Rapidly Disintegrating Tablets Prepared by the Wet Compression Method: Mechanism and Optimization

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Abstract □ To make rapidly disintegrating tablets with sufficient mechanical integrity, tablets were prepared by compressing wet granules under low compression force and then drying the resulting wet mass in a circulating-air oven (wet compression method). Lactose with various particle sizes was used as the excipient, and water was used as a wetting agent. The effect of drying time, compression force, size of lactose particles, and moisture content of wet granules on tablet properties indicated that the formation and disintegration time of tablets were related to the effect of the formation of solid bridges between lactose particles. By optimizing compression force, size of lactose particles, and moisture content of the granules, tablets meeting tensile strength greater than 0.5 MPa and disintegration time shorter than 15 s were obtained by the wet compression method.

Introduction

Due to a decline in swallowing ability with age, a great many elderly patients complain that it is difficult for them to take some currently used dosage forms such as tablets, capsules, or powders.[1] For this reason, tablets which can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Rapidly dissolving or disintegrating tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people.

Commercially available rapidly dissolving or disintegrating tablets are obtained by various methods.[2−4] Fast disintegrating tablets were developed using wet powders containing drugs. Such tablets were produced by two methods, compression[4] and molding.[5] The preparation processes are usually as follows: after blending the excipient with the drug, the powder mixture is moistened with solvent. The resultant wet powder will then be molded or compressed under low compression force, and after drying in ambient air or an oven, the desired tablets will be obtained. The most commonly used solvent is aqueous alcohol, although other volatile solvents such as acetone and hydrocarbons have also been used. To increase the hardness and reduce erosion of the edges of the tablets during handling, binding agents such as glucose, sucrose, acacia, or povidone are usually added to the solvent mixture.

As volatile solvents are often used, it is difficult to protect the wet mass from solvent evaporation. Therefore, the moisture content of the wet mass is prone to become uneven, which will result in poor uniformity of the tablets. The binding agent must also be added with care, since if used in excessive amounts such agents can markedly decrease the rate of disintegration of the tablets.

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Table 1—Physical Properties of Excipient

	lactose 450M	lactose 200M	lactose 80M
particle size (μm)[a]	13.2	23.9	61.4
SF = (A/ML)4π[b]	0.52	0.52	0.56
particle density (g/cm^3)	1.52	1.52	1.52

[a] Heywood diameter (n = 500). [b] Shape factor (SF) represents sphericity of particles (when particle is spherical, SF = 1). ML: maximum length of particle, A: projection area of particle (n = 500).

Previously, we developed rapidly disintegrating tablets by a direct compression method.[6−8] In the present study, we prepared rapidly disintegrating tablets by the wet compression method using lactose as the excipient. The objective of the study was to delineate the mechanism of formation and rapid disintegration of the tablets prepared by the wet compression method.

Experimental Section

Excipient and Its Physical Properties—α-Lactose monohydrate with various particle sizes (Pharmatose 80M, 200M, and 450M, DMV Co., Holland) was used as the excipient. Its particle density was measured with a helium−air pycnometer (Model 1302, Micromeritics Instrument Co., Norcross, GA). Heywood diameter and shape factor, SF, were determined with an image analyzer (Luzex 500, Nireco Co., Japan). Data are listed in Table 1.

Preparation of Tablets—Kneading was performed in a multipurpose powder handling mill (MECHANOMiLL, Okada Seiko, Co., Ltd., Japan) with the rotation speed of the paddles fixed at 2000 rpm. Distilled water was added to 50 g of lactose powder in milliliter increments, and then the powder was agitated for 60 s. To ensure moisture homogeneity of the mixture, water addition and agitation processes were conducted alternately until the moisture content of the powder mass reached a predetermined value.

The wet powder mass was then extruded through a sieve with a pore size of 710 μm into a container which was then covered with a wet paper towel. The wall of the container was high enough to prevent the wet granules coming into direct contact with wet paper towel. Wet granules were then compressed into flat-faced tablets 10 mm in diameter using a hydraulic press (O. J. Shop, press model 10, Osaka Jack MFG. Co., Japan). The necessary weight of wet granules was calculated from the true density of dry powder and the moisture content of the wet mass to make tablets with a dry weight of 300 mg. The wet tablets were dried in a circulating-air oven at 60 °C. After drying, the tablets were kept in a desiccator for 12 h at room temperature before testing of tablet properties.

Moisture Evaporation of Wet Granules—Wet lactose (450M) granules with a moisture content of 10% were placed in desiccators at 25 °C, each containing a different saturated solution of inorganic salt.[9] The samples were weighed every 10 min, and the moisture loss at each relative humidity (RH) was calculated. The moisture loss of wet granules kept in a container covered with a wet paper towel (our manufacturing humidity conditions) was measured by the same method.

Differential Scanning Calorimetry (DSC)—Samples (10 mg) were analyzed in crimped vented aluminum pans using a MAC Science 3100 type differential scanning calorimeter. Thermographs were recorded over a temperature range of 30−200 °C, with a scanning rate of 10 °C min^{-1}.

