tablet indicate that AYC is a novel unique material possessing contrary functions such as binding and disintegrating character. That is, AYC is a binder functioning as a disintegrant.

Water Absorption Into Tablet and Observation of Granules

To investigate the disintegration behavior of the tablets with AYC, water absorption behavior into the tablet and SEM observation of the granules were performed. **Figure 4** illustrates the water absorption behavior of tablets prepared via compression of ASA powder and granules granulated with 5% of various binders. In the case of the ASA tablet (no binder), water absorption was initially observed; however, a plateau was reached. The water absorption profiles of the HPC, PVP, or PUL tablets were similar to that of the ASA tablet. These results suggest that, in the case of the HPC, PVP, or PUL tablets in the dissolution medium, water scarcely penetrated into the inner region of the tablet,

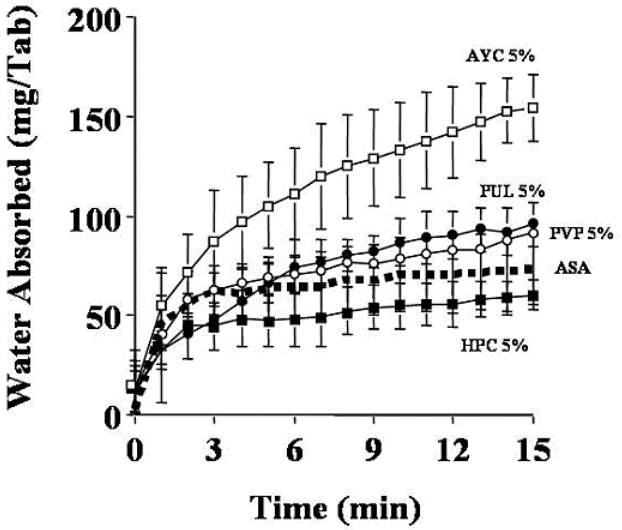

Figure 4. Water absorption behavior of tablets prepared via compression of ASA powder and granules granulated with various binders (5%). Each point represents the mean ± SD (n = 3).

causing no disintegration. The amount of water absorption of the AYC tablet was greater than that of the other tablets and increased with time. **Figure 5** exhibits water absorption behavior of the ASA tablets in the absence of binder and with AYC of various percentages. The AYC 3% tablet, which did not disintegrate within 30 minutes, revealed similar water absorption

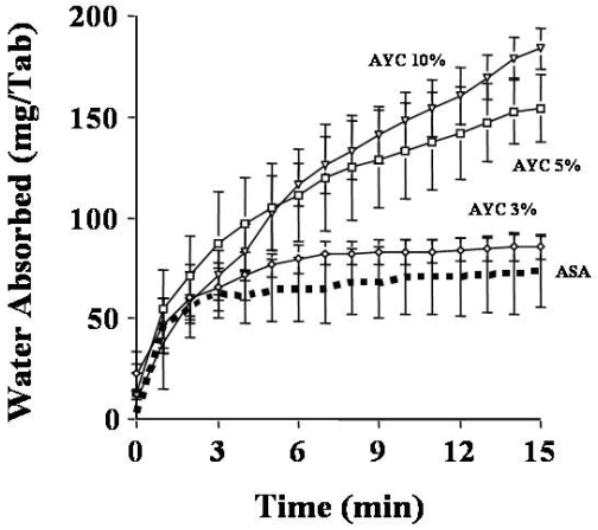

Figure 5. Water absorption behavior of tablets prepared via compression of ASA solo powder and granules granulated with various percentages of AYC. Each point represents the mean ± SD (n = 3).

