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Evaluation of rapidly disintegrating tablets containing glycine and carboxymethylcellulose

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Abstract

A rapidly disintegration tablet in the oral cavity was prepared using a glycine as a disintegrant. Effect of disintegrant on the disintegration behavior of the tablet in the oral cavity was evaluated. Wetting time prepared from carboxymethylcellulose (NS-300) having the hardness of 4 kg was 3 s. Tablet containing NS-300 showed fastest disintegration compared to other formulations. These results suggested that NS-300 possessed excellent wetting nature and resulted in the rapid disintegration of tablet. Ethenzamide and ascorbic acid were added to the formulation, and their disintegration behavior were evaluated. Ethenzamide did not affect the disintegration property, however, ascorbic acid prolonged disintegration time. It was suggested that the tablet formulation containing NS-300 and glycine was highly applicable to water-insoluble drug, such as ethenzamide.
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Keywords: Rapidly disintegrating tablets; Glycine; Carboxymethylcellulose

1. Introduction

Most eldery patients and children have difficulty swallowing conventional tablets or capsules. Therefore, fast dispersible tablets were developed to facilitate the administration of tablets for patients with oesophageal problems. For example, jelly preparations were developed as oral dosage forms for the elderly (Watanabe et al., 1994; Hanawa et al., 1995). Although, the water existing in them brought the physical, chemical and microbiological problems. Tablets were most favorite and popular among the currently used dosage forms, and efficacy of this type of tablets have been clinically evaluated (Maya et al., 2002; Lohitnavy et al., 2003; Carpay et al., 2004).

There have been some methods to prepare the rapidly disintegrating tablet. Many attempts having rapidly disintegrating behavior have been reported by lyophilizing or molding, and compressing wet powders to construct highly porous structure (Verley and Yarwood, 1990). However, these methods required the particular machines and the time consuming techniques, moreover, the hardness of the products was not enough to stand up to process of packaging and transportation. Therefore, direct compression is a convenient and cheap way to produce tablets with sufficient structural integrity. So far there have been many patents for fast disintegrating tablets, but only a few publications dealing with this dosage form (Shimizu et al., 2003a,b,c).

When the fast disintegrating tablet is orally applied, the drug substance has to be dissolved so that it can be absorbed. Dissolution process consists of various process, e.g. wetting, disintegration and dissolution. Fast disintegrating tablets which are generally contains several excipients are involved in a complex series of dissolution process that begin when the solvent contacts the solid and penetrates the tablet matrix. Effect of excipients are assumed to be related to the surface properties of the particles and solid matrix structure. We have already reported that glycine, one of an amino acid, presents excellent wetting nature and suitable for the fast disintegrating formulation (Fukami et al., 2005). Therefore, we prepared rapidly disintegrating tablets compressed from powder mixtures of filler, binder, lubricant, disintegrant and glycine. The aim of this study was to clarify the effect of excipients on the disintegrating properties of tablets

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containing glycine, and to clarify the dissolution mechanism of fast disintegration tablets.

2. Materials and methods

2.1. Materials

Carmellose (NS-300) and carmellose calcium (ECG-505, Gotoku Pharmaceutical Industries Ltd., Japan), croscarmellose sodium (Ac-Di-Sol, Asahi Kasei Co. Ltd., Japan), low-substituted hydroxypropylcellulose (L-HPC, LH-21, Shin-Etsu Chemical Co. Ltd., Japan), crospovidone (Polyplasdone, XL-10, I.S.P. Technologies Inc., USA) were used as disintegrants.

Lactose (200M, DMV, Japan) was used as a main excipient and hydroxypropylcellulose (HPC-L, Nihon Soda Co. Ltd., Japan) was used as a binding agent. Magnesium stearate (St-Mg, Taihei Chemical Industries Ltd., Japan) was used as a lubricant.

Ethenzamide (Yoshitomi Fine Chemicals, Japan) and L-ascorbic acid (Daiichi Pharmaceutical Industries Ltd., Japan) were chosen as a model drug having a different solubility.

2.2. Preparation of tablets

Granules were prepared to spray an HPC-L 4% aqueous solution using a fluidized bed granulator (MP-01, Powrex Co., Japan). The fluid addition rate was 10 g/min. The inlet air temperature was allowed to equilibrate to 70 °C. The initial blend in the fluid bed was 5 min using low air velocity. The spray nozzle was placed in the top port of the fluid bed. When the liquid addition began, the air velocity was increased so that the fluidizing excipients covered the nozzle. At the end of the liquid addition, the air velocity was increased for drying.