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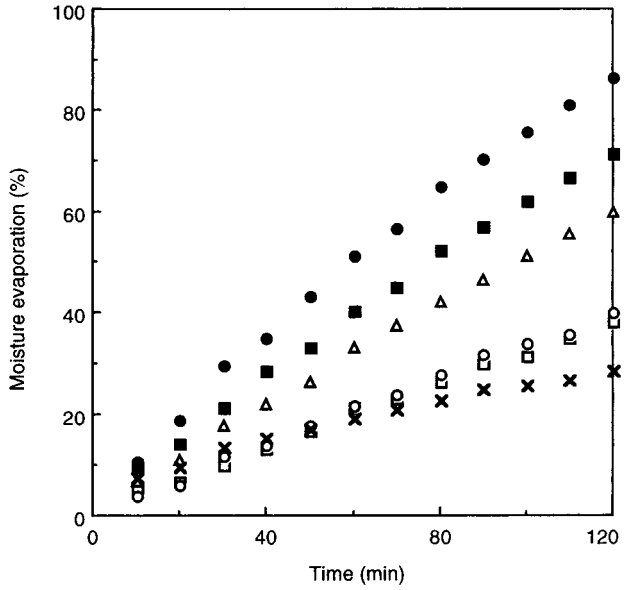

Figure 1—Water evaporation curves of lactose wet granules under various humidity conditions. Relative humidity: □ 100%, ○ 93%, △ 84%, ■ 75%, ● 61.8%, × water evaporation under our manufacturing humidity conditions.

Measurement of Tablet Tensile Strength—The tablet crushing load, which is the force required to break a tablet into halves by compression in the diametral direction, was measured using a tablet hardness tester (TS-50N, Okada Seiko Co., Ltd., Japan). The plunger was driven down at a speed of 20 mm/min. Tensile strength for crushing (T) was calculated using the following equation:

$$T = 2F/(\pi d h) \quad (1)$$

where F is the crushing load, and d and h denote the diameter and thickness of the tablet, respectively.

Measurement of Tablet Porosity—Tablet porosity ϵ was calculated as follows:

$$\epsilon = 1 - m/(\rho_t V) \quad (2)$$

where ρ_t is the true density and m and V are the weight and volume of the tablet, respectively.

Measurement of Disintegration Time—The disintegration test was performed using a JP 13 disintegration apparatus, using distilled water at 37 ± 1 °C.

All tablet property values are shown as averages of five determinations.

Results

Moisture Evaporation of Wet Lactose Granules under Various Humidity Conditions—The moisture content of wet granules markedly affected the properties of the resultant tablets (discussed later). Thus, it is necessary to regulate the ambient humidity to protect the wet granules from moisture evaporation during the tableting process. In our experiments, a wet paper towel covering on the container of wet granules was used for this purpose. Figure 1 shows the evaporation curves of wet granules under various humidity conditions.

The evaporation data of wet granules under our manufacturing humidity conditions are shown as crosses. Moisture evaporation percentage under such conditions was a little larger than that at 93% RH within 40 min, but after 50 min the moisture loss showed values even smaller than that at 100% RH. In our experiments, the tableting process finished within 20 min, during which time less than 10% of the moisture would be lost. In contrast, the moisture loss of wet granules at 61.8% RH was twice as fast as that under our manufacturing humidity conditions. The tablet

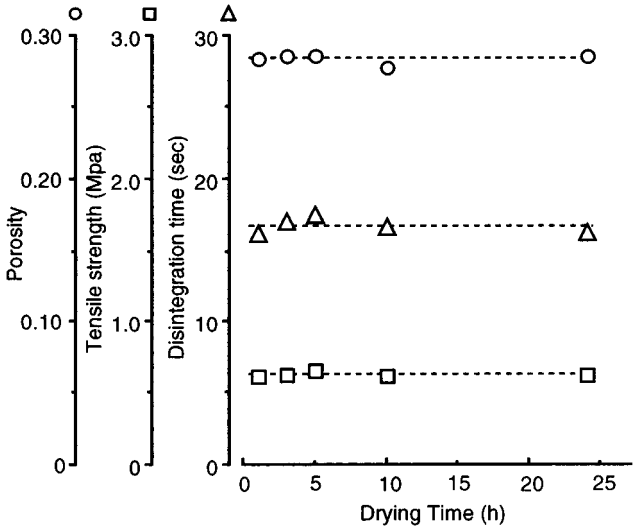

Figure 2—Effects of drying time in tablet properties. ○ Porosity, □ tensile strength (MPa), △ disintegration time (s) lactose: 450M, moisture content of wet granules: 8.56%, compression force: 500 kN.