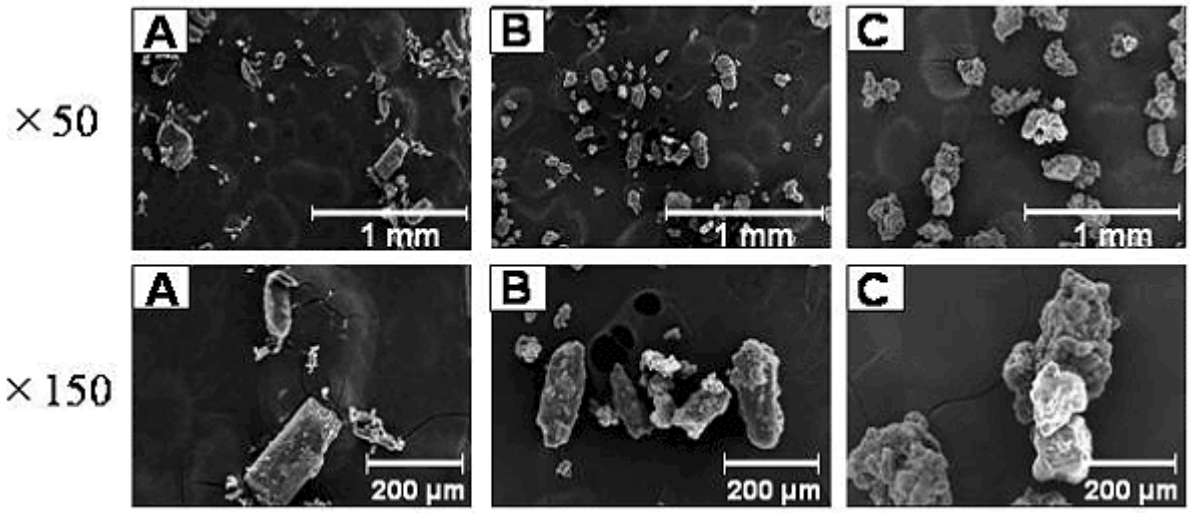

Figure 6. SEM photographs of ASA powder and granules immediately after granulation with AYC: (A) ASA powder, granules with AYC; (B) 3%; (C) 5%.

behavior in comparison with the ASA solo-tablet: water absorption was observed initially; however, a plateau was reached. In contrast, in the cases of the AYC 5% and AYC 10% tablets, which disintegrated in approximately 4 minutes, water absorption was greater and increased with time.

Figure 6 presents SEM photographs of ASA powder and the AYC 3% and AYC 5% granules. In the case of the AYC 3% granules, ungranulated ASA powder remained. In the case of the AYC 5% granules, ASA powder was granulated and covered with AYC. In the case of the tablets prepared by compression of the AYC 3% granules, the ungranulated ASA powder was compressed. Moreover, many portions were evident in which the level of water penetration into the inner aspects of the tablets was small, resulting in no disintegration within 30 minutes. At AYC concentrations of 5% and greater, ASA powder was granulated and the surface of aspirin particles was covered with AYC. In the case of tablets prepared by compression of the granules at AYC levels of 5% and greater, the AYC

absorbed water and swelled within the tablet, causing disintegration of the tablet.

CONCLUSION

Tablets prepared via compression of granules at AYC concentrations of 5% and greater displayed sufficient tensile strength and rapidly disintegrated; additionally, rapid drug release was observed, although the tablets included no other disintegrant. These findings arose because ASA powder was granulated and sufficiently covered with AYC at concentrations of 5% and greater.

The results obtained in the present study indicate that AYC functions as a binder at granulation; in addition, AYC acts as a disintegrant upon dissolution of drug from the tablets. AYC affords high utility as a novel unique pharmaceutical additive possessing opposing functions with respect to binding and disintegration.

REFERENCES

1. Kaneko K, Kanada K, Ouchi K, et al. Control of drug release from granules coated with sodium alginate and calcium lactate through insoluble gel formation. J Pharm Sci Technol. 1999;59:8-16.

2. Watanabe K, Yakou S, Takayama K, Machida Y, Nagai T. Drug release behaviors from hydrogel prepared with water soluble dietary fibers. J Pharm Sci Technol. 1991;51:29-35.

3. Ashford M, Fell J, Atwood D, Sharma H, Woodhead P. Studies on pectin formulation for colonic drug delivery. J Control Release. 1994;30:225-232.

4. Hou W, Miyazaki S, Takada M. Intragastric-floating and sustained-release tablets using chitosan and chitosan hydrochloride. J Pharm Sci Technol. 1991;51:93-99.