Granules which screened with a 22 mesh sieve were mixed with St-Mg using a V-shaped blender for 1 min, and were compressed into tablets with a rotary tableting machine (VIRGO, Kikusui Seisakusho Ltd., Japan) at a speed of 30 rpm at compression forces of 220–960 kgf (pre-compression force, one-third of the force in each case). The weight and diameter of the flat-faced tablet was 250 mg and 8.0 mm, respectively.

2.3. Measurement of tablet hardness

The tablet hardness was measured using a Monsanto hardness tester.

2.4. Measurement of tablet porosity

Tablet porosity (ε) is calculated using Eq. (1),

$$\varepsilon = \frac{1 - m}{\rho_t V} \tag{1}$$

where ρ_t is the true density and m and V are the weight and the volume of the tablet, respectively. Mercury penetration porosimeter (Amico, USA) was used for measurement of the pore volume distribution of tablet.

2.5. Measurement of wetting time and water absorption ratio of tablet using disintegrants

The single component tablet made of each disintegrant of 312 mg was prepared using hydraulic press with 10 mm die. The hardness of the prepared tablet was adjusted to 4 kg.

Wetting time of tablet using disintegrants was carried out using the method reported by Bi et al. (1996).

The water absorption ratio was calculated using Eq. (2),

$$R = \frac{W_b - W_a}{W_a} \tag{2}$$

where W_a and W_b are the weights before and after water absorption, respectively.

2.6. Measurement of the disintegration in the oral cavity

The time required for the complete disintegration in the oral cavity was collected from five healthy male volunteers, who were randomly administered five kinds of tablets at 1 h time intervals.

3. Results and discussion

3.1. Effect of disintegrants on disintegration time of the tablet in the oral cavity

Effect of disintegrants (Ac-Di-Sol, L-HPC, ECG-505, Polyplasdone XL-10 and NS-300) on disintegration time of tablet in the oral cavity was investigated. Obtained results are shown in Fig. 1a. The disintegration time in the oral cavity of the tablet containing NS-300 was about 30 s and the tablet containing L-HPC, Polyplasdone XL-10 and ECG-505 showed the disintegration time about 100 s, on the other hand, the disintegration of the table containing Ac-Di-Sol was more than 170 s. NS-300 containing tablet showed fastest disintegration among the five

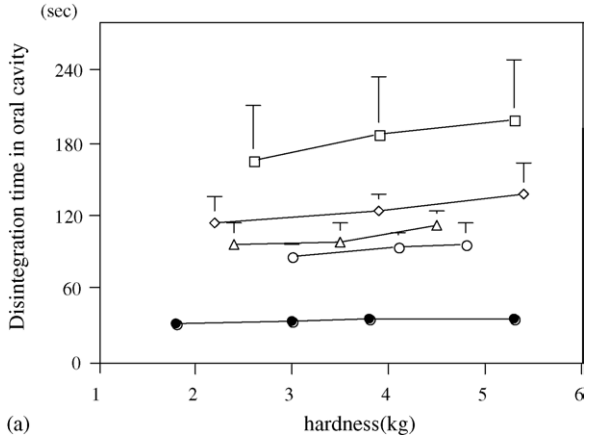


Fig. 1. (a) Effect of disintegrants on disintegration time in the oral cavity: (□) Ac-Di-Sol, (◇) L-HPC LH-21, (△) Polyplasdone XL-10, (○) ECG-505 and (●) NS-300. Data are expressed as means ($n = 5$). (b) Change in the appearance of tablets as formulated in Table 1 by wetting.

(b)

Fig. 1. (*Continued*).

disintegrants used, and the disintegration time was not affected by the tablet hardness.

Fig. 1b shows the change in the appearance of tablets formulated various disintegrants by wetting, the formulation is shown in Table 1. The tablet containing Ac-Di-Sol significantly swelled and loosed the shape. It has been known that Ac-Di-Sol, L-HPC and ECG-505 absorb a large amount of water, and swell. It was reported that disintegration type of Polyplasdone XL was wicking mechanism, because disintegration time of tablets contained Polyplasdone XL was delayed resulting the filling up of tablet porosity with formulating St-Mg which possessed hydrophobic property (Bolhuis et al., 1982). Observed results suggested that the disintegrants added into tablet formulations might cause the penetration behavior of water in the tablet, and the penetration rate of water would be altered.