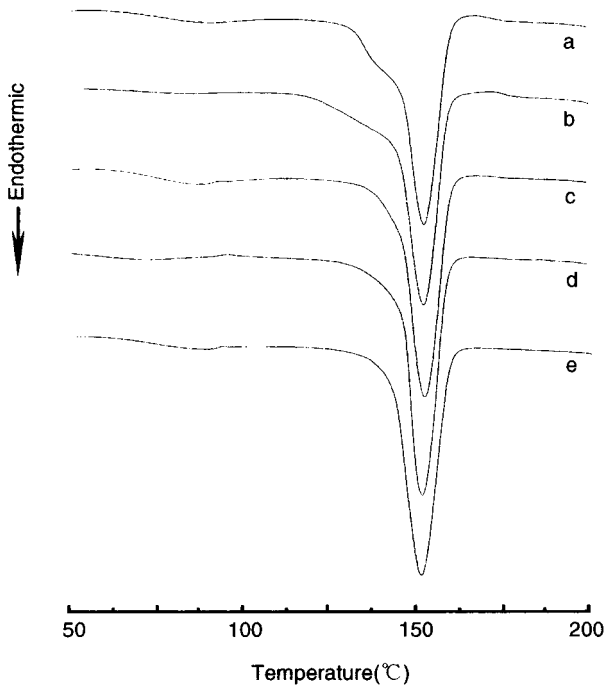

Figure 3—DSC thermograms of α-lactose monohydrate powder and lactose tablets. (a) α-lactose monohydrate powder (450M), (b) tablet being dried for 1 h, (c) tablet being dried for 3 h, (d) tablet being dried for 10 h, (e) tablet being dried for 24 h. Tablets used were the same as those described in Figure 2.

properties determined in our experiments showed small relative standard deviation (RSD) values, which confirmed that although a very simple procedure, covering the container with a wet paper towel is an effective method to slow the moisture evaporation rate.

Effects of Drying Time on the Properties of Tablets—The effects of drying time on porosity, tensile strength, and disintegration time of tablets were evaluated, and the results are shown in Figure 2. No obvious changes in tablet properties were found with increases in drying time.

DSC curves of α-lactose monohydrate raw powder and tablets dried for 1, 3, 10, and 24 h are shown in Figure 3. All samples showed an endothermic peak at about 152 °C, corresponding to the dehydration (elimination of crystal water) of α-lactose monohydrate crystals. Lactose raw

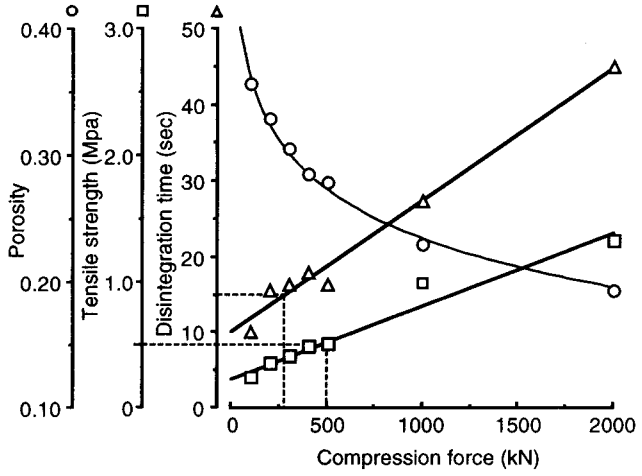

Figure 4—Effects of compression force in tablet porosity. Lactose: 450M; moisture content of wet granules: 8.56%. Dotted lines showed the compression forces corresponding to the tensile strength of 0.5 MPa and disintegration time of 15 s.

powder and tablets with a drying time of 1 h showed a shoulder peak before the endothermic peak of crystal water, suggesting that the two samples contained absorbed water. The DSC results were in agreement with the report of Lerk.[10] According to this report, an unstable anhydrous product was formed when α-lactose monohydrate crystals were heated at temperatures of 100−130 °C. When heated at temperatures below 100 °C, α-lactose monohydrate crystals do not undergo any change. The drying temperature (60 °C) was far lower than 100 °C, and hence drying time had almost no effect on the crystal water of α-lactose monohydrate. Although absorbed water was present in 1 h dried tablets, its amount was too little to affect the properties of the tablets (Figure 2).

The changes in tablet weight with drying time were also measured. After drying for 3 h, tablet weight became constant. Hence, in the following experiments, all tablets were dried at 60 °C for 3 h.

Effects of Compression Force in Tablet Properties—Properties of tablets compressed at 100−2000 kN were investigated. With the increase in compression force, a decrease in porosity and increases in tensile strength and disintegration time were observed (Figure 4). Furthermore, both tensile strength and disintegration time showed linear relationships with the logarithm of tablet porosity (Figure 5).

Compression forces corresponding to our requirements for rapidly disintegrating tablets, i.e., tensile strength greater than 0.5 MPa and disintegration time shorter than 15 s, were found (Figure 4). The results were >500 kN and <280 kN, respectively; i.e., no conditions meeting the requirements were found. Although compression force is a very important factor regulating tablet properties, it is not the only such factor. To obtain tablets with desirable properties, the effects of other factors on tablet properties were investigated. Here, because tablets prepared under 500 kN had a disintegration time of shorter than 20 s, which is close to the requirement, in the following section tablets were prepared under 500 kN.

Effects of Moisture Content and Particle Size on the Properties of Tablets and Optimization of the Two Factors—Besides compression force, many factors affect properties of wet compressed tablets. Among these, particle size and shape of raw materials and moisture content of wet granules are supposed to be the most important. Consequently, lactoses with various particle sizes were used. Wet granules with various moisture contents were made into 14 kinds of tablets to evaluate the effects of factors other than compression force on tablet properties. The shapes of the lactose particles with various sizes were almost the same (see Table 1). Therefore, particle size of lactose and moisture content of wet granules were selected as controlling factors, tablet tensile strength and disintegration time were selected as response variables, and a polynomial regression algorithm was used to relate the controlling factors to the response variables.

