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RESEARCH PAPER

Study of Standard Tablet Formulation Based on Fluidized-Bed Granulation

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ABSTRACT

In this study, acetaminophen, ascorbic acid, and ethenzamide were selected as model drugs for tableting granules. Agitation and fluidized-bed granulation were carried out at three drug contents of 30, 50, and 70%.

Compared with agitation granulation, granules made by fluidized-bed granulation showed superior compressibility with wide formulation allowance for drug type and amount. Fluidized-bed granulation resulted in less granule hardness and greater plastic deformability. The granules had considerable compactness and for tablets containing 70% ethenzamide, prolonged disintegration and dissolution times were noted. These are typical features of granules produced by fluidized-bed granulation.

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INTRODUCTION

Although fluidized-bed granulation (FBG) equipment provided by Wurster (1) and Scott (2) et al., and FBG studies conducted by Davies (3), Schaefer (4), Nishimura (5), and Shinoda (6) et al. have been reported, standard operating conditions based on common vehicles, and the effects of standard granulation on tableting have not appeared in the literature. The Standard Formulation Research Association (SFRA) has endeavored to determine standard operating conditions of granulation based on standard materials using a 7:3 lactose/starch mixture as vehicle. The effects of three types of granulation (namely, agitation granulation [AG] FBG, and agitation FBG) on tablet properties have been clarified.

The operating conditions of FBG and how they determine tablet properties are discussed in this paper and the results are compared with those of AG.

METHODS

Materials

Acetaminophen (ACE) JP XII, Yoshitomi Pharmaceuticals Co., Osaka, Japan), ethenzamide (ETZ) (JP XII, Yoshitomi Pharmaceuticals Co.), and ascorbic acid (Vc) (JP XII, Takeda Chemical Industries, Ltd., Osaka, Japan) were chosen as model drugs.

Lactose (Pharmatose 200 M, DMV Co., Holland) and corn starch (Nihon Shokuhin Kako Co., Ltd., Tokyo, Japan) were used as standard vehicles. Hydroxypropylcellulose (Shin-Etsu Chemical Co., Tokyo, Japan) were used as the binding agent and magnesium stearate (Mg-St) (Taihei Chemical Industries Co., Osaka, Japan) was used as a lubricant.

Equipment

The following instruments were used: FD-3S (Powrex Co., Ltd., Itami, Japan) and WSG-5 (Okawara Chemical Industries Co., Yokohama, Japan) VG-25 agitation granulator (Powrex Co., Ltd.), LASD-3400 spray mist diameter (Meiwa Shoji Co., Tokyo, Japan); Wet Eye II infrared moisture meter (Fuji Powdal Co., Osaka, Japan); Oscillator (22 mesh), Comil Steve (type 197); Powrex Co., Ltd.); P-3 power mill, 1.5 mm Φ (Showa Kagaku Kikai Co., Ltd., Osaka, Japan); Clean-press Correct 12HUK rotary tableting machine (Kikusui Seisakusho Co., Tokyo, Japan), 8 mm Φ, bevel flat and concave 6.5 R; scraper pressure detecting system (Okada Seiko Co., Tokyo, Japan); V-type mixer (V-5, Tokuju Seisakusyo Co., Tokyo, Japan); Hygroskop DT equilibrium relative humidity meter (Roto Lone-Gunze-Sangyo, Inc., Switzerland); EB-280-MOC electronic moisture meter (Shimazu Seisakusyo Co., Tokyo, Japan); Powder Tester particle size analyzer (Hosogawa Micron Co., Hirakata, Japan); ES-65 particle size analyzer (Iida Seisakusyo Co., Osaka, Japan); bulk density tester (Kuramochi Kagaku Kikai Co., Tokyo, Japan); Flow Sorb 2300 specific surface area analyzer (Micromeritics Co.) GRANO granule hardness tester (Okada Seiko Co.) tablet physical property tester (WAC-4, Kikusui Seisakusyo Co., Kyoto, Japan); Speed Checker hardness tester (Okada Seiko Co.); Roche friabilator (Kayagaki Rika Kogyo Co., Tokyo, Japan); Spin Analyzer tablet boring strength analyzer (SA 100, Japan Electron Optics Laboratory, Ltd., Tokyo, Japan); disintegration tester (Kayagaki Rika Kogyo Co. and Shimazu Seisakusyo Co., Tokyo, Japan); JP XII dissolution tester, paddle method (50 rpm, distilled water 900 ml) (Toyama Sangyo Co., Ltd., Toyama, Japan); and S-2300 scanning electron microscope (Hitachi Co., Tokyo, Japan).