Table 1
Formulations of prepared tablets

Materials	Weight (mg/tablet)				
	Ac-Di-Sol	L-HPC	ECG-505	Polyplasdone	NS-300
Lactose	195.0	195.0	195.0	195.0	195.0
Ac-Di-Sol	50.0	0	0	0	0
L-HPC LH-21	0	50.0	0	0	0
ECG-505	0	0	50.0	0	0
Polyplasdone XL-10	0	0	0	50.0	0
NS-300	0	0	0	0	50.0
HPC-L	2.5	2.5	2.5	2.5	2.5
St-Mg	2.5	2.5	2.5	2.5	2.5
Total	250.0	250.0	250.0	250.0	250.0

3.2. Factors affecting the disintegration property of the tablet containing NS-300

Despite NS-300 has not been favorably used compared to other disintegrants in pharmaceutical formulations, NS-300 demonstrated good disintegration performance. Tablet disintegration was affected by the wicking and swelling of the disintegrants, and the wicking property would be closely related to the porosity of them. Therefore, we have investigated the factors affecting the disintegration properties of the tablet containing 20% of NS-300. The relationship between the porosity and hardness of tablet is shown in Fig. 2. Both the porosity and average pore size of tablets in all formulations decreased with increase of the tablet hardness. Porosity of tablets contained NS-300 were 0.2–0.3 in the range of tablet hardness 2–5 kg, and there was no significant difference in the porosity of the samples. It was suggested that the disintegration of the tablet containing 20% of NS-300 was not due the tablet porosity.

The wicking property of the tablet may also correlate to the wetting behavior of the tablet. The wetting time of tablets were measured and the relationship between wetting time and tablet hardness is shown in Fig. 3a. Wetting time of tablet containing 20% of Ac-Di-Sol, Polyplasdone XL-10, ECG-505 were 360 s more over. Wetting time of tablet containing 20% of NS-300 showed most quick wetting and observed wetting time was about 60 s. In the range of tablet hardness of 2–5 kg, wetting time was not affected by tablet hardness. Fig. 3b shows the relationship between wetting time and disintegration time in the oral cavity for the tablets containing L-HPC or NS-300. The disintegration time of the tablets in the oral cavity increased with increase the wetting time. To shorten the disintegration time in the oral cavity for the tablet, the addition of the disintegrant having a property of quick water uptake in the formulation would be preferable. It was considered that the rapid disintegration would be due to its wettability.

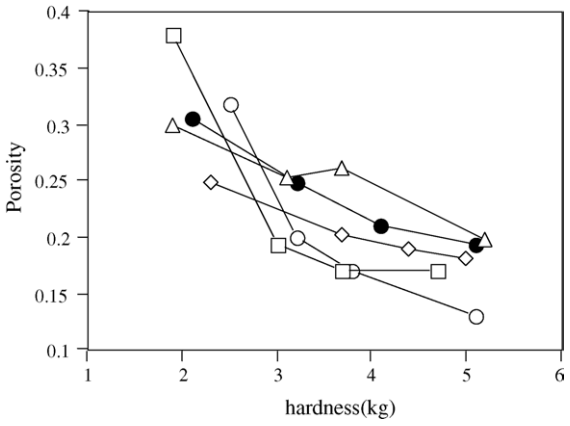


Fig. 2. Porosity of tablets as a function of tablet hardness: (□) Ac-Di-Sol, (◊) L-HPC LH-21, (△) Polyplasdone XL-10, (◯) ECG-505 and (●) NS-300. Data are expressed as means ($n = 10$).

