Preparation and Evaluation of Combination Tablet Containing Incompatible Active Ingredients

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Combination preparation plays an important role in clinical treatment because of its better and wider curative synergism and weaker side effects. However, the existence of incompatibility between active ingredients or between active ingredients and excipients presents a serious obstacle in the preparation of such combination solid dosage forms. In this study, aspirin and ranitidine hydrochloride, between which there existed a chemical interaction, were selected as model drugs. Aspirin powders without any additives were granulated with hydroxypropyl methyl cellulose (HPMC) water solution as a binder using a Wurster coating apparatus and the operation conditions were optimized by Artificial Neural Network (ANN) analysis. Under these conditions, the aspirin granules prepared showed good flowability and compressibility. On the other hand, ranitidine hydrochloride was coated with Aquacoat (ethyl cellulose aqueous dispersion) after preliminary granulation with the Wurster coating apparatus. The aspirin granules and coated ranitidine hydrochloride particles were compressed into tablets with suitable excipients. The combination tablets showed good dissolution, content uniformity and improved stability of active ingredients.

Key words aspirin; ranitidine chloride; combination tablet; Wurster fluidized bed; granulation; coating

With the development of pharmaceutical research, dosage forms of two or more active ingredients in combination have attracted much interest because they can show synergistic curative effects and/or decreased side effects.[1—8] But at the same time, there also exist some problems in the process of preparing such combination solid dosage forms, such as incompatibility between the active ingredients or between the active ingredients and excipients, which result in toxic or no clinical effects.[9—18] Therefore, how to prevent this incompatibility and design dosage forms of these drugs that are easy to use has become the focus of such development. For instance, because of the formation of a eutectic mixture between ibuprofen and ethenzamide, three-layer tablets have been developed in which the two active ingredients are not in contact.[19] It is actually a good idea to prepare multi-layer tablets in order to prevent interaction. However, the multilayer tablets not only raise the tablets cost but also might bring some potential problems if certain ingredients such as analgesics are included. For example, the combination of aspirin and codeine phosphate shows a stronger pain-relieving effect and lower addiction,[20] but an acetylation reaction exists between them.[18] Preparing multi-layer tablets in which aspirin and codeine are in different layers can prevent the chemical reaction between them. However, in recent years, there have been reports of codeine abuse since drugs containing aspirin and codeine could be separated.[21,22] Therefore, since codeine can be easily separated in a multi-layer tablet, preparing a common single-layer tablet might perhaps avoid this problem if the interaction between aspirin and codeine can be overcome.

In order to study how to prepare single-layer combination tablet containing incompatible active ingredients, aspirin and ranitidine hydrochloride were selected as model drugs because of the serious interaction between them.[23] Ranitidine chloride has very poor stability because of high moisture absorption and is discolored by light and aspirin (acetyl salicylic acid) can be easily hydrolyzed into salicylic acid and acetic acid. When the two drugs come into contact, the degradation can be further accelerated. We selected a mixing ratio of aspirin and ranitidine hydrochloride of 50 : 1 in accordance with the aspirin–codeine combination ratio,[24,25] and attempted to prepare an aspirin–ranitidine combination tablet using common methods. As is well known, granulation and coating are the most popular methods to decrease and prevent interaction. In this study, a Wurster coating apparatus was employed as the main apparatus because the many operations of mixing, granulating, coating and drying can be carried out in a single vessel at the same time.[26—28] Aspirin was granulated using the Wurster coating apparatus and the operation conditions were optimized by Artificial Neural Network (ANN) analysis.[29] Ranitidine hydrochloride was coated with Aquacoat (ethyl cellulose aqueous dispersion) film after preliminary granulation. The aspirin granules and coated ranitidine hydrochloride particles were then compressed into tablets and the physical and chemical properties of the combination tablets were investigated.

Experimental

Materials As model drugs, aspirin (acetylsalicylic acid≧99.5%) and ranitidine hydrochloride in fine powder form were obtained from Sankyo Chemical Industries, Ltd. (Tokyo, Japan) and Glaxo·Smithkline Inc., respectively. Hydroxypropyl methyl cellulose (HPMC, type E) as the binder for aspirin granulation was provided by Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). Lactose (DMV Japan Co., Pharmatose 200 M, Tokyo, Japan) was selected as the flow assistant for preliminary ranitidine hydrochloride granulation and hydroxypropyl cellulose (HPC-L) as the binder was supplied by Nisso Co., Ltd. (Tokyo, Japan). Aquacoat (FMC Corporation, U.S.A.) used to coat the ranitidine chloride preliminary granules was obtained from Asahi-Kasei Corporation (Tokyo, Japan). Triacetine (TAG) as a plasticizer was purchased from Kanto Chemical Co., Inc. (Tokyo, Japan). When preparing the tablets, microcrystalline cellulose (Avicel PH-101, Asahi-Kasei Co., Tokyo, Japan) was used as the filler and carboxyl methyl cellulose calcium (ECG-505, Gotoku Chemical Co., Ltd.) was used as the disintegrative.