Granulation and Tableting Conditions

The model drugs used were hydrophobic ACE, which is easy to cap, water-soluble Vc, and poorly water-soluble ETZ. Drug content in granules was set at 70, 50, or 30%. Tablet formulations are shown in Table 1.

Operating conditions for granulation and tableting are shown in Fig. 1. More detailed operating conditions were determined empirically (Table 2). Granule nomenclature is presented in Fig. 2.

For AG, a binding agent was added as a powder; for FBG, binding agent was added as a 5 wt % aqueous solution.

RESULTS AND DISCUSSION

Granule Properties

Mean particle size and particle density of FBG and AG granules containing the model drugs are shown in Table 3. Mean particle size of FBG granules was larger and the bulk density was less than those of AG granules, regardless of drug type or concentration. During the FBG process, the granules are subjected to less shear stress, consequently, granulation is an aggregation pro-

Table 1

Tablet Formulation

	70%		50%		30%	
Drug[a]	126.0 mg	(70.0%)	90.0 mg	(50.0%)	54.0 mg	(30.0%)
Lactose/cornstarch	46.8	(26.0%)	62.8	(46.0%)	118.8	(66.0%)
HPC	6.3	(3.5%)	6.3	(3.5%)	6.3	(3.5%)
Magnesium stearate	0.9	(0.5%)	0.9	(0.5%)	0.9	(0.5%)
Total	180.0 mg	(100.0%)	180.0 mg	(100.0%)	180.0 mg	(100.0%)

[a]A: acetaminophen, E: ethenzamide, C: ascorbic acid.

cess caused by sprayed binder solution droplets; porous granules are the result.

In FBG, the relationship between drug concentration and granule properties is dependent on the particular drug used. Vc dissolves in water during the granulation process and when its content was increased, both mean particle size and bulk density showed a tendency to increase. In contrast, for granules containing ETZ, which has the largest contact angle with water, bulk density decreased with increasing drug content. For ACE granules, increased particle size and bulk density have been observed. Thus drug–water solubility and wettability are important factors which affect the process of granule formation. Other physical properties of model drugs such as adhesivity, particle size distribution, and viscosity may also affect the granule properties, but conclu-