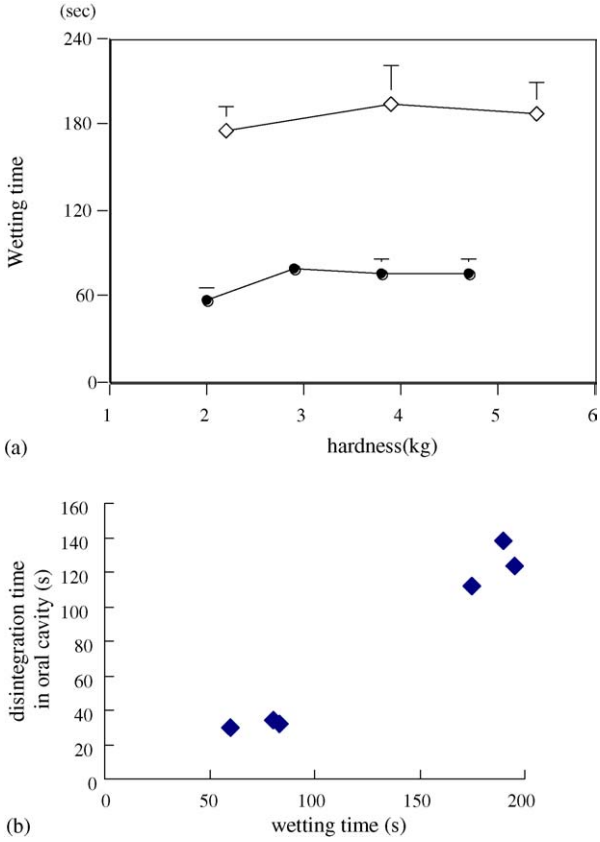
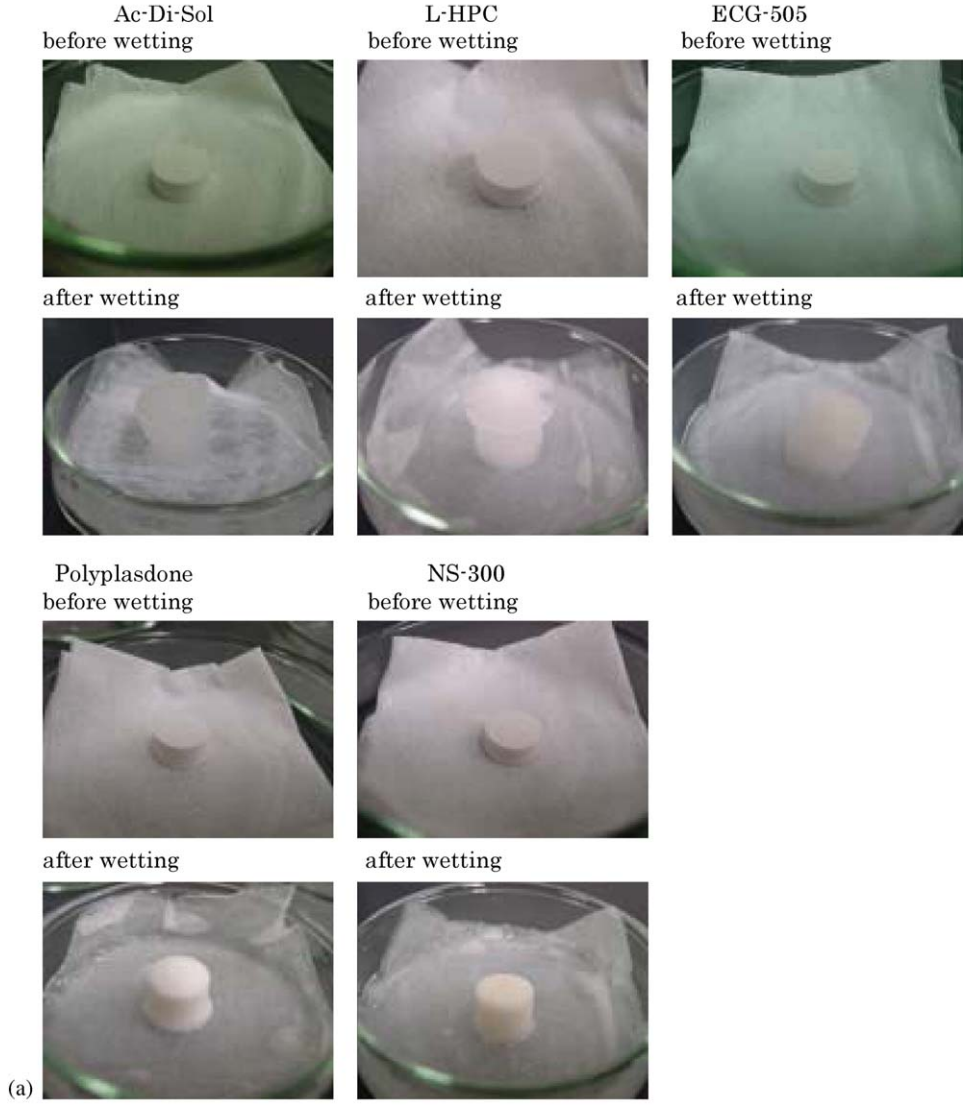


Fig. 3. (a) Wetting time of tablets as a function of hardness: (◊) L-HPC LH-21 and (●) NS-300. Data are expressed as means ($n = 10$). (b) Relationship between wetting time and disintegration time in the oral cavity for the tablets containing L-HPC or NS-300.