Apparatus Aspirin granulation, and preliminary ranitidine hydrochloride granulation and coating were all carried out in the same Wurster coating apparatus (MP-01-SCP, Powrex Corporation, Itami, Japan).

HPLC Conditions In this study, the aspirin and ranitidine hydrochlo-

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Table 1. List of Data from Practical Experiments[a)]

Experiment No.	Controlling factors				Experimental results			
	Powder supplied F (g)	Spray liquid concentration C (%)	Spray speed V (g/min)	Spray liquid used W_s (g)	Particle yield Y (%)	Median diameter d_{50} (μm)	Angle of repose θ (°)	Aspirin degradation D (%)
1	300	3	6	800	79.0	178.8	40	0.10
2	500	3	5	800	90.0	160.6	38	0.14
3	500	5	5	800	87.0	168.1	36	0.22
4	500	5	6	1200	90.5	180.8	35	0.25
5	500	5	7	800	92.4	171.7	34	0.21
6	500	5	7	1200	91.5	189.0	35	0.26
7	500	5	7	1500	92.6	202.6	36	0.28
8	800	5	7	1500	94.5	160.5	36	0.27
9	500	7	6	800	88.9	172.3	45	0.31
10	500	7	7	800	90.7	178.8	41	0.34
11	800	7	7	1500	95.2	198.5	37	0.33
12	600	7	7	1000	92.7	195.5	40	0.30
13	600	7	7	1200	93.8	217.0	39	0.34
14	600	7	8	1200	94.0	229.0	38	0.36

a) Operation conditions using MP-01-SCP: inlet temperature, 75 °C; outlet temperature, 25 °C; air flow rate, 5.56×10^{-3} m^3/s; atomizing flow volume, 5.0×10^{-4} m^3/s.

ride contents were determined by HPLC. The mobile phase was 0.05 M KH_2PO_3 and methanol in a ratio of 28 : 72 and the pH was adjusted with phosphate acid to 3.5. The liquid chromatograph was equipped with a 280 nm detector and a 4.6 mm×250 mm column that containing 5 μm ODS-C_{18} packing. The flow rate was about 0.8 ml/min. Determination was carried out with a Shimadzu Liquid Chromatograph (LC-9A) and Shimadzu UV Spectrophotometric Detector (SPD-6A) (Shimadzu Corporation, Kyoto, Japan).

Aspirin Granulation Granulation Conditions and Optimization: Original aspirin powder was granulated with HPMC aqueous solution as a binder in the Wurster coating apparatus. By changing the binder solution concentration, the amount of powder added, the spray rate and the amount of spray liquid added, the physical properties of the resulting granules could be widely varied. So ANN was employed to optimize the operation conditions. In the optimization process, median particle size (d_{50}), yield of product (Y), the angle of repose (θ) and aspirin degradation in the process of granulation (D) were selected as the response variables. The binder solution concentration (C), the amount of powder added (F), the spray rate (v) and the amount of spray liquid added (W_s) were employed as controlling factors. The results are shown in Table 1.

Evaluation of Aspirin Granules: The granules prepared under the optimum operation conditions were evaluated in terms of the median diameter by a laser micron sizer (LMS-30, Seishin Enterprise Co., Ltd. Tokyo, Japan), the angle of repose and compressibility by Multi Tester (MT-1000, Seishin Enterprise Co., Ltd. Tokyo, Japan), and the degradation of aspirin by HPLC. The shape and the surface of the granules were observed by Scanning Electron Microscope (SEM, JSM-T20, JEOL Co., Ltd. Tokyo, Japan).

Coating for Ranitidine Hydrochloride Preparation of Core Particles: Because there are many fine particles smaller than 106 μm in original ranitidine hydrochloride powder, it is difficult to coat the original ranitidine hydrochloride powder directly. Furthermore, a large amount of coating material is needed because of the large surface area. Therefore, it is necessary to carry out a preliminary granulation for ranitidine hydrochloride before coating. Lactose, as the flow-assistant, was mixed with ranitidine hydrochloride at a ratio of 1 : 6 to prepare the core particles. Solutions of 2, 3, 4 and 5% HPC-L ethanol were used as the binder and the spray rate was varied from 6.5 g/min to 8.0 g/min. The operation conditions are shown in Table 2.

