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# Dissolution Characteristics of pH-dependent Antacid Granules Agglomerated in High Speed Agitation Type Granulator

**Woo Sik Choi and Jung Sun Lee**

*College of Pharmacy, Pusan National University, Pusan 609-735, Korea*

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Antacid granules were prepared by agglomeration and powder coating method in high speed agitation type granulator. The compositions of the test antacids were sodium bicarbonate and magnesium carbonate and a coating material was powder of polyvinylacetal diethylaminoacetate (AEA) and an additive material was talc powder. The dissolution characteristics of base from the antacid granules were investigated to evaluate neutralization capacity of hydrochloric acid and timed-release properties of the antacid granules. From the examination on the dissolution profile of base and neutralization behavior, the following results were obtained: The prepared granules showed a pH-dependent dissolution pattern of a base. The dissolution profile of a base was varied with addition of talc powder as well as coating amount of AEA. The relationship between the ratio of dissolution retarded time for 20% and 10% AEA coated granules $\theta_{20}/\theta_{10}$ and the diameter reduction of the granules was explained by the rate process of neutralization of hydrochloric acid.

**Key words :** Antacid, Polyvinylacetal diethylaminoacetate(AEA), pH-dependent dissolution

## INTRODUCTION

Gastric antacids are drugs which on ingestion react with the hydrochloric acid of the gastric contents to lower acidity. The goal of antacid therapy is to reduce the concentration and the total load of acid in gastric juice. Antacids also have the ability to irreversibly inactivate pepsin if the gastric contents are brought to a pH value above 6 (Swinyard, 1985). The ultimate goal of therapy is to bring the gastric contents to a pH between 3.5 and 5, but it is difficult to maintain the desired pH because antacids tend to increase the acidity of secreting gastric cells, and their effects are temporary and disappear when medication is discontinued. In addition, the excess use of any antacid may produce adverse side effects (Swinyard, 1985).

Both the physical and chemical nature of antacid granules have been studied by many researchers (Kawashima and Takenaka, 1974; Kihara *et al.*, 1986, Yamada *et al.*, 1990). Developments of particulate design technique for the drug play an important role in manufacturing solid pharmaceutical dosage forms. One interesting application is the preparation of antacid granules of which release can be controlled by the level of pH value of gastric juice in stomach within desired pH.

*Correspondence to*: Woo Sik Choi, College of Pharmacy, Pusan National University, Pusan 609-735, Korea.

In this paper, the agglomerates of antacids were prepared with sodium bicarbonate, magnesium carbonate and/or a hydrophobic material (talc) and coated by a pH-dependent soluble material (AEA). And the dissolution behavior of the base from the coated antacid granules into hydrochloric acid was examined by modified Fuchs' stomach model (Fuchs, 1949).

## MATERIALS AND METHODS

### Materials

The antacid $NaHCO_3$ was purchased from Yakuri Pure Chemical Co., Ltd. Tokyo, Japan and the antacid $MgCO_3$ from Junshei Chemical Co., Ltd. Tokyo, Japan. The coating powder, AEA (polyvinylacetal diethylaminoacetate) was donated from Sankyo Co., Ltd. Tokyo, Japan and the marker drug acetaminophen (APP) was a product of Yuhan Pharmaceutical Co., Ltd. The other samples were of reagent grade commercially available. The function and physical properties of materials used are summarized in Table 1. The particle size of sodium chloride powder used as nuclei of agglomeration process is classified with two successive standard test sieves (through 35-mesh/on 50-mesh sieve). AEA used as coating material is stable of heat and light and excellent for damp-proof. AEA is soluble in most of inorganic solvents and has a unique solubility dependent