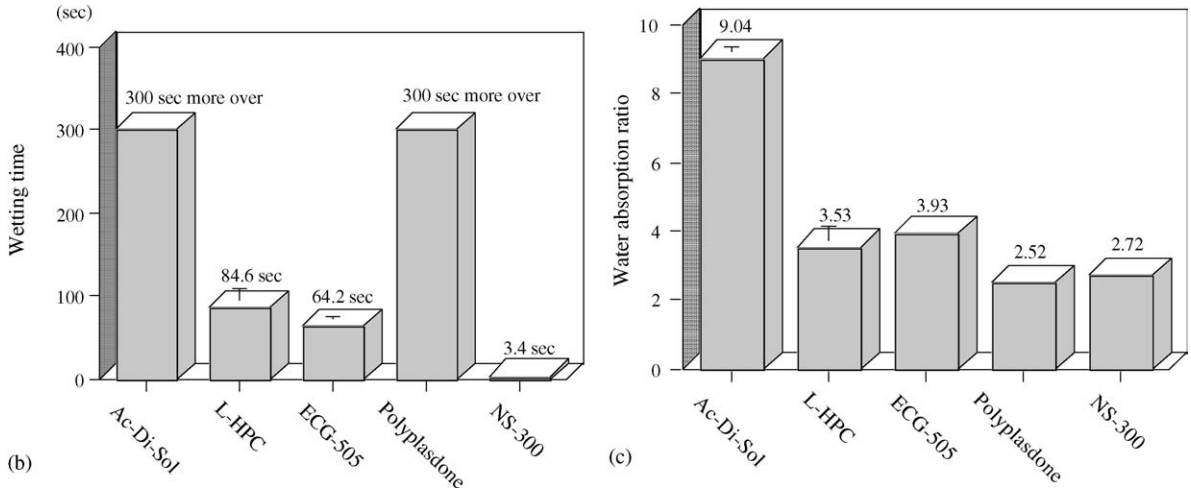


Fig. 4. (a) Change in the appearance of tablets prepared from various disintegrants by wetting. (b) Wetting time of tablets of various disintegrants. Data are expressed as means ($n = 10$). (c) Water absorption ratio of tablets for various disintegrants. Data are expressed as means ($n = 10$).

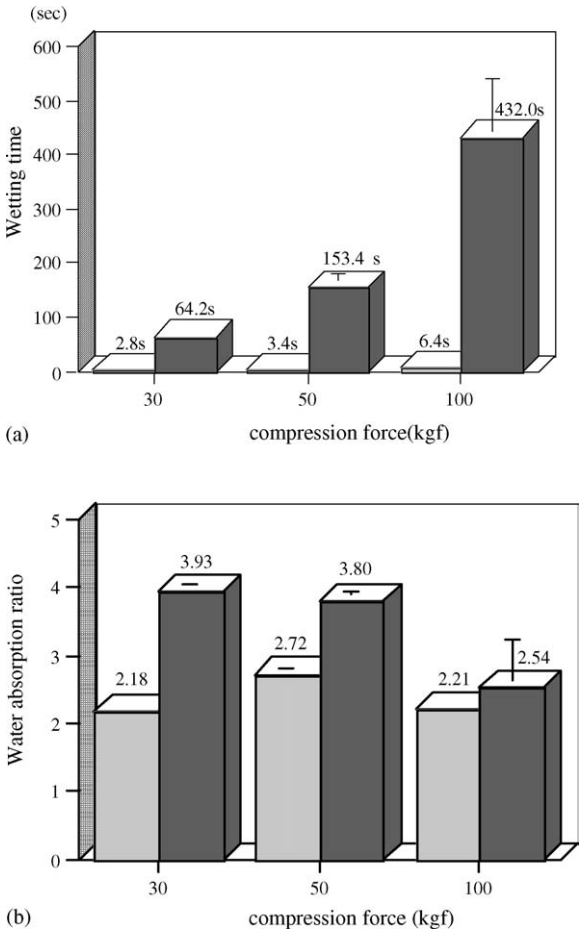


Fig. 5. (a) Wetting time of tablets containing NS-300 or ECG-505: (□) NS-300 and (■) ECG-505. Data are expressed as means ($n = 10$). (b) Water absorption ratio of tablets containing NS-300 or ECG-505: (□) NS-300 and (■) ECG-505. Data are expressed as means ($n = 10$).