The values of 14 groups of controlling factors and response variables are listed in Table 2, and the resultant multiple regression equations are as follows:

$$T_s = -0.1426x + 0.1540y - 0.0312xy + 0.5736 \quad (3)$$

$$N = 14 \quad R^2 = 0.968 \quad T < 0.05 \quad F(3,10) = 10.4842$$

$$\mathrm{Dis} = -10.328x + 15.625y + 18.683 \quad (4)$$

$$N = 14 \quad R^2 = 0.563 \quad T < 0.05 \quad F(2,11) = 7.093$$

Where T_s is tablet tensile strength (MPa), Dis is the disintegration time (s). x and y stand for the transformed

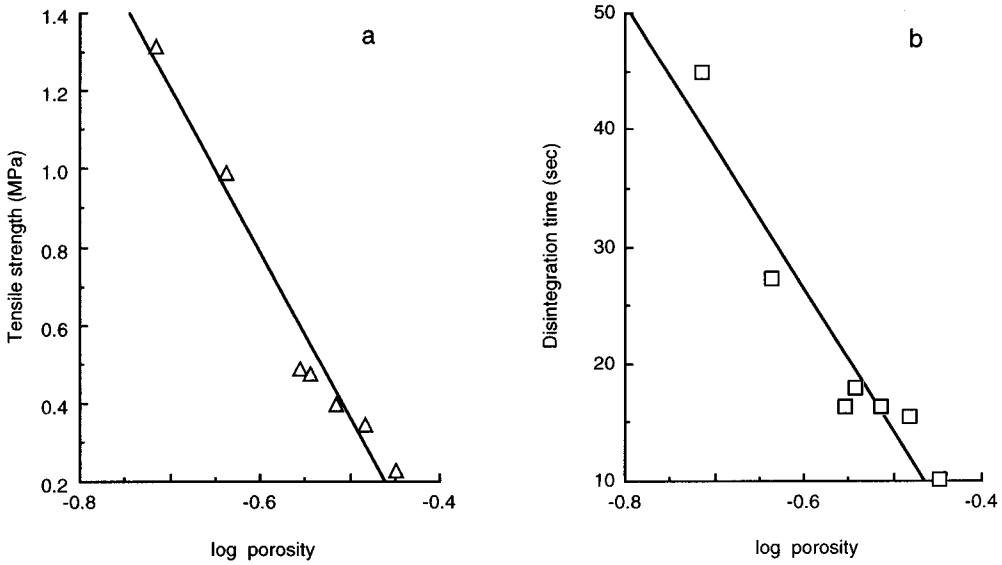

Figure 5—Relationship between common logarithm of porosity and tensile strength and disintegration time of tablets. (a) Tensile strength, (b) disintegration time. Lactose: 450M; moisture content of wet granules: 8.56%.

Table 2—Experimental Values of Controlling Factors and Response Variables

formulation number	particle size (μm)	x	moisture content (%)	y	tensile strength (MPa)	disintegration time (s)	porosity
1	13.18	–1.00	4.70	–1.00	0.503	16.23	0.279
2	13.18	–1.00	8.56	–0.45	0.667	19.97	0.275
3	13.18	–1.00	14.20	0.35	0.809	31.06	0.261
4	13.18	–1.00	18.80	1.00	0.836	82.45	0.275
5	23.90	–0.55	4.70	–1.00	0.454	9.55	0.261
6	23.90	–0.55	7.56	–0.59	0.563	11.02	0.265
7	23.90	–0.55	10.20	–0.22	0.608	11.23	0.272
8	23.90	–0.55	14.20	0.35	0.755	16.12	0.256
9	23.90	–0.55	18.80	1.00	0.843	21.47	0.263
10	61.35	1.00	4.70	–1.00	0.326	2.86	0.285
11	61.35	1.00	8.56	–0.45	0.358	4.89	0.274
12	61.35	1.00	10.20	–0.22	0.382	6.20	0.273
13	61.35	1.00	14.20	0.35	0.505	10.85	0.280
14	61.35	1.00	18.56	0.97	0.531	21.47	0.270