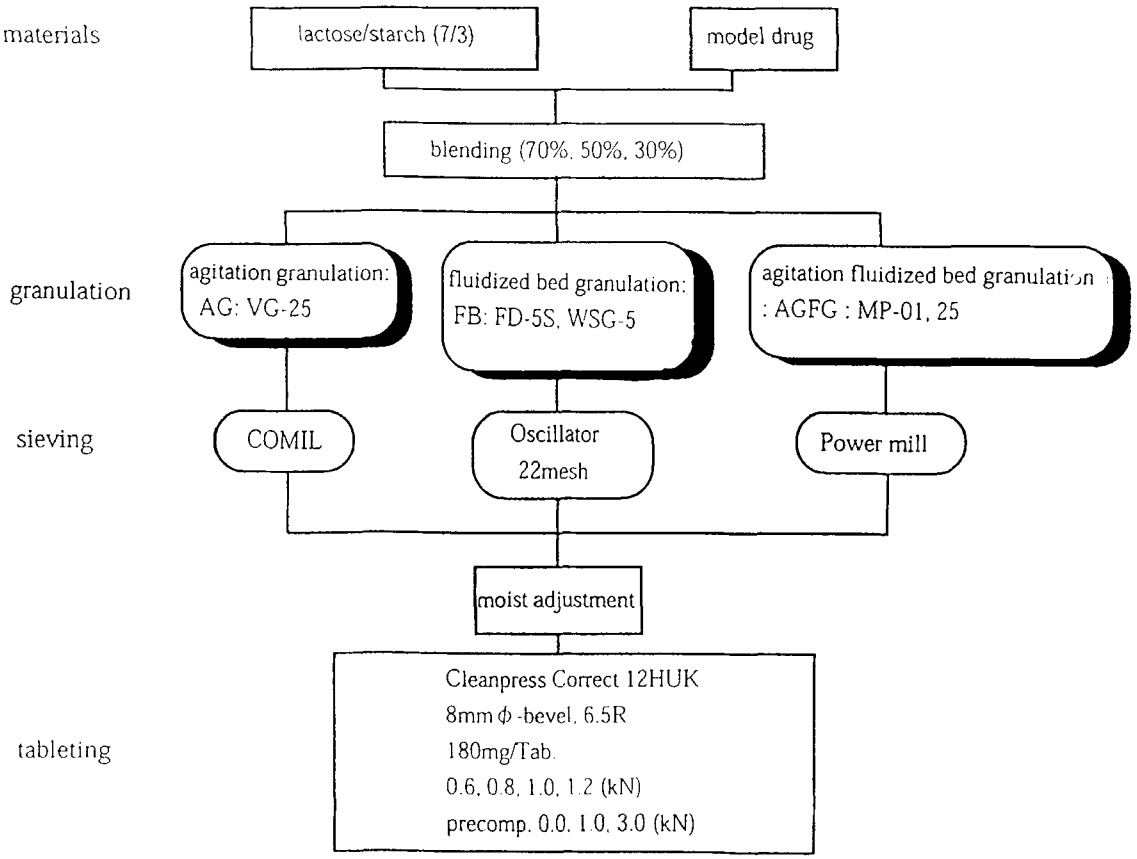

Figure 1. Operating conditions for granulation and tableting (three types of granulation were used in SFRA's study and they are all shown here for comparison).

Table 2

Operating Conditions for Granulation

	Agitation Granulation	Fluidized-Bed Granulation
Load (g)	4975	4975
Purified water (g)	650	3325
Binder conc. (%)	–	5
Inlet air temp. (°C)	–	85
Outlet air temp. (°C)	–	29
Flow rate (m^3/min)	–	3.5
Spray air pressure (kg/cm^2)	–	2
Spray rate (ml/min)	–	90–100
Rotational speed (rpm)	240	–
Granulation time (min)	1	–
Size reduction	Wet/Dry	Dry
Drying temp. (°C)	85	
Drying finishing temp. (°C)	33	

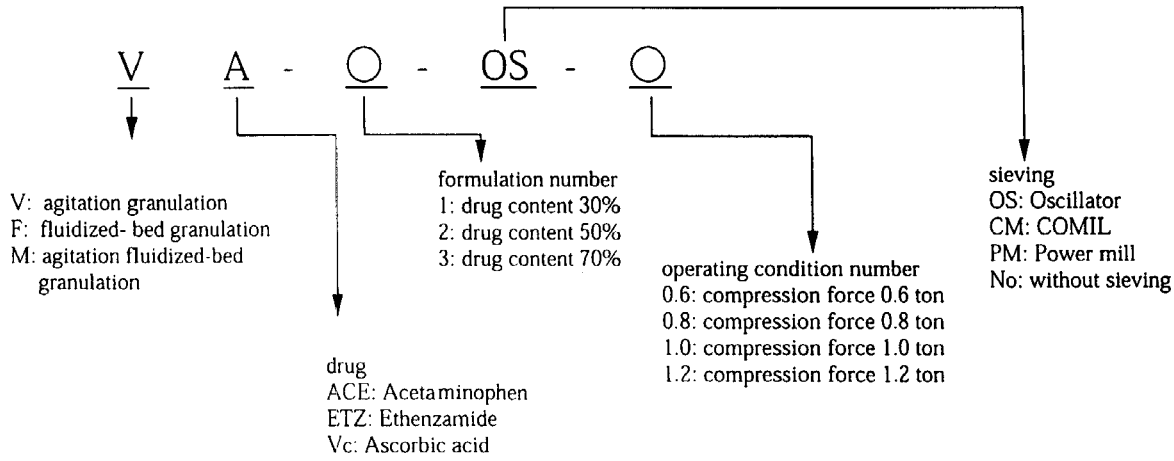

Figure 2. Granule nomenclature.