3.3. Wetting time and water absorption ratio of compressed disintegrants

To confirm that the mechanism for the rapid disintegration of the tablet containing NS-300 was brought to the wettability of NS-300, we investigated the wetting time and water absorption ratio of disintegrants. Fig. 4a shows the change in the appearance of tablets prepared from various disintegrants by wetting. Tablet formulated Ac-Di-Sol, L-HPC, ECG-505 were significantly swelled and collapsed, on the other hand, NS-300 kept the shape after the wetting. Fig. 4b and c shows the wetting time and water absorption ratio of disintegrants. Wetting time of the NS-300 tablet was 3.4 s and most rapid among the disintegrants used. On the other hand, the water absorption ratio was 2.72 and this value was not differed from the others. The water absorption ratio of Ac-Di-Sol was 9.04 and the obtained value was more than twice compared to the others. Moreover, the wetting time of Ac-Di-Sol was about 3.5 h, suggesting the dominant disintegration mechanism was not wicking but swelling. These results suggested that rapid disintegration of tablets contained 20% of NS-300 was due to the excellent wetting nature of NS-300 itself.

Table 2
Formulations of prepared tablets

Materials	Weight (mg/tablet)				
	NG-1	NGE-1	NGE-2	NGA-1	NGA-2
Lactose	105.0	80.0	55.0	80.0	55.0
NS-300	50.0	50.0	50.0	50.0	50.0
Glycine	90.0	90.0	90.0	90.0	90.0
Ethenzamide	0	25.0	50.0	0	0
Ascorbic acid	0	0	0	25.0	50.0
HPC-L	2.5	2.5	2.5	2.5	2.5
St-Mg	2.5	2.5	2.5	2.5	2.5
Total	250.0	250.0	250.0	250.0	250.0

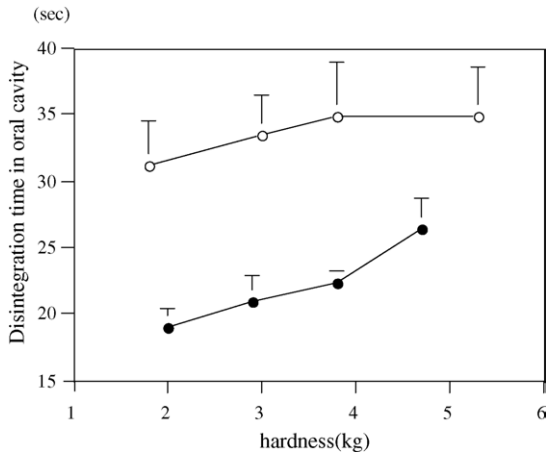


Fig. 6. Effect of glycine on disintegration time in the oral cavity: (◯) NS-300 and (●) NS-300 and glycine. Data are expressed as means ($n = 5$).

We have investigated the effect of compression force on wetting time and water absorption ratio of the tablets composed from NS-300 and ECG-505. As shown in Fig. 5a and b, the excellent wetting nature of NS-300 was hardly affected by the compression force, but the wetting time of ECG-505 prolonged with the increase it. Furthermore, the water absorption ratio of NS-300 was not affected by the compression force, but that of ECG-505 showed a reverse tendency against compression force. There were many reports concerning the disintegration mechanism of tablet (Kanig and Rudnic, 1984; Lowenthal, 1973). Main mech-

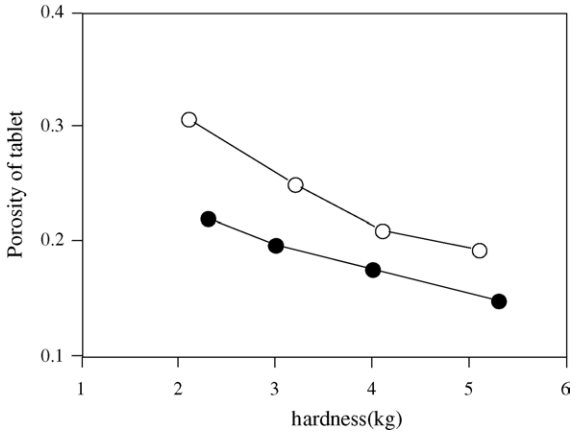


Fig. 7. Effect of glycine on the porosity of tablets containing NS-300: (◯) NS-300 and (●) NS-300 and glycine. Data are expressed as means ($n = 10$).

anisms related to the disintegration were known as wicking and swelling. In spite of the excellent water uptake performance, NS-300 did not swell. On the other hand, ECG-505 absorbed a large amount of water and swelled. These results suggested that the disintegration type of NS-300 and ECG-505 was different, and their major character was resulted in the wicking and swelling of them, respectively. It was reported that tablet disintegration was affected by the particle size, the degree of substitution and the extent of crosslinkage of disintegrants (Smallenbroek et al., 1981; Pitkanen et al., 1987; Rudnic et al., 1983, 1985). In this case, the molecular structure of ECG-505 is chelated by Ca^{2+} between two molecules of NS-300, the structure difference