**Table 1.** Summary of function and physical properties of sample used

| Function | Material | Physical properties | | | | | Maker or Source of supply |
|---|---|---|---|---|---|---|---|
| | | Particle size (μm) | Repose angle[d] (°) | Density True ($g/cm^3$) | Loose ($g/cm^3$) | Tapping[e] ($g/cm^3$) | |
| Antacid | $NaHCO_3$ | - | 54 | 2.16 | 0.703 | 0.960 | Yakuri pure Chem. Co. |
| 〃 | $MgCO_3$ | - | 39 | 2.20 | 0.087 | 0.173 | Junsei Chemical Co. |
| Nucleus | NaCl | 399 | 36 | 2.16 | 1.180 | 1.270 | Duksan Pharm. Co. |
| Coating | AEA[a] | 29.2[f] | 40 | 1.26[g] | 0.240 | 0.380 | Sankyo Co. |
| Binder | MCC[b] | - | 54 | 1.55 | 0.237 | 0.443 | Daesin Pharm. Co. |
| Marker drug | AAP[c] | - | 54 | 1.29 | 0.420 | 0.740 | Yuhan Pharm. Co. |

[a] AEA= Polyvinylacetal diethylaminoacetate, [b] MCC=Microcrystal cellulose, [c] AAP=Acetaminophen, [d] Measured by fixed cone method, [e] Measured by tapping compact method, [f] Measured by Coulter Counter TAII, [g] Measured by air comparison pycnometer Model 930

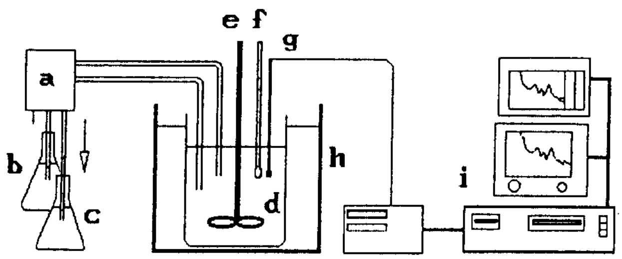


**Fig. 1.** Schematic diagram of experimental apparatus for measurement of pH-time curve. a: Peristalitic pump (LKB. Broma), b: 0.1 N HCl stored flask, c: Waste stored flask, d: Beaker, e: Stirrer, f: Thermometer, g: pH electrodes and pH meter (Orion SA720), h: Water bath(Jeio Tech. Co.), i: PC NEC 9801, printer, and monitor

**Table 2.** Ingredients and quantity per batch in antacid granulation formulas

A). Agglomeration process

| Formula symbol | Antacid granule | Ingredients | Quantity per batch Mass (g) | Percent (%) |
|---|---|---|---|---|
| A1 | $NaHCO_3$ | NaCl | 92 | 46 |
| | | $NaHCO_3$ | 95 | 47.5 |
| | | MCC | 8 | 4 |
| | | AAP | 5 | 2.5 |
| A2 | $MgCO_3$ | NaCl | 100 | 66.7 |
| | | $MgCO_3$ | 40 | 26.7 |
| | | MCC | 5 | 3.3 |
| | | AAP | 5 | 3.3 |

Binder: Distilled water poured.

B). Coating process

| Formula symbol | Coating agent | Quantity per batch Granule (g) | AEA (g) | Talc (g) |
|---|---|---|---|---|
| B1 | AEA | 100 | 10 | - |
| B2 | 〃 | 〃 | 20 | - |
| B3 | A E A | &100 | 10 | 10 |
| B4 | Talc | 100 | 10 | 20 |
| B5 | 〃 | 100 | 20 | 10 |

Binder: Ethyl alcohol sprayed.

upon pH and temperature of the solution, which is soluble below 5°C and in acidic solution, but swelling and insoluble over pH 5.8 (Motoyama, 1975). Acetaminophen was also used as marker drug to investigate whether the state of the coating layer of AEA is stable.