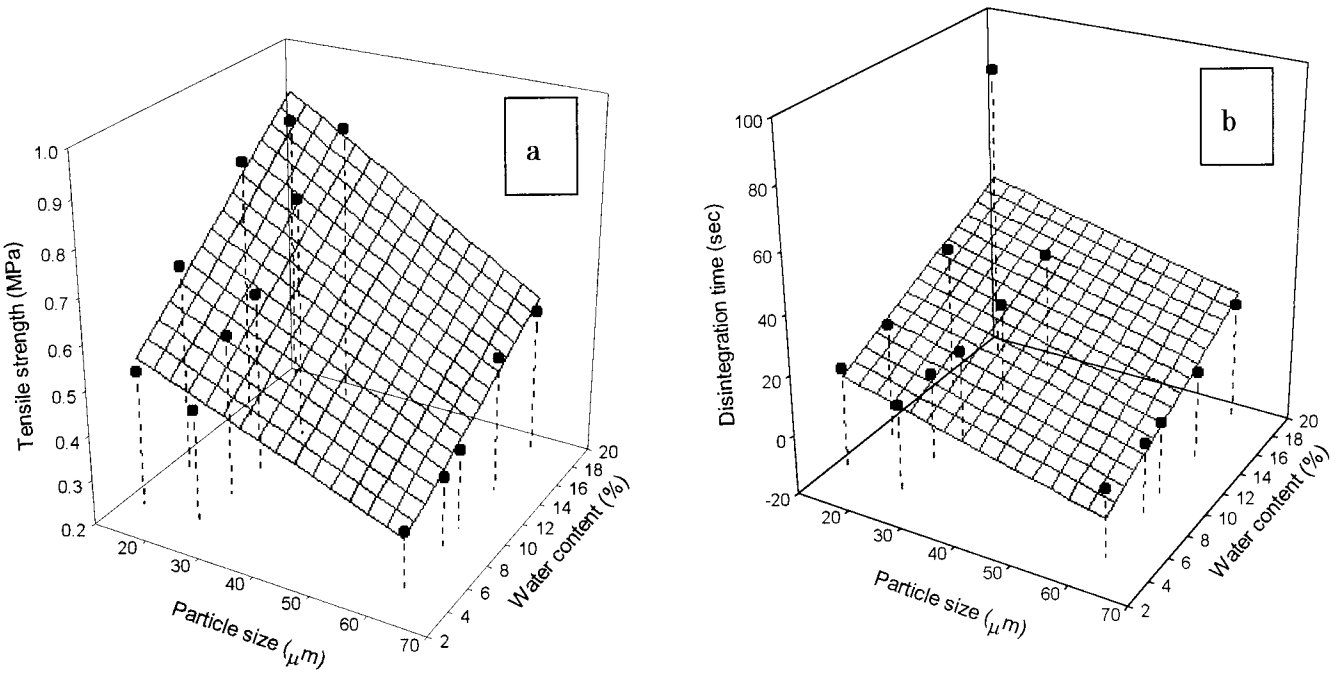

Figure 6—Response surfaces of tablet tensile strength and disintegration time obtained by multiple regression analysis as a function of particle size and moisture content. (a) Tensile strength, (b) disintegration time. Black dots stand for the experimental data.

particle size and moisture content, respectively, and the transformation was processed using the method described in our previous report.[7] N is the number of samples, and R is the multiple correlation coefficient. T denotes the P value determined by Student's t-test, and F, that obtained by F-test. Student's t-test showed that coefficients for all the components on the right side of eqs 3 and 4 were highly significant ($P < 0.05$).

In the multiple regression equation of disintegration time, the multiple correlation coefficient R was not very large. Therefore, an artificial neural network (ANN) was also constructed by Takayama's method to relate the controlling factors to the response variables.[11–13] Three-dimensional surface plots based on multiple regression and ANN are shown in Figures 6 and 7, respectively. The surface plots of tensile strength obtained by multiple regression analysis and ANN were almost the same. In detail, tensile strength increased with increases in moisture content. When moisture content was constant, tablets made of small lactose particles showed higher tensile strength. Disintegration time increased with increases in moisture content and decreases in particle size, which is analogous to the tendency of tensile strength. Although the tendencies of disintegration plots obtained by the two methods were similar, the disintegration plot obtained by ANN method more accurately reflected the experimental data.

Disintegration time showed a similar tendency to tensile strength with the changes in particle size and moisture content. However, the requirements of tensile strength and disintegration time of rapidly disintegrating tablets are the converse of this tendency. A rapidly disintegrating tablet should disintegrate rapidly in the mouth, while having sufficient structural integrity to withstand handling without substantial breakage. To find suitable tableting conditions under which desired tablets could be obtained, contour plots response to surface plots in Figure 7a,b were also constructed and are shown in Figure 8a,b. With 0.5 MPa as the minimum expected tensile strength, and 15 s as the maximum expected disintegration time, we superimposed the contour plots and obtained the optimum particle size and moisture content combination (the region marked with horizontal lines in Figure 8c). More desirable particle size and moisture content combination could be obtained by changing the target tablet property values. For example, tablets with tensile strength greater than 0.75 MPa and disintegration time shorter than 15 s can be found in the region marked with both horizontal and vertical lines in Figure 8c.