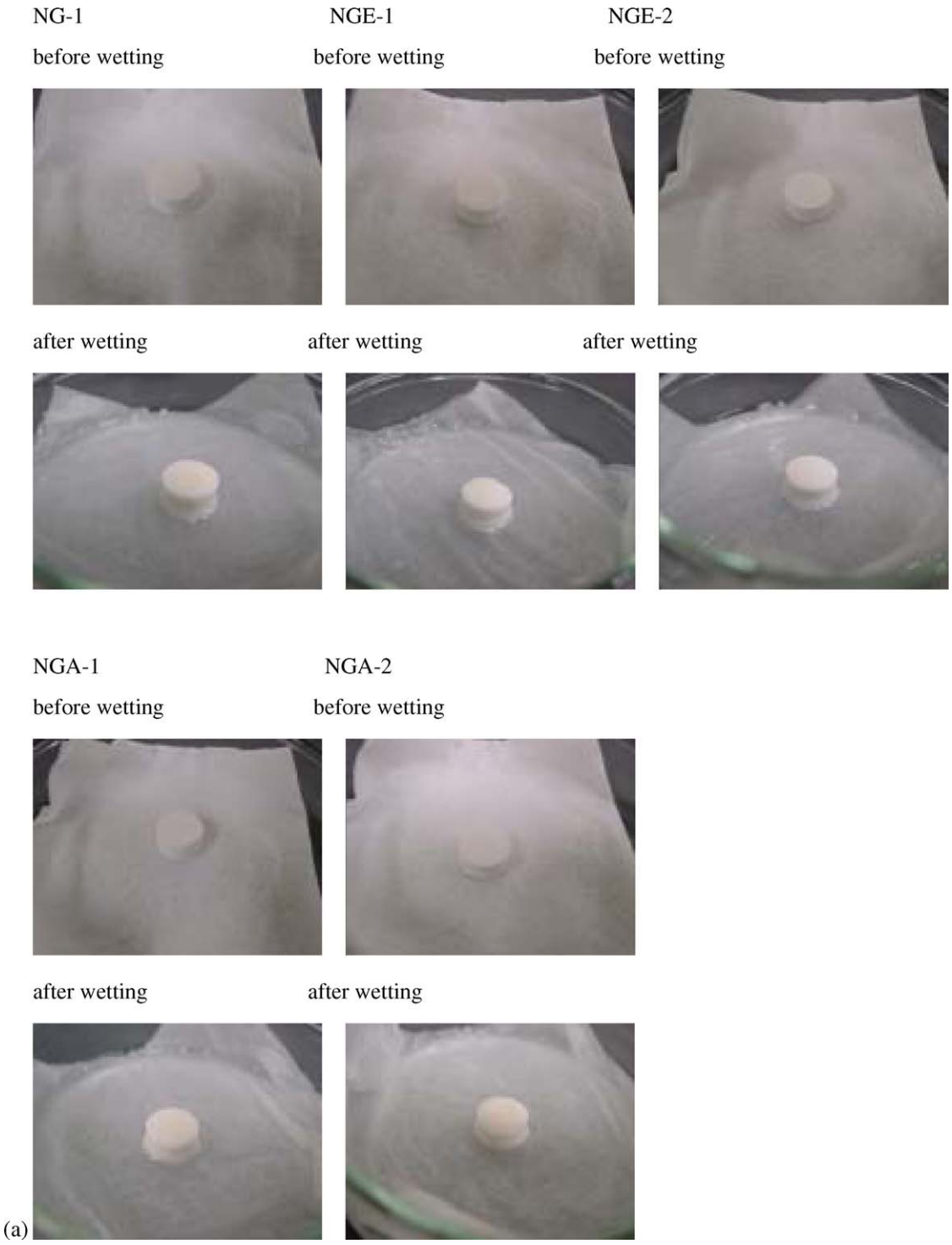


Fig. 8. (a) Change in the appearance of the tablets as formulated in Table 2 by wetting. (b) Effect of ethenzamide on the disintegrateing property: (●) NS-300 and glycine, (□) 20% and (◊) 10%. Data are expressed as means ($n = 5$). (c) Effect of ascorbic acid on the disintegrating property: (●) NS-300 and glycine, (□) 20% and (◊) 10%. Data are expressed as means ($n = 5$).