## Apparatus

A high speed agitation type granulator, LFS-GS-1J (FUKAE POWTEC Corp. Japan) was used for the granulation and powder coating of aggregates (Choi, 1989; Iwata, 1983, Terashita *et al.*, 1990). A usual main agitation blade in agglomeration vessel of the granulator was replaced with a disc and a usual chopper blade on the side wall was removed. Fig. 1 shows the schematic diagram of experimental apparatus for measurement of pH profile curve. And the operating conditions of experimental factors are based upon Fuchs' stomach model (Fuchs, 1949).

## Preparation of antacid granules (Agglomeration and coating)

The preparation of antacid granules and AEA coated granules was carried out as follows according to the formulas shown in Table 2 and the flow chart of Fig. 2.

First, in agglomeration process of antacid granules, nuclei powder of sodium chloride were fed into the granulator and the disc was set to run at 300 rpm. Three processes were repeated 5 times: the first was the wet process of nucleus surface by spraying the binder, distilled water, the second the agglomeration process of premixed antacid powder on wetted nucleus surface, and the third the drying process by using a hair dryer. Here, the total massive antacid powder was subdivided into 5 groups and each quantity was slowly fed by hand. After a series of repeated processes, antacid granules were prepared and un-

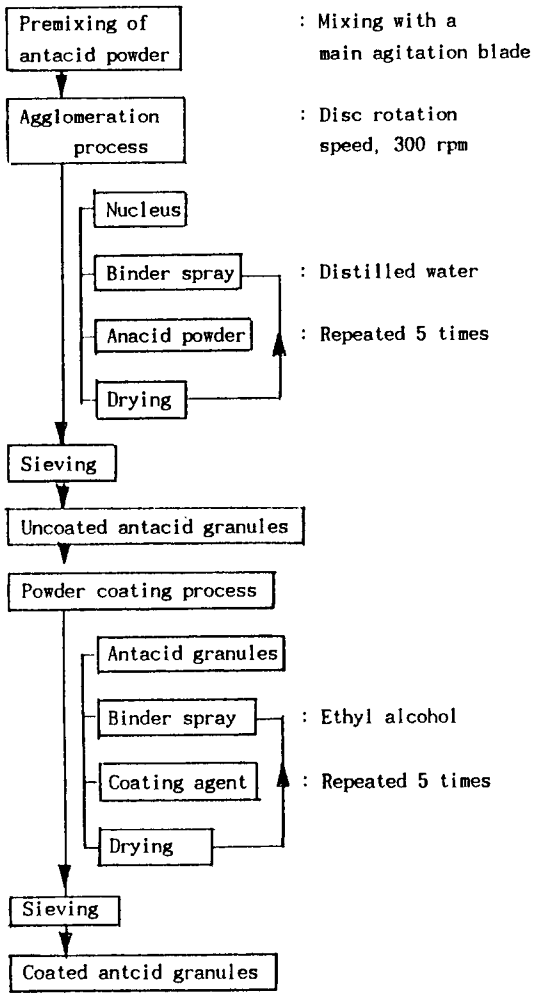


**Fig. 2.** Flow chart for preparation of antacid granules by powder coating method

iformly classified by standard sieve. The granule size distribution was determined by sieve analysis with a rotating sieve shaker.

Second, in coating process of AEA and/or talc, the procedure was the same as that of agglomeration process. Coating amount of AEA on the surface of antacid granules was varied with 10% and 20% of uncoated antacid granules by weight basis as shown in Table 2. The binder liquid in coating process was ethyl alcohol. The overall weight of ethyl alcohol was 30 g for 10% coating of AEA, 40 g for 20% coating of AEA. However, this amount was not the net amount of binder because of loss from spraying of binder liquid with the cover of the vessel opened. The total coating time was taken about 1 hour.