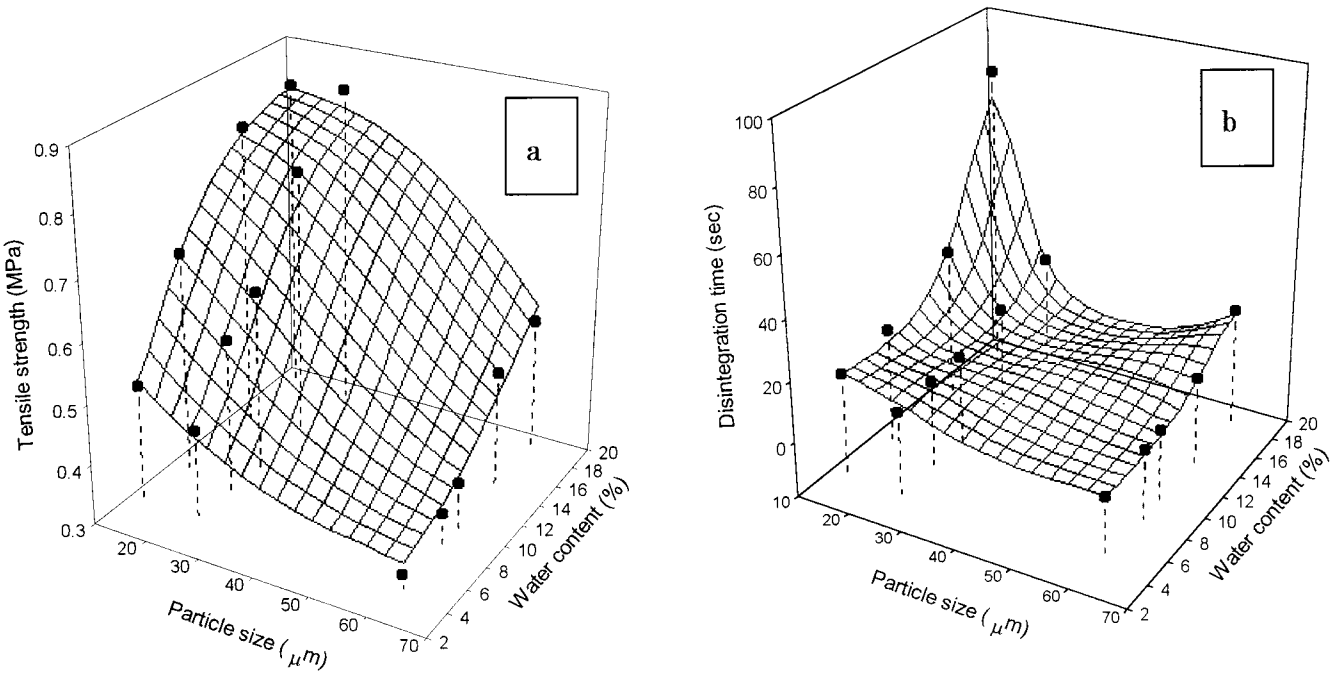

Figure 7—Response surfaces of tablet tensile strength and disintegration time obtained by ANN using particle size and moisture content as input factors. (a) Tensile strength, (b) disintegration time. Parameters of ANN: input layer unit: 2, output layer unit: 2, hidden layer unit: 3, reconstruction: 0, sigmoid curve: 2, training times: 1000, mean error: <0.03, neuron weight: 12. Black dots stand for the experimental data.

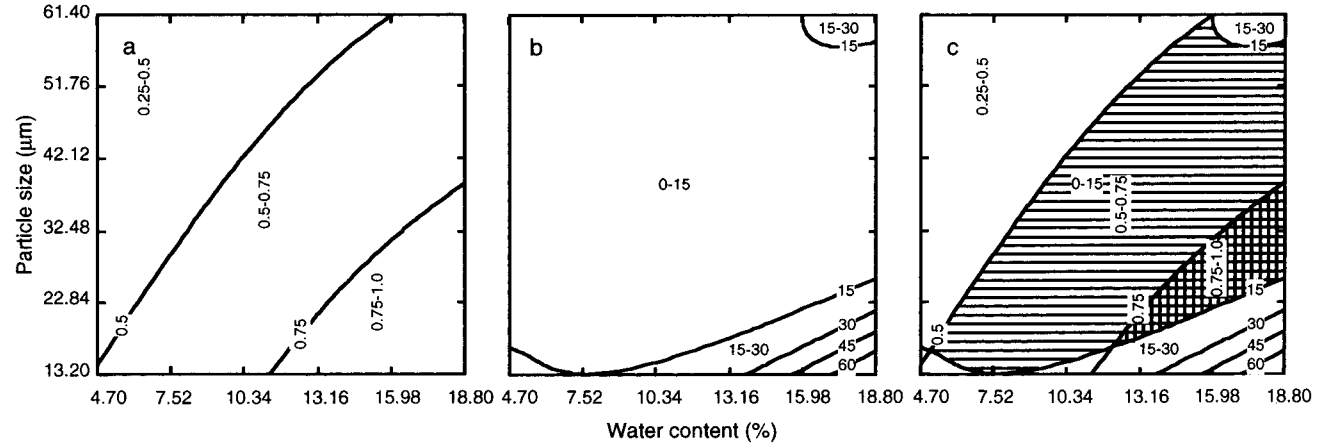

Figure 8—Contour plots of tablet tensile strength and disintegration time obtained by ANN using particle size and moisture content as input factors. (a) Tensile strength, (b) disintegration time, (c) superimposition of plots a and b. The values marked vertically within plots refer to tensile strength (MPa), while values marked horizontally refer to disintegration time (s).