Table 3

Relationship Between Drug Content and Granule Properties

	Agitation Granulation			Fluidized-Bed Granulation		
	30%	50%	70%	30%	50%	70%
Acetaminophen						
Mean particle size (μm)	171	193	183	197	248	386
Bulk density (g/ml)	0.57	0.54	0.54	0.45	0.54	0.52
Ethenzamide						
Mean particle size (μm)	105	108	134	246	233	218
Bulk density (g/ml)	0.59	0.58	0.47	0.45	0.42	0.40
Ascorbic acid						
Mean particle size (μm)	164	314	348	302	281	345
Bulk density (g/ml)	0.71	0.72	0.78	0.45	0.47	0.50

Table 4

Relationship Between Drug Content and Tablet Properties

Drug Content	Agitation Granulation			Fluidized-Bed Granulation		
	ACE	ETZ	Vc	ACE	ETZ	Vc
30%	○	○	Insufficient hardness	○	○	○
50%	○	○	Insufficient hardness	○	○	○
70%	Capping, insufficient hardness	○	Insufficient hardness, sticking	○ Capping	Slow disintegration	Sticking

○: Good compressibility.
ACE: acetaminophen, ETZ: ethenzamide, and Vc: ascorbic acid.

sive results have not been obtained regarding the effects of such characteristics.

Tablet Properties

The effects of drug content on tablet properties are shown in Table 4. In the Vc system, FBG tablets were completely compact, while AG tablets were only slightly so. At 70% Vc, sticking occurred in both types of tablets. This may have been due to the bulk density of granules. With increasing bulk density, the specific surface area of granules significantly increases; Mg-St tends to be insufficient to lubricate all of the granules, and sticking occurs. ACE tablets showed capping at a drug content of 70%. ETZ tablets made of FBG granules showed a slow disintegration. At a drug concentration of more than 70%, the properties of drug became a decisive factor and tablet properties were not satisfactory.

Tablet Hardness

Tablet hardness data are shown in Fig. 3. Compactness and hardness of granules produced by FBG were better than those produced by AG for all drugs and all drug contents examined. FBG is thus a granulation method which is widely applicable regardless of drug type or amount. Vc granulation by AG is difficult as reported by Kitamori et al. (7). Vc dissolved in water will recrystallize when dried, and the poor coherence of crystals was considered to be the reason for the difficulties in granulation. For concave 6.5 R tablets containing ACE and Vc, hardness decreased significantly, accompanied by capping with increases in drug concentration.

Granule hardness may be one reason for the perfect compactability of FBG granules (8). Granule hardness data are shown in Fig. 4. FBG granules had less hardness, and when compressed a more compact tablet was formed due to their great plastic deformability. The perfect granule compactness may also have been due to the small size of binder solution droplets (D50: 50–60 μm) formed by spraying in FBG, which would facilitate the homogenous distribution of binder solution (9–11).

Tablet Disintegration Time

Values for tablet disintegration time are shown in Fig. 5. In FBG, when drug content increased to 70%, the disintegration of tablets containing poorly water-soluble ETZ and ACE was delayed. As mentioned above, the FBG granules, a compact tablet can be formed by compression and the binding force among granules was thus increased. The penetration speed of disintegrating fluid would therefore be slowed down. No effects of granulation method and model drug content on the disintegration of water-soluble Vc tablets were observed.