Coating of Core Particles: Triacetine, as the plasticizer, was added to Aquacoat aqueous dispersion little by little while agitating with a homomixer at 5000 rpm, after which agitation of the coating liquid was continued for 30 min. Then, it was left standing for 24 h before use, which was necessary for the plasticized aqueous dispersion polymer to reach a constant minimum film forming temperature. The curing process was carried out after the coating in the same apparatus at 45 °C for 30 min. The coating operation conditions for the core particles and the coating liquid formulations are listed in Tables 2 and 3, respectively.

Evaluation of Coating Particles: The particle diameter changes were investigated by a laser micron sizer. The surface and the internal structure of the particles were observed by SEM photos.

Table 2. Operation Condition for Granulation and Coating of Ranitidine Hydrochloride

Conditions and method	Preparation of core particles	Coating of core particles
Sample	Ranitidine : lactose=6 : 1	Core particles
Sample supplied (g)	490	400
Inlet temperature (°C)	45	45
Outlet temperature (°C)	25	25
Air flow rate (m^3/s)	9.72×10^{-3}	11.1×10^{-3}
Atomizing air flow (m^3/s)	0.5×10^{-3}	0.5×10^{-3}
Spray rate (g/min)	6.0, 7.0, 8.0	2.5
Weight gained (%)	5.0	10
Curing time (min)	—	30

Table 3. Formulation of Coating Liquid

	Sample	Concentration (%)
Film former	Aquacoat	8
Plasticizer	TAG	0.96
Pore former	HPMC	2
Solvent	Distilled water	89.04

Table 4. Formulations of Tablets

	Formula		
	A	B	C
Aspirin (mg)	200[a)]	200	—
Ranitidine (mg)	4.2[b)]	4.2	4.2[b)]
MCC (mg)	50	50	250
CMC-Ca (mg)	12.5	12.5	—
Talc (mg)	2.5	2.5	—

a) Granules including 200 mg aspirin. *b*) Coating particles including 4.2 mg ranitidine.

Preparation and Evaluation of Tablets Preparation of Tablets: The tablet formulations are shown in Table 4. Aspirin-optimized granules, ranitidine hydrochloride-coated particles and excipients, according to the formulation, were mixed with a twin shell mixer (S-5, Tsutsui Rikagaku Kikai Co., Ltd. Tokyo, Japan) at 50 rpm for 15 min. The mixed powders were com-

pressed into tablets (tablet A) by AUTOGRAPH (AG-5000D, Shimadzu Corporation, Kyoto, Japan). Original Aspirin, ranitidine hydrochloride powders and the excipients with the same formulation as tablet A were compressed into tablets (tablet B) by the same method. In order to observe the coated ranitidine hydrochloride particles inside the tablet, tablet C was prepared.

Evaluation of Tablets: Tensile Strength and Porosity of Tablet A and Tablet B: On the basis of the formulations, tablets A and B were compressed with 1, 2, 3, 5 and 8 kN and the tensile strength of the tablets was measured using a tablet hardness tester (TS-50N, Okada Seiko Co., Ltd. Tokyo, Japan), and the true density was determined with a true density tester (ULTRAPYCNOMETER 1000, Yuasa Ionics Co., Ltd. Tokyo, Japan). The porosity of the tablet was calculated using the following equation:

$$\varepsilon = 1 - 4M_t/(\rho_t \times \pi \times D^2 \times H)$$

where ε is the porosity, and M_t, ρ_t, D, H denote the weight, true density, diameter and thickness of the tablet, respectively.

Observation of the Internal Structure of Tablets: Tablet C was compressed with 2.5 kN and 8 kN and a cross sectional observation was carried out by taking SEM photos.

Content Uniformity of Tablets: Tablets A and B (10 of each) were solved in 100 ml mobile phase. The aspirin and ranitidine hydrochloride contents in the tablets were determined by HPLC.

Dissolution Test of Tablets: The dissolution of tablets was determined using a dissolution tester (NTR-3000, Toyama Sangyo Co., Ltd. Osaka, Japan). Distilled water (900 ml) at 37 °C was selected as the dissolution solvent and the paddle speed was 100 rpm.

Stability of Aspirin and Ranitidine Hydrochloride in Tablets: Brown glass bottles were filled with tablets A and B, sealed and set under conditions of 40 °C, RH75%. The changes in aspirin and ranitidine hydrochloride content with time were determined by HPLC and compared to those determined immediately after the tablet preparation.