Discussion

Preliminary experiments indicated that for lactose tablets with the same porosity (0.31), the tensile strength of tablets made by the wet compression method (0.4 MPa) is 10-fold greater than that of tablets prepared by the common compression methods (0.035 MPa). Such results suggested that the mechanisms of formation of the two tablets are different.

Discussion of tablet formation must necessarily start with a consideration of the particle–particle bonding mechanism involving adhesion and cohesion of particles. Several forces that can act between small neighboring particles have been identified. Among these, although van der Waals forces are not very large (1kal/mol), they can act over distances up to 1000 Å and must be considered capable of forming interparticle bonds. This intermolecular force plays the most important role in the formation of common compressed tablets. Lactose has many hydroxyl groups, and therefore hydrogen bonding is also an important interparticle force that cannot be neglected. The formation of lactose tablets prepared by the common compression method was thought to be mainly due to the above two forces. In contrast, for tablets prepared by the wet compression method, the solvent (water in this study) plays a key role in the tableting process. The postulated mechanism of formation of wet compressed tablets is shown in Figure 9. After mixing with water, the surface of lactose particles will be wetted and dissolve in water, and the particles will be coated with a layer of lactose solution. During the drying process, interparticle bonds, the so-called solid bridges, will result from recrystallization of lactose. It is these solid bridges which endow wet compression tablets with greater tensile strength, while maintaining relatively high porosity. This mechanism of formation of wet compressed tablets is similar to that of powder metallurgy, which is quite different from that of common compressed tablets.

For common compressed tablets, the number of contact points between particles is another factor which plays an

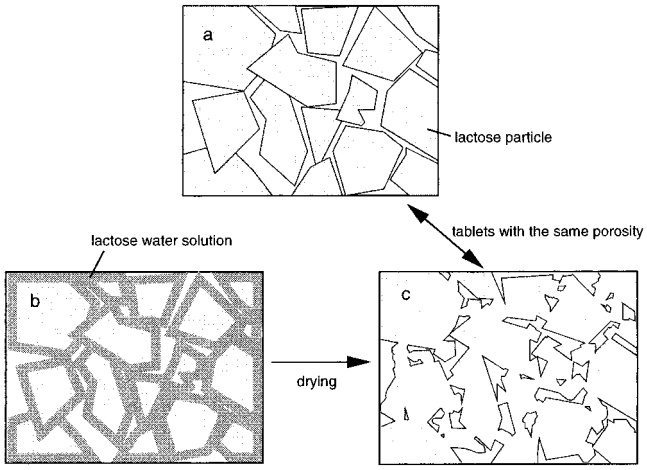

Figure 9—Hypothesized mechanism of formation of wet compressed tablets. (a) Tablets prepared by common compression method. (b) Wet compressed tablets before drying. (c) Wet compressed tablets after drying.

important role in tablet tensile strength.[14] With decreases in tablet porosity, the number of contact points increases, and tensile strength of the tablets shows a higher value. For wet compressed tablets, with increase in compression force, tablet porosity decreases, and the distances between particles become small. Thus, more solid bridges can be formed between particles. As a result, the tensile strength of wet compressed tablets increases linearly with the logarithm of porosity (Figure 5a).

Disintegration time showed a similar tendency to tensile strength with changes in tablet porosity (Figure 5b). Our previous studies indicated that porosity, hydrophilicity (solubility if the tablet constituents are water-soluble), swelling ability of the particles, and interparticle force are important factors for tablet disintegration.[6] Lactose is not a swellable material, and thus for lactose tablets the most important factors for disintegration are tablet porosity and interparticle force. With increases in compression force, tablet porosity decreases. Consequently, water penetration into the tablets would slow with decreases in porosity.[15] This is one reason disintegration time was prolonged with decreases in tablet porosity. When porosity decreases, more solid bridges are formed, which would make the annihilation of interparticle force more difficult. For such reasons, the effect of tablet porosity on disintegration time is similar to that on tensile strength.

Tensile strength and disintegration time of wet compressed tablets were markedly affected by tablet porosity, which can be easily controlled by compression force. In this study, size of lactose particles and moisture content of wet granules showed little effect on tablet porosity (see Table 2, porosity values of all tablets were around 0.3). However, they were shown to be the other two factors which are very important for determining tensile strength and disintegration time of wet compressed tablets (Figures 6 and 7).

As mentioned above, the number of contact points is one of the key factors regulating the integrity of tablets. When tablet porosity and the shape of the constituent particles of tablets are the same, the number of contact points per unit cross-sectional area of the fracture plane of a tablet is mainly dominated by particle size of tablet constituents. Smaller particle size is accompanied by a large number of contact points, as confirmed by SEM (Figure 10a–c). With