Tablet Dissolution Rate

Figure 6 shows the dissolution rates of tablets. FBG tablets with high ACE, ETZ, and Vc contents (70%) showed slow dissolution. The dissolution of 70% ETZ tablets was dependent to some extent on compression force, unlike Vc tablets. When disintegrant (Ac-Di-Sol, ECG 505, or L-HPC) was added to 70% ETZ tablets, disintegration occurred more easily and no longer de-

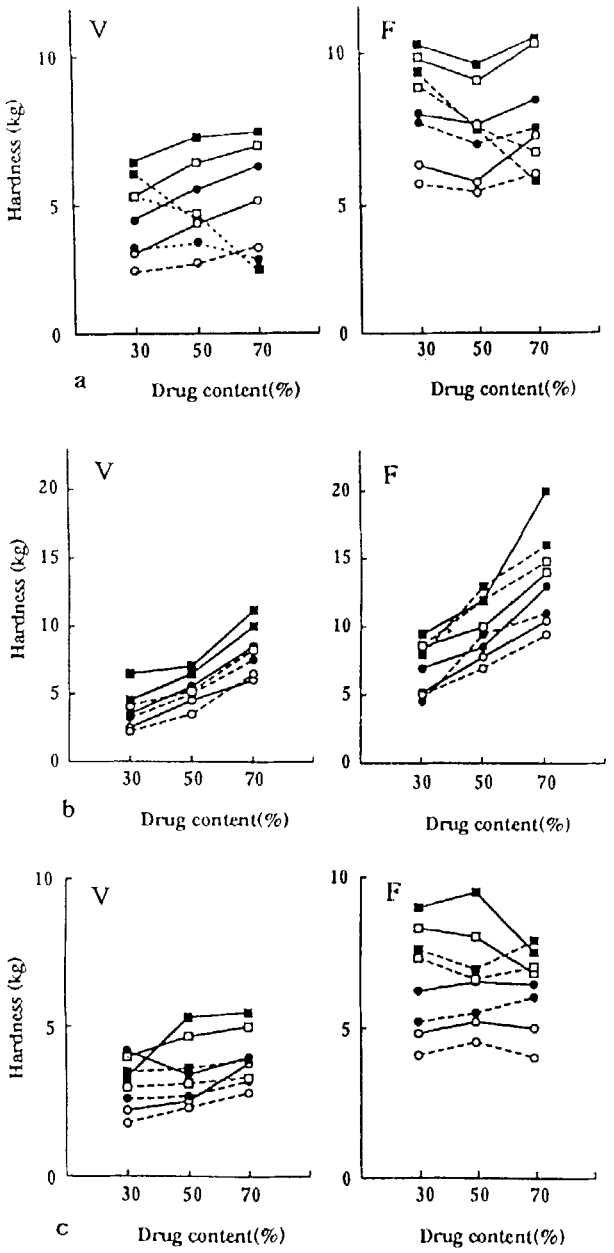

Figure 3. Relationship between drug content and tablet hardness. V: agitation granulation, F: fluidized-bed granulation compression force (ton), ○: 0.6; ●, 0.8; □: 1.0; ■: 1.2 ---- : flat bevel; ---: concave: (6.5 R). (a) acetaminophen, (b) ethenzamide, (c), ascorbic acid.