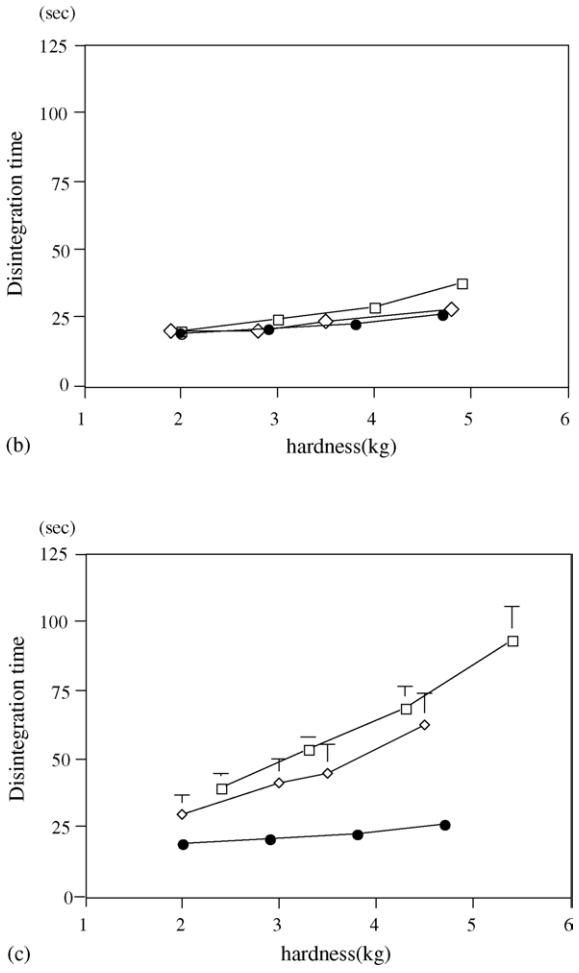


Fig. 8. (*Continued*).

between NS-300 and ECG-505 may cause the different disintegration behavior that are wicking and swelling, respectively.

3.4. Effect of glycine on the disintegration of tablets

We have demonstrated that glycine possessed an excellent wetting nature and rapid disintegration of tablet (Fukami et al., 2005). Effect of glycine on the tablet disintegration for the formulation was studied. The formulation is shown as NG-1 in Table 2. Effect of glycine on disintegration time in the oral cavity is shown in Fig. 6. The tablet containing glycine was disintegrated faster than the tablet without glycine.

Effect of glycine on the porosity of this tablet was also investigated. As shown in Fig. 7, the porosity of the tablet was less than that of the ordinary tablet. It was suggested that rapidly disintegrating property of the tablet formulated NS-300 and glycine was not brought to the porosity of the tablet but the fine wetting nature.

3.5. Application of model drugs for the formulation containing NS-300 and glycine

Ethenzamide and ascorbic acid were used as a poorly water soluble and a water soluble drug, respectively. The formulations containing the drugs are shown in Table 2. The disintegration time in the oral cavity of tablets with ethenzamide were compared with the tablets without the drug. Fig. 8a shows the change in the appearance of the tablets as formulated in Table 2 by wetting. All tablets maintained their shape after wetting. The disintegration time for various tablets are shown in Fig. 8b and c. There was no significant difference in the disintegration time of the tablets with or without ethenzamide. The disintegration time of ethenzamide was not affected by the tablet hardness. In case of ascorbic acid, shown in Fig. 8c, disintegration was delayed compared to the control tablet and the increase of the hardness increased the disintegration time. Adding a water soluble drug such as ascorbic acid into NG-1 formulation, during disintegration, the water penetrated and dissolved ascorbic acid. Therefore, the penetrated water was obstructed and the space was clogged with the dissolved ascorbic acid, resulting the delay of the disintegration time in the oral cavity. On the other hand, in case of poorly water soluble drug such as ethenzamide, the penetration inhibitory effect would not occur and rapid disintegrating property was maintained. These results suggested that the formulation containing NS-300 and glycine would not be suitable for the drug of highly water soluble.

4. Conclusions

We have prepared rapidly disintegrating tablets having a hardness of 4 kg using NS-300 and glycine using ordinary manufacturing method. The good disintegrating property of product was closely related to the excellent wetting nature of ingredients. The major wetting property was brought to the excellent wicking behavior of NS-300, suggesting the significant difference from other swelling type disintegrants. The tablet formulated with NS-300 and glycine would be especially applicable to practically insoluble drug, such as ethenzamide.

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