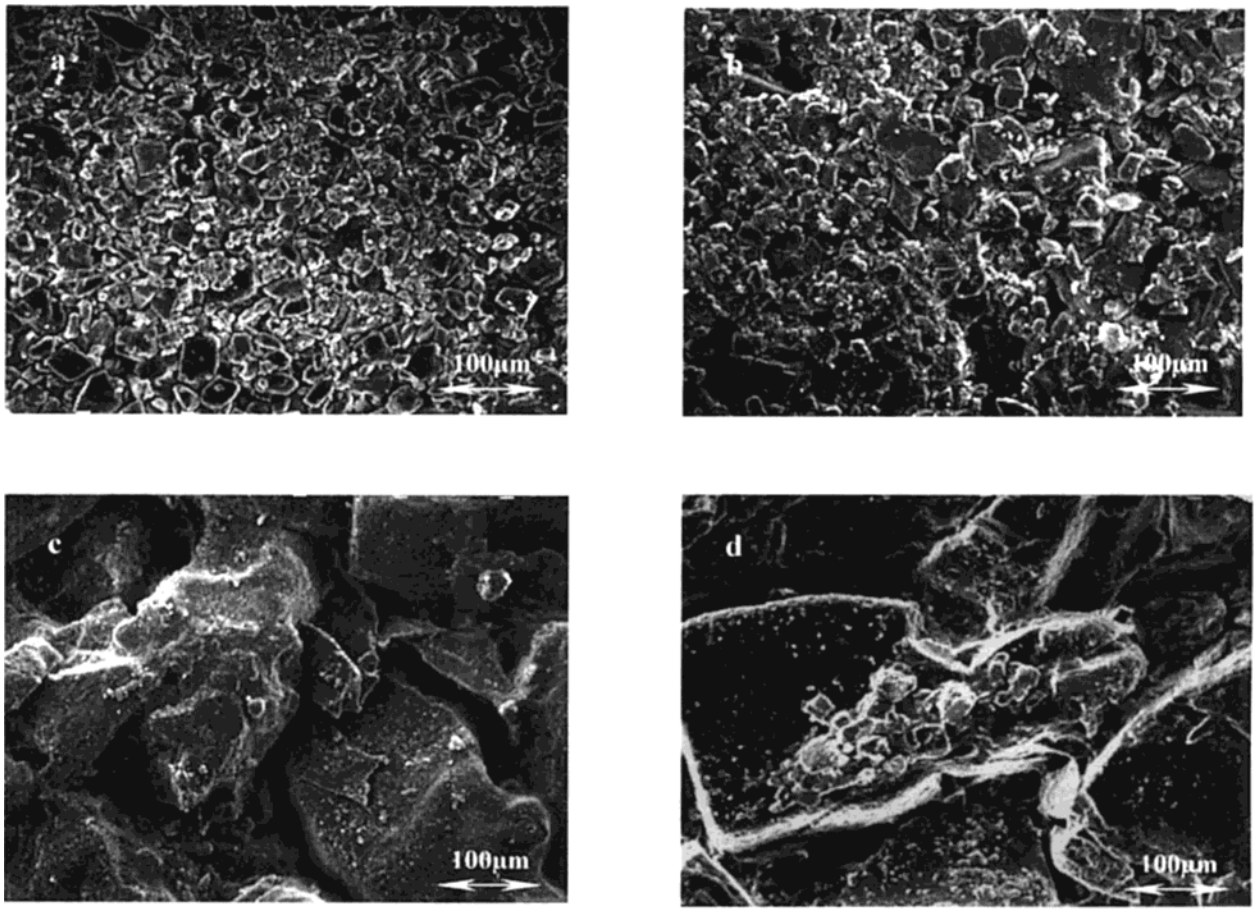

Figure 10—Scanning electron microscopic analysis of wet compressed lactose tablets. (a) Lactose: 450M; moisture content of wet granules: 8.56%. (b) Lactose: 200M; moisture content of wet granules: 8.56%. (c) Lactose: 80M; moisture content of wet granules: 8.56%. (d) Lactose: 80M; moisture content of wet granules: 18.80%.

increases in lactose particle size, the cracks and pores between particles became larger and the number of contact points decreased. This may explain why tensile strength increased with decreases in lactose particle size.

The effect of moisture content on tablet tensile strength can also be readily explained by the hypothesized mechanism of formation mentioned above. When more water is added in the kneading process, more lactose will dissolve in water, and then more small lactose crystals will recrystallize between the existing lactose particles, and stronger tablets will be formed. When moisture content of wet granules was 8.56%, the cracks between particles could be distinguished clearly, while when moisture content was increased to 18.8%, so many small lactose crystals recrystallized that the large cracks almost disappeared (Figure 10c,d).

Disintegration time showed the same tendency as tensile strength for the reasons mentioned above (Figures 6b and 7b). As the porosity values of these tablets were almost the same, disintegration time was only affected by interparticle force.

All our experimental results can be explained by the hypothesized mechanism of formation of wet compressed tablets.

Conclusions

In this study, we proposed a mechanism of formation of wet compressed tablets which was then confirmed by experimental results.

Tensile strength and disintegration of wet compressed tablets are closely related to the formation and annihilation of the solid bridges formed between lactose particles. The intensity and number of the solid bridges are influenced by compression force, moisture content, and size of lactose particles.

With increases in compression force and moisture content, and the decreases in particle size, the distances between constituent particles will become shorter, more lactose will dissolve and recrystallize, and the number of contact points between particles will increase. Consequently, the resulting tablets will become harder and disintegrate less readily.

By optimization of compression force, moisture content of wet granules, and particle size, rapidly disintegrating lactose tablets meeting our design specifications were obtained by the wet compression method.

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