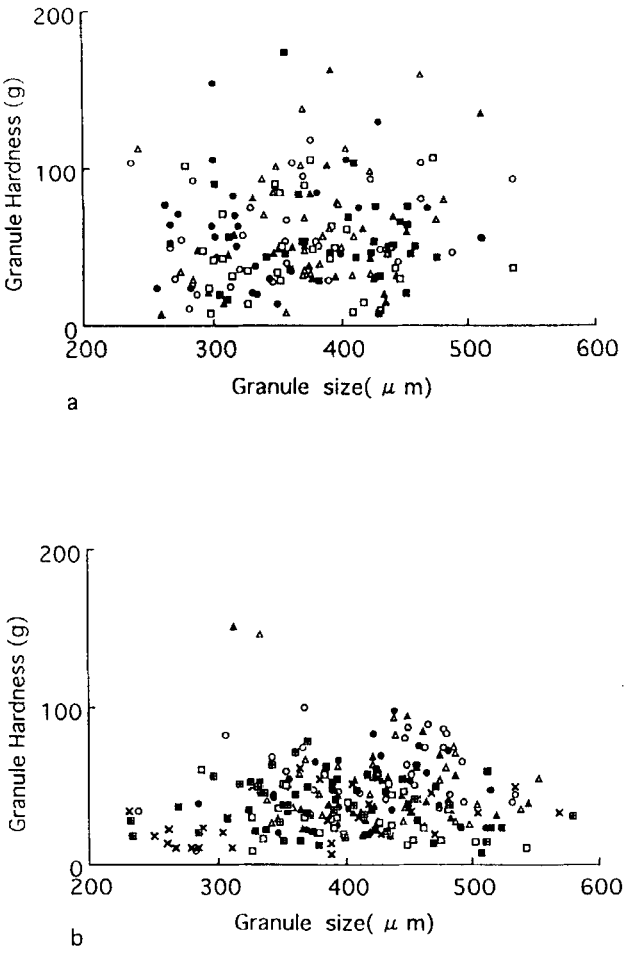

Figure 4. Relationship between drug content and granule hardness. (a) Agitation granulation. □: VA-1-OS; ●: VA-1-CM; Δ: VA-2-OS; ▲: VA-2-CM; □: VA-3-OS; ■: VA-3-CM. (b) Fluidized-bed granulation. □: FA-1-OS; ●: FA-1-PM; Δ: FA-2-OS; ▲: FA-2-PM; □: FA-3-OS; ■: FA-3-PM; X: FA-4-OS; ⊞: FA-4-PM.

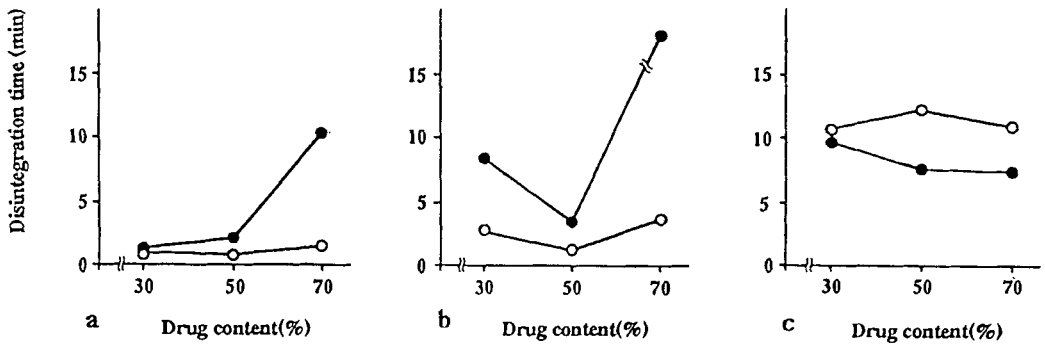

Figure 5. Relationship between drug content and tablet disintegration time. (Flat bevel tablet compressed at 0.8 ton.) ○: Agitation granulation; ●: fluidized-bed granulation. (a) Acetaminophen, (b) ethenzamide, (c) ascorbic acid.