### Dissolution of acetaminophen from the antacid granules

In order to compare the dissolution behavior between uncoated and coated antacids, acetaminophen (AAP) was used as a marker drug in antacid granules. The paddle method (Korean Pharmacopeia 4th ed., 1988) was employed to investigate the dissolution behavior of AAP from the antacid granules. The rotation speed was 100 rpm and the dissolution medium was 1000 ml of 0.01 N hydrochloric acid solution or McIlvain buffer solution, and maintained at 37°C. Release of AAP into the medium was determined by measuring the absorbance at 294 nm using Shimadzu UV-120-02 spectrophotometer.

### Acid neutralization studies

Acid neutralization test for antacid granules was followed by measuring the pH of the solution using the pH meter with calomel and glass electrodes as shown in Fig. 1. A dose amount of antacid granules(1. 0 g for sodium bicarbonate antacids, 0.5 g for magnesium carbonate antacids) was added to an acidic medium(500 ml) and maintained at 37°C in a water bath. The acidity of initial acidic medium was varied with three levels of 2, 4, and 6 in pH value. A dispersed system was continuously agitated using four-blade stirrer and 0.1 N hydrochloric acid added at feed rate of 2 ml/min, which is equivalent to tenth normal acid secreted by the hyperchlorohydric stomach, and the neutralized medium discharged at the same rate as feed rate. This procedure was followed for two hours or until the pH drops below 3.0.

## RESULTS AND DISCUSSION

### Particle size distribution of granules

Initial sodium chloride powder or agglomerates is acted as the nuclei. These nuclei readily pick up the fine feed powder in layer growth since the pendular liquid bond between two particles increases in strength as the size difference between the granules becomes larger (Ouchiyama, 1974). The values of parameters of Rosin-Rammler distribution law and the coefficient of determination, $r^2$ by the fitted regression are summarized in Table 3 together with coating percent of AEA. It is generally considered that the granule size distribution can be fitted for the law of R.R. distribution from the good linearity due to the mechanism of growing the product size such as coalescence and layering in this type granulator.

### Dissolution behavior of acetaminophen

Fig. 3 shows the dissolution profile of marker drug acetaminophen released from sodium bicarbonate antacid granules for various levels of coating percent of AEA. The remarker drug acetaminophene was replaced with the antacid, $NaHCO_3$ of formular symbol A1 in Table 2. In the case of uncoated granules the

**Table 3.** Summary of parameters in Rosin-Rammler's distribution law for antacid granule size distribution

| Antacid granules | Formula symbol | Coating percent (%) | Parameters | | | Correlation |
|---|---|---|---|---|---|---|
| | | | $D_{av}$ (μm) | n (-) | $D_e$ (μm) | coeff. $r^2$ (-) |
| $NaHCO_3$ | A1 | 0 | 830 | 3.3 | 810 | 0.9847 |
| " | B1 | 10 | 1730 | 3.4 | 1920 | 0.9508 |
| " | B2 | 20 | 2760 | 3.5 | 2530 | 0.9941 |
| $MgCO_3$ | A2 | 0 | 1100 | 3.0 | 1210 | 0.9958 |
| " | C1 | 10 | 2640 | 4.1 | 2370 | 0.9556 |
| " | C2 | 20 | 3190 | 5.2 | 2830 | 0.9698 |

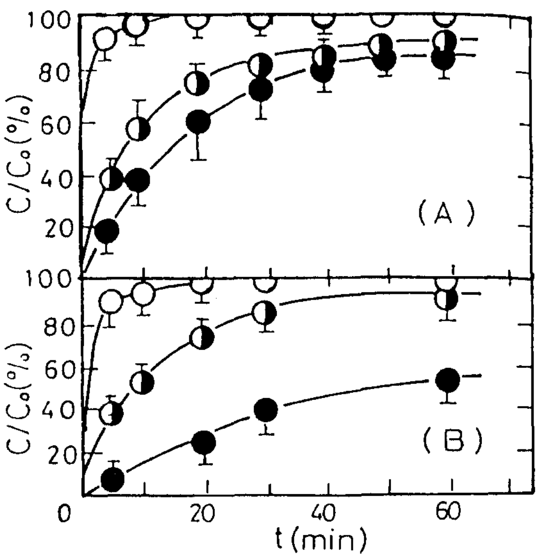


**Fig. 3.** Dissolution profile of acetaminophen in sodium carbonate antacid granules. (A) In 0.01 N HCl soln. (B) In pH 7 buffer soln. Key: ○, uncoated (A1); ◑, 10 % AEA coated (B 1); ●, 20 % AEA coated (B2)