Table 5. Optimum Operation Conditions of ANN

	d_{50}	Y	θ	D
Hidden layer unit	4	4	4	3
Reconstruction	0	0	0	0
Sigmoid curve	2	2	2	2
Initial UD matrix	1	1	1	1
Training times	500	500	385	1000
Mean error	0.044	0.012	0.007	0.002
Newron weight	20	20	20	15

Results and Discussion

Optimization of Aspirin Granulation and SEM Observation The ANN structure for each response variable is shown in Table 5. Using this structure, the relationship between controlling factors and response variables is represented by contour figures, as shown in Fig. 1. The figure shows that the product yield had a good correlation with the amount of powder added. There are some reports in which the relationship between the operation factors such as air flow rate, atomizing air pressure, binder concentration and amount of binder applied and the yield were analyzed.[27,30,31] In this study, many operation conditions were fixed except the four controlling factors of the binder concentration (C), the amount of powder added (F), the spray rate (v) and the amount of binder added (W_s). Furthermore, the binder concentration, the spray rate and the amount of binder added influenced the yield mainly because of the fine powder scatter and the production of coarse agglomerate during granulation process.[27,30] In this study, aspirin granulation went on smoothly overall and powder scatter and coarse agglomerate were restrained efficiently when these three factors changed in the range listed in Table 1. Therefore, the yield was mainly influenced by the amount of powder added (F). Figure 1 shows that the more the powder added, the higher the yield. It is considered that on condition that the granulation process can go on well, the loss of product is mainly due to the powder attachment to the device wall and bag-filters. However, the amount of powder attachment would not change a lot with the amount of the powder added. Therefore, the more powder added resulted in the higher yield. The median diameter of particles increased with increasing spray liquid con-

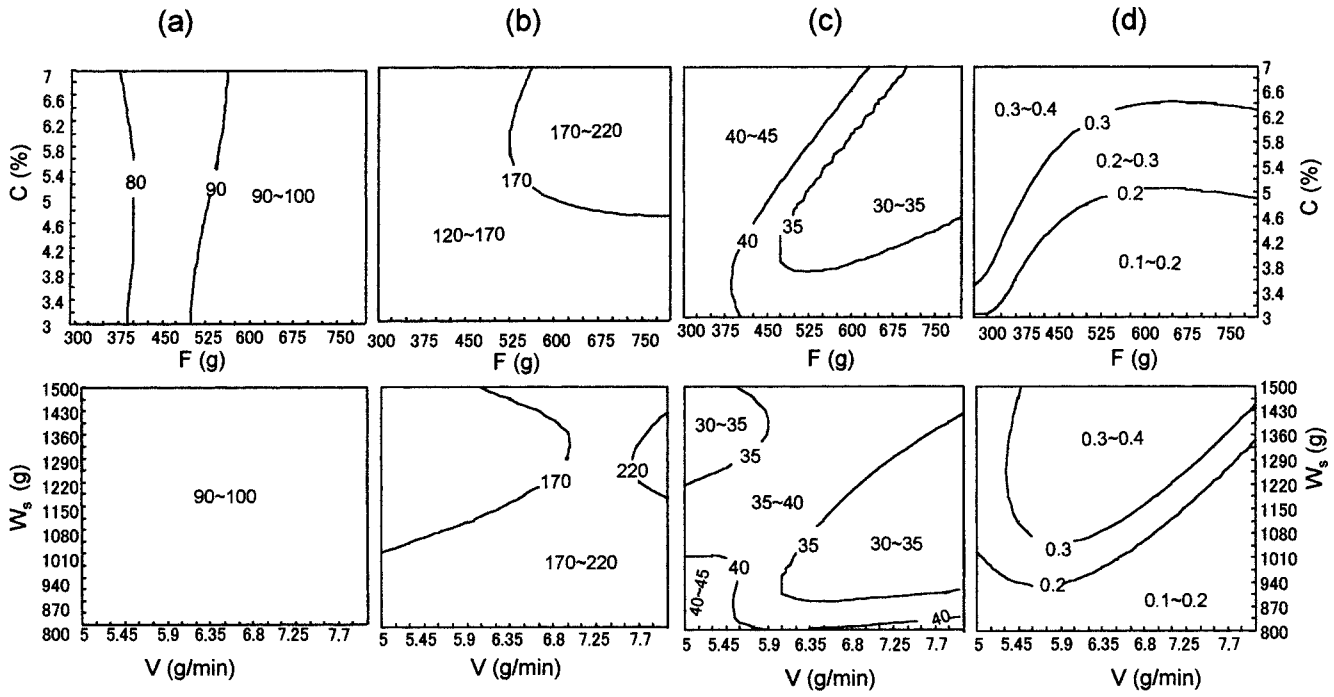

Fig. 1. Relationship between Controlling Factors and Response Variables

(a) Effect of controlling factors on yield; (b) effect of controlling factors on granule diameter; (c) effect of controlling factors on angle of repose; (d) effect of controlling factors on aspirin degradation.