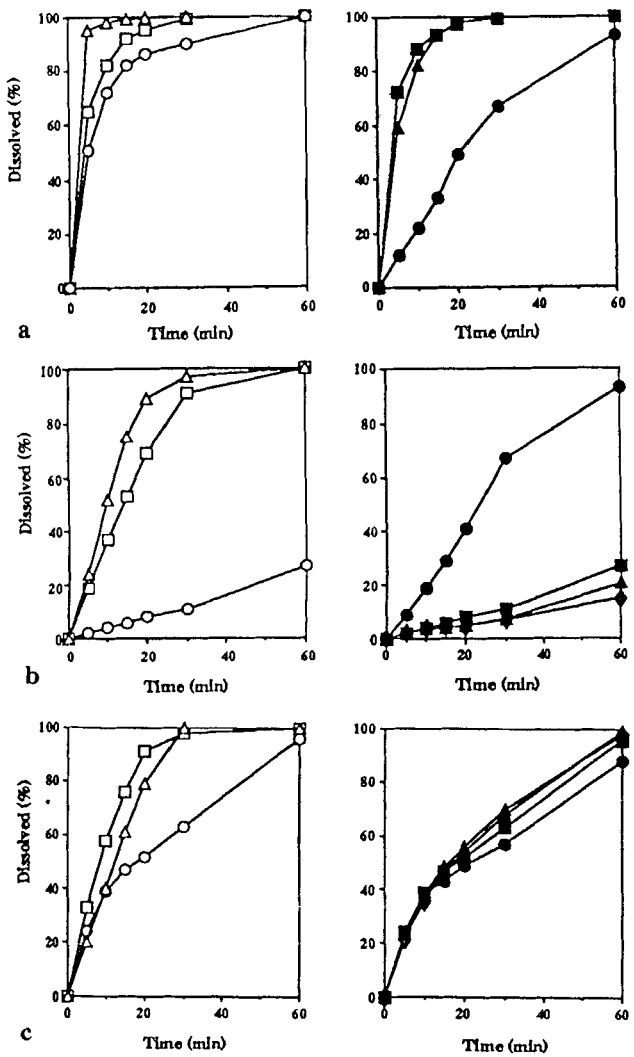

Figure 6. Relationship between dissolution rate and compression force (drug content: 70%). (a) Acetaminophen, agitation granulation. ○: VA-1-CM-00, 0.8; □: VA-2-CM-00, 0.8; Δ: VA-3-CM-00, 0.8. Fluidized-bed granulation. ●: FA-2-OS-00, 0.8; ■: FA-3-OS-00, 0.8; ▲: FA-3-OS-00, 0.8. (b) Ethenzamide, fluidized-bed granulation. ○: FE-1-OS-00, 0.8; □: FE-2-OS-00, 0.8; ▲: FE-3-OS-00, 0.8, Δ: FE-1-OS-00, 0.6; ●: FE-1-OS-00, 0.6; ■: FE-1-OS-00, 0.8; ▲: FE-1-OS-00, 1.0; ◆: FE-1-OS-00, 1.2. (c) Ascorbic acid, fluidized-bed granulation. ○: FC-1-OS-00, 0.8; □: FC-2-OS-00, 0.8; Δ: FC-3-OS-00, 0.8; ●: FC-1-OS-00, 0.6; ■: FC-1-OS-00, 0.8; ▲: FC-1-OS-00, 1.0; ◆: FC-1-OS-00, 1.2.

Table 5

Properties of 70% Vc Granules

	Agitation Granulation	Fluidized-Bed Granulation
Mean particle size (μm)	348	345
Bulk density (g/ml)	0.78	0.50
Specific surface area (m^2/g)	0.16	0.83