most of acetaminophen is dissolved within 10 minutes. But in the case of coated granules the time retarded to dissolve the same level of AAP concentration is longer according to increase of the coating percent of AEA and the initial pH of dissolution medium.

This result suggests that the powder coating method of AEA on surface of antacid granules can be sufficiently applied to the design of controlled release systems. However, since it cannot be said from dissolution at initial pH of 6 that all the granules are coated with uniform thickness of AEA, further study on operating conditions for the control of shape and uniform coating thickness of antacid granules is required.

### Acid neutralization

i) Consideration of dissolution rate: The rate at which a solid dissolves in a solvent was proposed in quantitative terms by Noyes and Whitney as follow (Martin *et al.*, 1983):

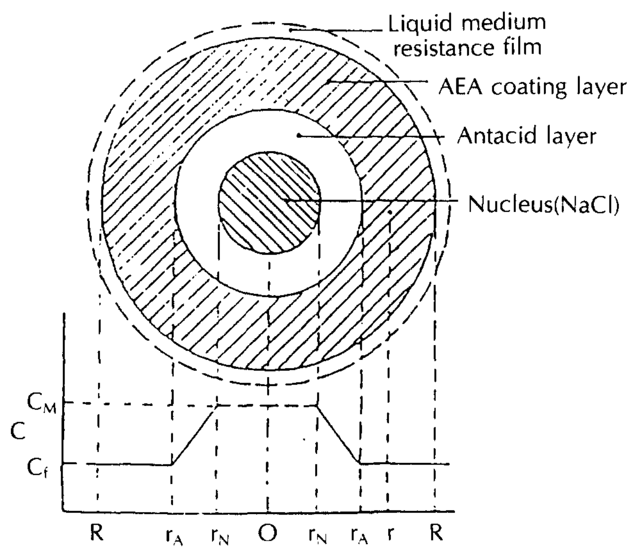


**Fig. 4.** Schematic model on dissolution of AEA coating layer and antacid layer for powder coated granules. Subscript: A, Agglomerates; N, Nucleus

$$dM/dt = (DS/h)(C_s - C(t)) \quad (1)$$

where M is the mass of solute dissolved in time t, dM/dt the mass rate of dissolution, D the diffusion coefficient of the solute in solution, S the surface area of the exposed solid, h the thickness of the diffusion layer, Cs the solubility of the solid, and C (t) the concentration of solute at time t. The spherical particle shown in schematic model on dissolution of Fig. 4 has a radius r and a surface area 4 $r^2$ (Tanaka, 1981). In Fig. 4, C, $C_f$, and $C_M$ are the concentration of solute, feed and maximum, respectively. R and r are the radius of granules from center O and subscript A and N indicate the agglomerates and nucleus, respectively. Through dissolution, radius is reduced by dr, and the infinitesimal volume of this section is lost by dV.

$$dV = 4\pi r^2 dr \quad (2)$$

The infinitesimal volume loss and total surface area of N particles can be obtained from Eq. (2) and a surface area. All the volume loss and the surface area are substituted into Eq. (1) and divided through by $4\pi r^2$ to give

$$-dr/dt = k(C_s - C(t)) / \rho_p \quad (3)$$

where k is D/h and $\rho_p$ is density of particle.