centration and the spray rate because these two factors can affect the drying speed of granules.[27] However, aspirin particles showed a low growth rate in the whole process of granulation. From Fig. 1, it can be seen that the flowability of aspirin granules showed complex changes with the change of controlling factors. There are few reports on the relationship between operation conditions and granule flowability. However, there are some papers to elucidate the relationship between operation conditions and granule shape index Φ ($0<\Phi\leqq 1$).[32—34] In general, the higher value Φ is, the more spherical the granule. Φ increased with the increase of granule moisture content because the agglomerates of high moisture content were subjected to a favorable tumbling motion in the drying process to promote sphericity.[33] In Fig. 1, it shows that the angle of repose of the granules decreased with the increase of spray liquid concentration and spray rate, suggesting the similar results described above because these two factors also mainly influence the moisture content of granules. The angle of repose also decreased with the increase of spray liquid added. It can be explained that with advancing granulation, the amount of fine powder was decreased and the particle shape became spherical resulting in an improvement of flowability. However, the increase in the spray liquid used was not advantageous to the stability of aspirin because aspirin could be easily hydrolyzed under conditions of high temperature and high moisture content.

Based on these analyses, the optimum operation conditions were determined by superimposing the contour figures.[35] An optimum operation condition of the four controlling factors for aspirin granulation is listed in Table 6. Table 7 shows a comparison between optimized granules and original powder, and from these results, it was clear that the optimized granules had better physical properties than the original powder.

The SEM photos of the original powder and granules are shown in Fig. 2. From this figure, it can be seen that the amount of fine powder decreased and the sphericity of granules increased after granulation.

Coating of Ranitidine Hydrochloride and SEM Observation The effects of concentration of HPC-L ethanol solution and the spray rate on the size of core particles are shown

Table 6. Optimum Operation Condition[a] of Aspirin Granulation

Powder supplied F (g)	Binder concentration C (%)	Spray speed V (g/min)	Spray liquid used W_s (g)
650	5	7.5	1000

a) Operation conditions using MP-01-SCP: inlet temperature, 75 °C; outlet temperature, 25 °C; air flow rate, 5.56×10^{-3} m^3/s; atomizing flow volume, 5.0×10^{-4} m^3/s.

Table 7. Properties of Aspirin before and after Granulation

	d_{50} (μm)	Angle of repose (°)	Compressibility (%)	Degradation (%)
Before	123.5	50	23.5	<0.01
After	180.2	34	14.0	<0.1

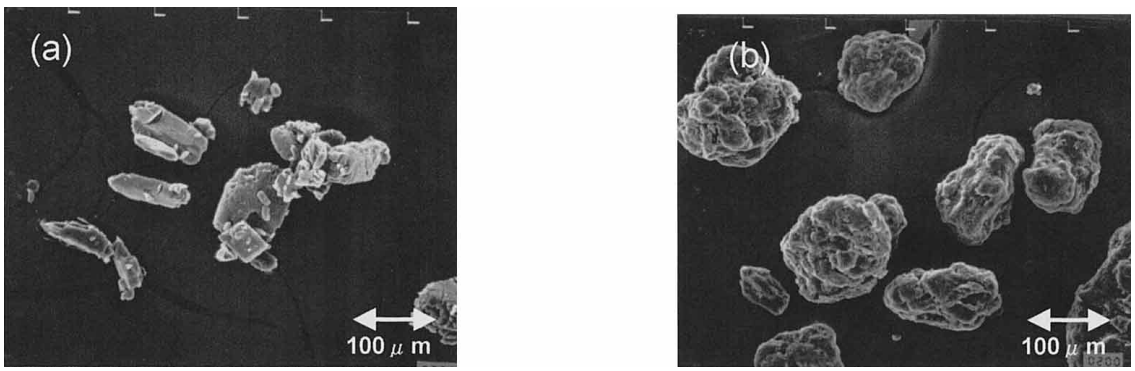

Fig. 2. SEM Photos of Original Aspirin Powder and Granulation Particles
(a) Original powder; (b) particles after granulation.