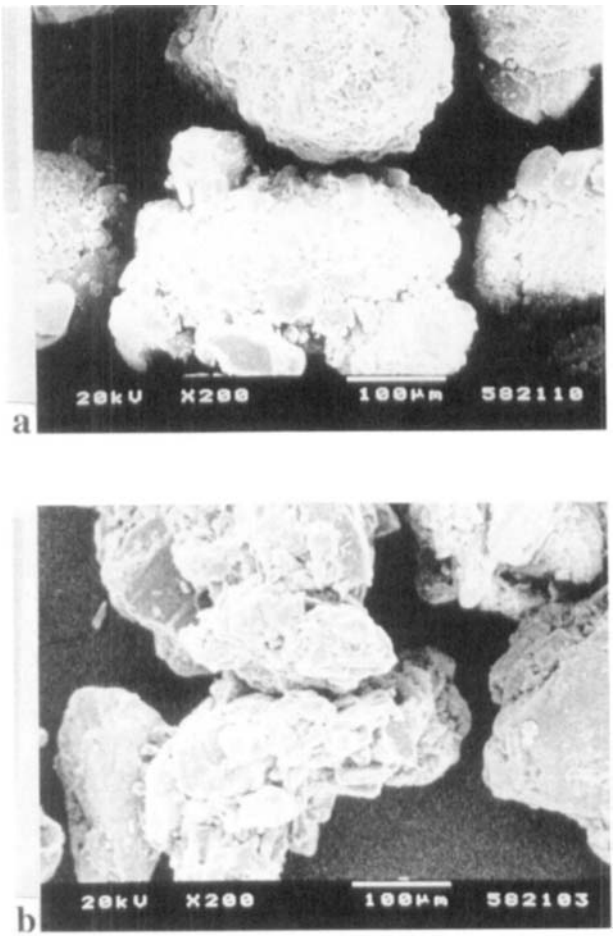

Figure 7. Scanning electron micrographs of granules containing 70% ascorbic acid. (a) Agitation granulation (VC-1-OS), (b) fluidized-bed granulation (FC-1-OS).

pended on compression force. It seems that if disintegration is the rate-limiting step in the dissolution process, the addition of a disintegrant would be effective in increasing the rate of dissolution.

Tablet Problems

Sticking

At 70% Vc, sticking occurred in FBG and AG tablets. Specific surface areas of FBG and AG granules are shown in Table 5, and were proportional to sticking. Scanning electron micrographs (SEM) of 70% Vc granules (Fig. 7) showed that FBG granules were porous, irregular lumps with small bulk density, while AG granules were spherical and compact. Specific surface areas of the two granules would thus be different.

Capping

At 70% ACE, AG tablets showed capping. Boring strength (12,13) was used as an indicator of capping: i.e. when a tablet is drilled with a constant load from the surface, the boring speed will change when capping occurs. Figure 8 shows the effects of precompression.

CONCLUSIONS

ACE, ETZ, and Vc were used as model drugs in this study based on FBG and the results were compared with those for AG. FBG granules showed better compactability and wider formulation allowance for drug type and drug content compared with AG granules. FBG granules showed less hardness and good plastic

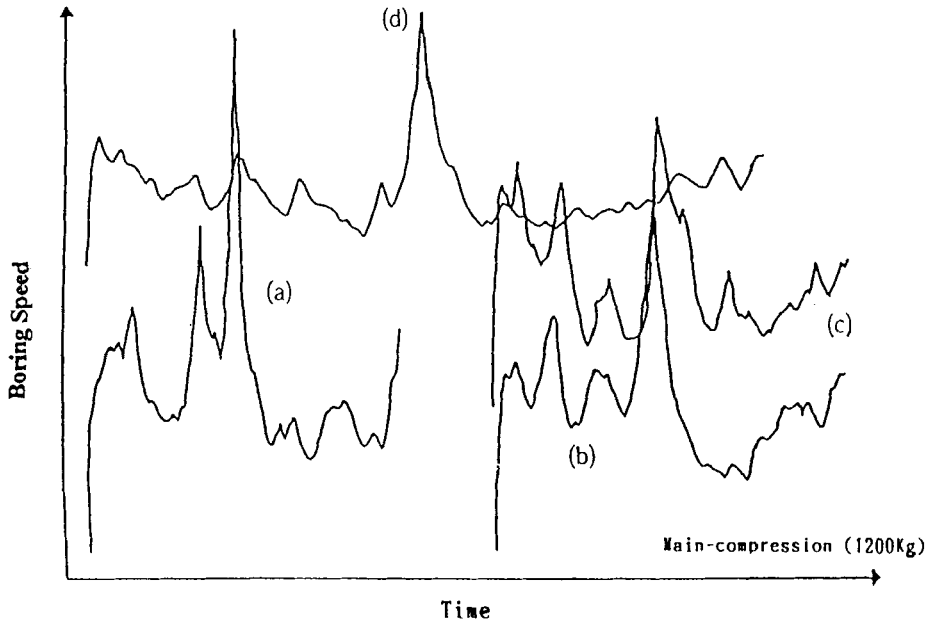

Figure 8. Pattern of boring speed (70% acetaminophen tablet; VA-1-00) precompression force (kN). (a) Without precompression, (b) 100, (c) 300, (d) 500.

deformation. The distribution of binder solution in granules was homogenous because of the spraying which occurred during the granulation process. High ETZ concentration prolonged the times for disintegration and dissolution.

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