Integration with r=R at t=0 and with sink conditions C (t)~0 produces the following expression:

$$r = R - (kC_s/\rho_p)\, t \quad (4)$$

Therefore, from the Eq. (4), the ratio of dissolution retarding time for 20% AEA coated granules to that for 10% AEA coated granules can be expressed as follows:

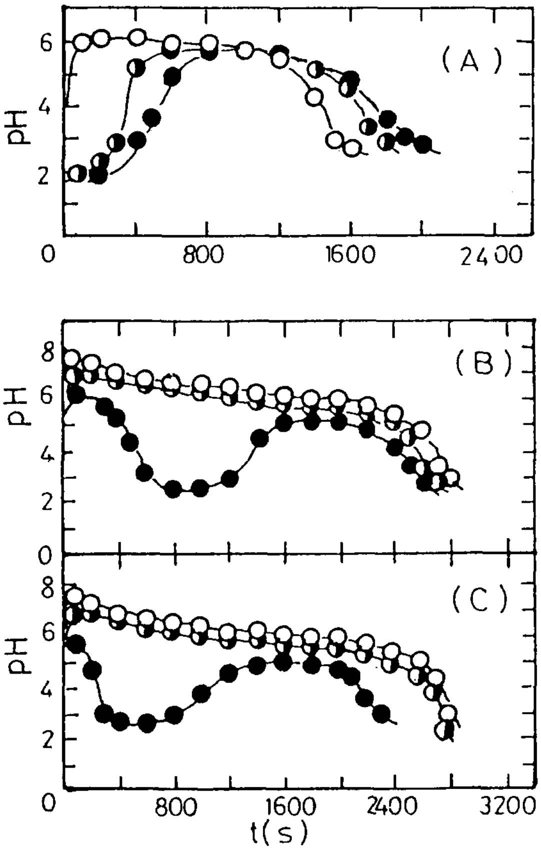

**Fig. 5.** The pH-time curve for sodium bicarbonate antacid granules coated by AEA. (A) In 0.01 N HCl soln. (B) In pH 4 soln. (C) In pH 6 soln. Key: ○, uncoated(A1); ◑, 10 % AEA coated(B1); ●, 20 % AEA coated(B2)

$$\theta_{20}/\theta_{10} = (R_{20} - r_A)/(R_{10} - r_A) \quad (5)$$

where $R_{20}$ and $R_{10}$ are radius of 20% and 10% AEA coated granule, respectively and $r_A$ is the radius of uncoated antacid granule.

ii) Effect of AEA coating percent and initial pH

Fig. 5 shows the pH-time curve for sodium bicarbonate granule antacids at three levels of initial pH value of dissolution medium. The initial pH values for A, B, and C of Fig. 5 are 2, 4, and 6, respectively.

As shown in Fig. 5, the pH-time curve is significantly varied with the initial pH values of dissolution medium and AEA coating percent. Fig. 5(A) shows that uncoated antacid granules reacts immediately with the excess acid in the beaker and then has maintained a certain level of equilibrium state of neutralization reaction for long time and then has fallen due to continuous feeding of 0.1 N hydrochloric acid solution. With increase of AEA coating percent the pH-time curve are shifted to the right side and the time to reach the maximum pH value is retarded and the maximum pH value itself becomes a little bit lower than that of uncoated granules.