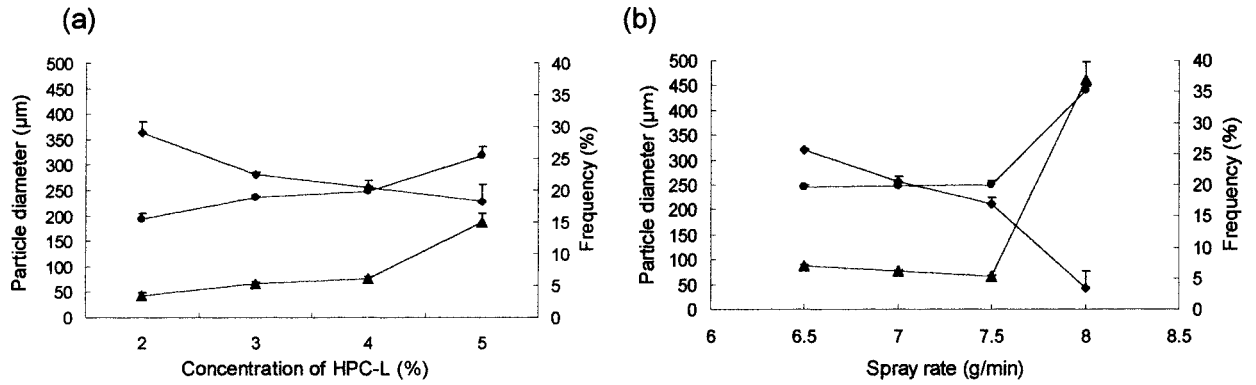

Fig. 3. Effect of Operation Conditions on Particle Distribution for Preliminary Ranitidine Hydrochloride Granulation
Each point represents the mean±S.D. (n=3). (a) Effect of concentration of HPC-L ethanol solution (7.0 g/min, 800 ml spray liquid); (b) effect of spray rate (3.0% concentration, 800 ml spray liquid). —●—, d_{50}; —◆—, pass 106 μm; —▲—, over 500 μm.

in Fig. 3. The figure shows that fine powder smaller than 106 μm was decreased greatly and coarse particles bigger than 500 μm were limited when the concentration reached 3% with a spray rate of 7.0 g/min.

In order to assure the stability of ranitidine chloride in the coating process, it was necessary to control the coating temperature and the coating spray rate because ranitidine chloride is sensitive to water and temperature. Therefore, it was necessary to add a plasticizer to the coating dispersion. Triacetine not only showed good affinity for Aquacoat but also was good for the stability of ranitidine hydrochloride.[36,37] The addition of triacetine equal to 40% of the amount of solid form ingredients of Aquacoat can decrease the minimum film-forming temperature (recommended by the maker), which provided stability to the coated drug. Moreover, the addition of a plasticizer can make the film softer and more flexible, so that in the process of compression the film was not apt to break, which is protective to the drugs contained inside.

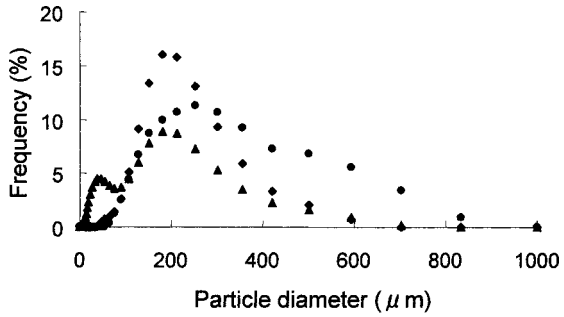

Fig. 4. Distribution of Ranitidine Chloride Particles

▲, ranitidine chloride powder; ◆, core particles; ●, coating particles.

As can be seen in Fig. 4, fine powder smaller than 106 μm was clearly decreased and the size distribution became sharper during the preliminary granulation, which were beneficial for coating. The shape of the original ranitidine hydrochloride powder, core particles, the coating particles and the cross section of coating particles are shown in Fig. 5.

Evaluation of Tablets The tensile strength and porosity changes at different compression pressures are illustrated in Fig. 6. The figure shows that the formulation of tablet A had a better compressibility than tablet B. At the same compression pressure, the tensile strength of tablet A was about twice that of tablet B. Aspirin was the main ingredient in the tablet, about 70% of the tablet weight, so the property of aspirin had a decisive influence on the tablet. The compressibility of aspirin was greatly improved by granulation, so tablet A showed a tensile strength over 0.5 MPa even if compressed at a lower pressure of 2 kN. At the same time, the porosity of tablet A was also larger than that of tablet B, which indicated that at the same compression force, the contact between granules in tablet A was looser. Furthermore, from the observation of the internal structure of tablet C shown in Fig. 7a, it was found that almost all the ranitidine hydrochloride coating granules kept an intact shape in the tablet compressed at a lower pressure of 2.5 kN, which was good for the stability of the tablet. From Fig. 7b, showing the inside structure of the tablet compressed at 8 kN, it was clear that the ranitidine hydrochloride coating particles had a high degree of contact with the excipients and deformation and breaking occurred, so it was difficult to identify the coated particles and the excipients separately. Therefore, a lower compression force will improve the stability.