5. Kasai T, Eguchi T, Ishiwaki N, Kaneshige J, Ozeki T, Yuasa H. Application of acid-treated yeast cell wall (AYC) as a pharmaceutical additive, I: AYC as a novel coating material. Int J Pharm. 2000;204:53-59.

6. Yuasa H, Kaneshige J, Ozeki T, Kasai T, Eguchi T, Ishiwaki N. Application of acid-treated yeast cell wall (AYC) as a pharmaceutical additive, II: effects of curing on the medicine release from AYC-coated tablets. Int J Pharm. 2000;209:69-77.

7. Yuasa H, Kaneshige J, Ozeki T, Kasai T, Eguchi T, Ishiwaki N. Application of acid-treated yeast cell wall (AYC) as a pharmaceutical additive, III: AYC aqueous coating onto granules and film formation mechanism of AYC. Int J Pharm. 2002;237:15-22.

8. Yuasa H, Katsuyama H, Ozeki T, et al. Acid-treated yeast cell wall (AYC) as a novel binder. J Pharm Sci Technol. 2002;62:153-160.

9. Northcote DH, Horne RW. The chemical composition and structure of the yeast cell wall. Biochem J. 1952;51:232-236.

10. Fleet GH, Manners DH. Isolation and composition of an alkali-soluble glucan from the cell walls of Ssaccharomyces cerevisiae. J Gen Microbiol. 1976;94:180-192.

11. Lampen JO. External enzymes of yeast: their nature and formation. Antonie Van Leeuwenhoek. 1968;34:1-18.

12. Kidby DK, Davies R. Invertase and disulphide bridges in the yeast wall. J Gen Microbiol. 1970;61:327-333.

13. Joneja SK, Harcum WW, Skinner G, Barnum PE, Guo JH. Investigating the fundamental effects of binders on pharmaceutical tablet performance. Drug Dev Ind Pharm. 1999;25:1129-1135.

14. Salib NN, El-Gamal SA. Application of some polymers in the physicochemical design of tablet formulation. Pharmazie. 1976;31:718-721.

15. Kawaguchi T, Sunada H, Yonezawa Y, et al. Granulation of acetaminophen by a rotating fluidized-bed granulator. Pharm Dev Technol. 2000;5:141-151.

16. Lipps DM, Salr AM. Characterization of wet granulation process parameters using response surface methodology, I: top-spray fluidized bed. J Pharm Sci. 1994;83:937-947.

17. Thiel WJ, Nguyen LT. Fluidized bed granulation of an ordered powder mixture. J Pharm Pharmcol. 1982;34:692-699.

18. Chowhan ZY, Chow YP. Compression properties of granulations made with binders containing different moisture contents. J Pharm Sci. 1981;70:1134-1139.

19. Meshali M, El-banna HM, El-Sabbagh H. Use of a fractional factorial design to evaluate granulations prepared in a fluidized bed. Pharmazie. 1983;26:323-325.

20. Soyeux P, Delacourte A, Delie B, Lefevre P, Boniface B. Influence and optimisation of operating parameters with a new binder in wet granulation. Eur J Pharm Biopharm. 1998;46:95-103.

21. Gissinger D, Stamm A. A comparative evaluation of the properties of some tablet disintegrants. Drug Dev Ind Pharm. 1980;6:511-536.

22. Kanig JL, Rudunc EM. The mechanisms of disintegrant action. Pharm Technol. 1984;April:50-63.

23. Dumoulin Y, Clement P, Mateescu MA, Cartiler L. Cross-linked amylase as a binder/disintegrant in compressed tablets. S.T.P. Pharma Sci. 1994;4:329-335.

24. Collin-Beach DP, Hollenbeck RG. Determination of the energy of tablet formation during compression of selected pharmaceutical powders. Int J Pharm. 1983;17:313-324.

25. Christer N, Maria G. Studies on direct compression of tablets, XIII: The effect of some dry binders on the tablet strength of compounds with different fragmentation propensity. Int J Pharm. 1985;23:255-263.