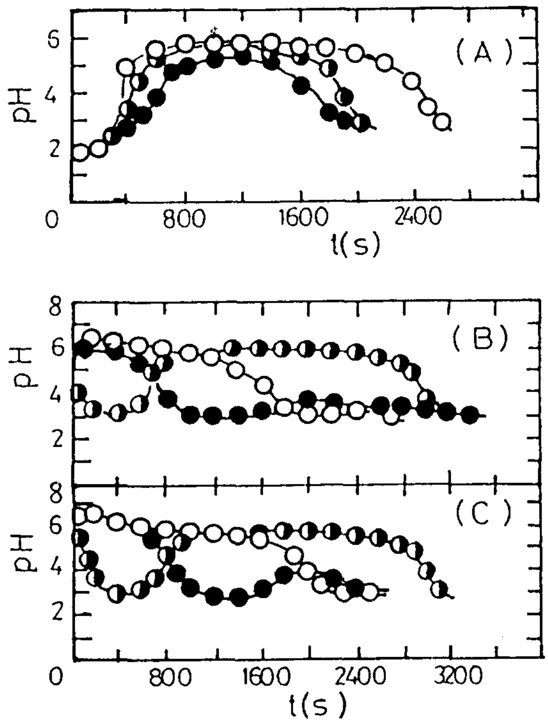

**Fig. 6.** The pH-time curve for sodium bicarbonate antacid granules coated by AEA and talc. (A) In 0.01 N HCl soln. (B) In pH 4 soln. (C) In pH 6 soln. Key: ○, 10% AEA and 10% talc (B3); ◑, 10% AEA and 20% talc(B4); ●, 20% AEA and 10% talc (B5)

**Table 4.** Comparison of dissolution retarded time for AEA coated sodium bicarbonate granules in initial pH 2.0 solution

| Formula symbol | Coating amount (%) | Time (s) | | $\theta_{20}/\theta_{10}$(-) | | | |
|---|---|---|---|---|---|---|---|
| | | Initial state | Terminal state | Initial Exp. | Initial Cal. | Terminal Exp. | Terminal Cal. |
| A1 | 0 | 64 | - | - | - | - | - |
| B1 | 10 | 114 | 400 | - | - | - | - |
| B2 | 20 | 260 | 660 | 2.3 | 2.2 | 1.7 | 1.8 |

In the case of initial pH value of 4 and 6, the pH-time curve of 10% AEA coated granules was similar to that of uncoated granules while the pH-time curve of 20% AEA coated granules was distinct from other two granules. That is, the pH profile of 20% AEA coated granules was gradually down with continuous feeding of 0.1 N hydrochloric acid and then maintained at the lowest level and then was up and down as similar behavior to that of initial pH value 2.0.

As shown in Fig. 5, it is considered that the shape of pH-time curve shows the relationship on dynamic rate process such as neutralization reaction and solubility of coating layer. The result of examination using Eq. (4) on data of Fig. 5(A) was shown in Table 4, where initial state indicates the dissolution starting time to reach pH 2.0, dissolution starting of antacid layer and terminal state indicates the time to saturated maximum pH level, dissolution ending of antacid layer. The ratio of dissolution retarded time $\theta_{20}/\theta_{10}$ is in fair agreement with calculated by Eq. (4) from mean size data of granules shown in Table 3 and the experimental values.

### Effect of talc powder

Fig. 6 shows the pH-time curves for sodium bicarbonate antacid granules coated by various mixing ratio of AEA and talc. The mixing effect of AEA for 10% talc by weight basis of antacid granules are compared with formulas B3 and B5 while the mixing effect of talc for 10 % AEA are compared with formulas B3 and B4. The dissolution for mixed antacid granules of talc in addition to AEA is retarded by the comparison with Fig. 5.

It was confirmed that the dissolution behavior could be significantly varied with the mixing content of hydrophobic powder such as talc. And it was also confirmed from data for various initial pH that the dissolution pattern was largely varied with hydrophilicity of mixed pharmaceutical powder and solubility of film material.

## CONCLUSIONS

The dissolution profile and neutralization behavior for antacid granules prepared by powder coating method in high speed agitation type granulator were investigated by modified Fuchs' stomach model and the following main results were obtained.

1. It was confirmed in vitro test that the dissolution profile of antacid granules could be significantly varied with the hydrophilicity of powder in antacid granules and the solubility of coating material.
2. It was also confirmed that the relationship between the ratio of dissolution retarded time for 20% and 10% AEA coated granules ($\theta_{20}/\theta_{10}$) and the diameter reduction of the granules could be explained by the rate process of neutralization reaction.

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