Basing on the analysis described above, the other properties were evaluated using tablets A and B compressed at

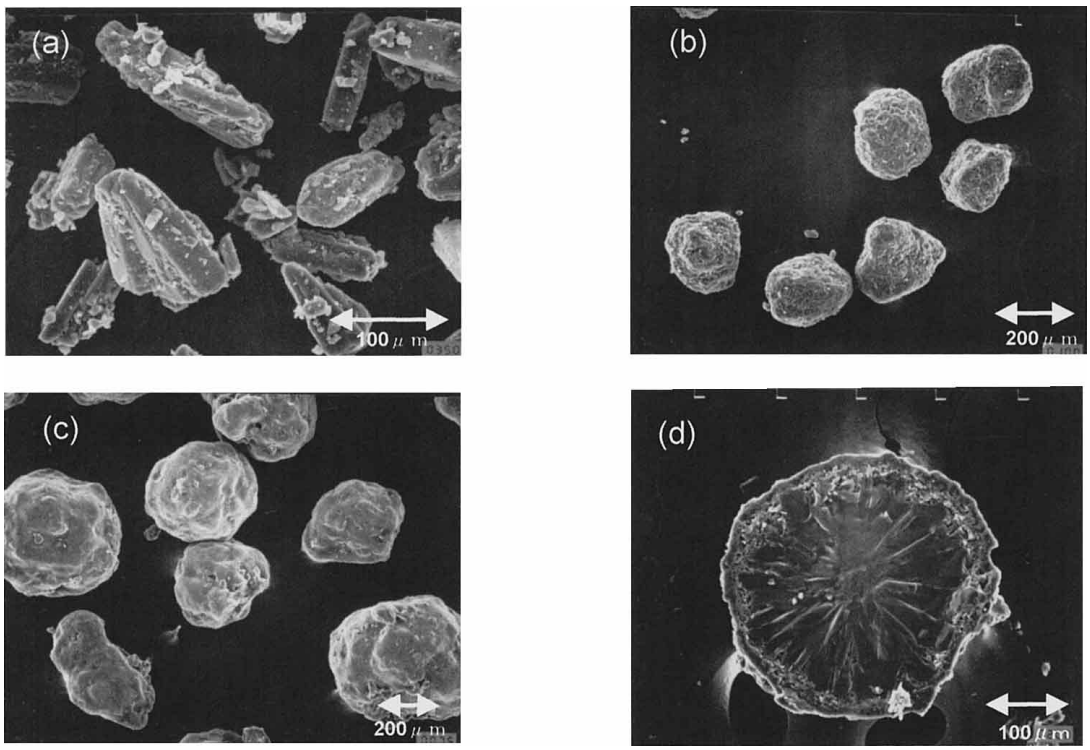

Fig. 5. SEM Photos of Ranitidine Chloride Particles

(a) Original ranitidine chloride powder; (b) core particles of ranitidine chloride; (c) coating particle; (d) cross-section of coating particles.

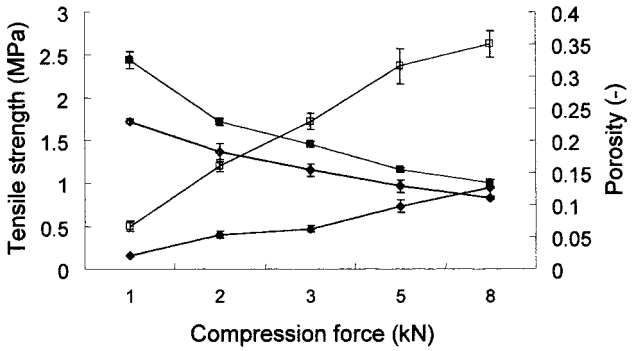

Fig. 6. Effect of Compression Force on the Tensile Strength and Porosity of Tablet

Each point represents the mean±S.D. (n=5). —□—, tensile strength of tablet A; —◆—, tensile strength of tablet B; —■—, porosity of tablet A; —◇—, porosity of tablet B.

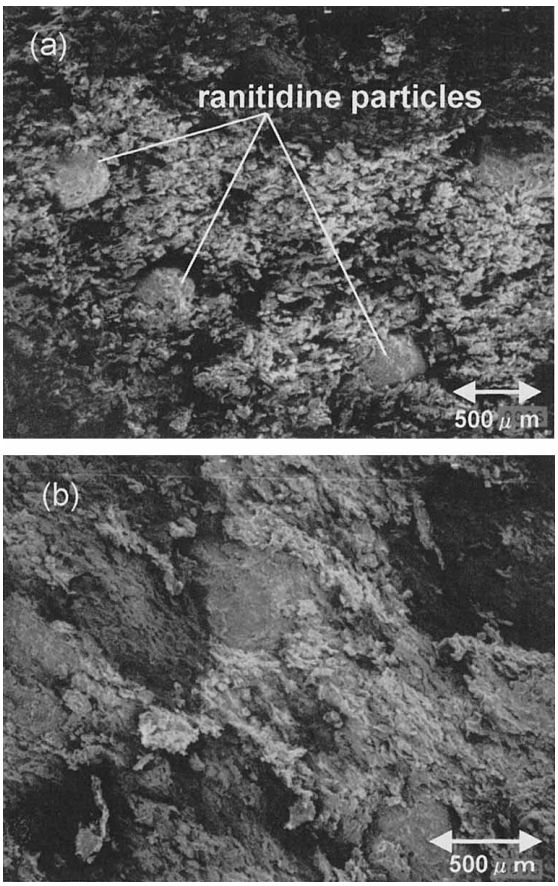

Fig. 7. Internal Structure of Tablet C

(a) Tablet compressed at 2.5 kN; (b) tablet compressed at 8 kN.

2.5 kN. Aspirin and ranitidine hydrochloride content in tablet A, which were 67.7±0.44% and 1.39±0.06% , whereas in tablet B, the contents of aspirin and ranitidine hydrochloride were 71.8±0.82% and 1.60±0.11%, respectively. From the results of content determination, it can be known that the two drugs contents in tablet A showed lower values of standard deviation than in tablet B, suggesting that through granulation and coating, the flowability of the two drugs was improved and the mixing uniformity was assured. Figure 8 shows the dissolution of tablet A and tablet B. Less ranitidine hydrochloride was released in tablet A than tablet B in the

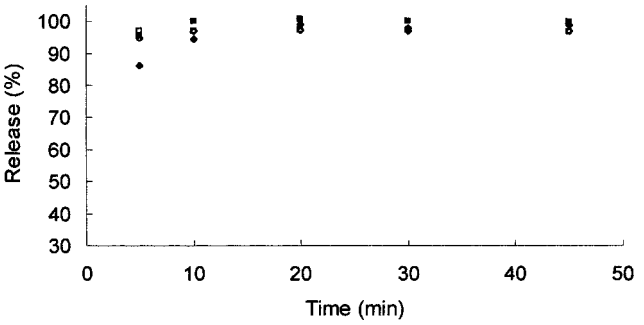

Fig. 8. Aspirin and Ranitidine Chloride Dissolution in Tablets A and B

◆, ranitidine chloride in tablet A; ■, aspirin in tablet A; ◇, ranitidine chloride in tablet B; □, aspirin in tablet B.

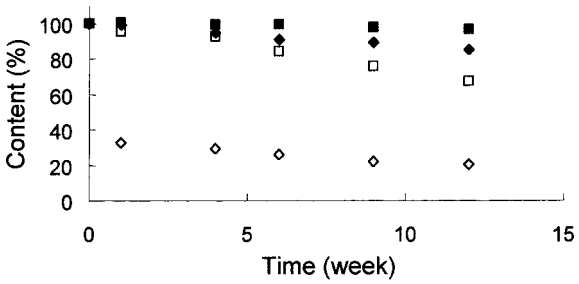

Fig. 9. Content Changes of Aspirin and Ranitidine Hydrochloride in Tablets A and B

◆, ranitidine hydrochloride in tablet A; ■, aspirin in tablet A; ◇, ranitidine hydrochloride in tablet B; □, aspirin in tablet B.

first 10 min, although the release of aspirin showed little difference between tablets A and B. Aspirin and ranitidine hydrochloride both in tablet A and in tablet B could be released almost completely in 20 min. It could be said that granulation and coating had little influence on the release of the two drugs. As shown in Fig. 9, aspirin and ranitidine hydrochloride contents in tablet B decrease much more than in tablet A, indicating that the stability of the combination tablet was improved greatly by using granulation and coating, just like expressed in tablet A.

Conclusion

With granulation and coating, it is possible to prepare combination tablets by a common compressing method which do not show incompatibility between the main active ingredients. The great improvement in flowability and compressibility of the main ingredients make it possible to compress the tablets at a lower pressure, thus enabling the coated particles to maintain their intact shape and decrease the contact between the active ingredients inside and incompatible ingredients. Furthermore, the combination tablet has good tensile strength, content uniformity and dissolution, and improved stability of the active ingredients.

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