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Improvement of Hospital Preparation for Patient Oriented Service –Tablet of Bitter Tasting-Stomachic Powder–

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A bitter stomachic powder, named NGD powder, has been prepared at our hospital. However, a questionnaire survey conducted by the Japanese Society of Hospitai Pharmacists reveals that elderly patients complain of difficulty in taking this formula because of its bitter taste and dustiness. Therefore, we attempted to reformulatier this NGD powder in tablet form and to study the pharmaceutical properties of the subsequently produced NGD tablets. Microcrystalline cellulose (MCC) was added in amounts of 20%, 30% and 40% to its amount of NGD powder, and compressed using a compression force of 0.5, 1.0, 1.5 or 2.0 ton/cm^2 These tablets were then examined for their crushing strength, friability, disintegration time, neutralizing capacity and amylosaccharifying activity. Moment analysis was carried out especially for the neutralizing capacity of the tablets. Optimum regression equations were obtained using multiple regression analysis for each of the characteristics. The results suggest that the optimum amount of MCC and compression force are 30% and 1.0 ton/cm^2, respectively.

Key words —— bitter stomachic powder, tablet, microcrystalline cellulose, formulation, compression force, multiple regression analysis

Introduction

Many drugs for stomach disorders containing digestants have been used widely. Five hundred and sixty of these have been marketed in Japan as prescription drugs. Many old-fashioned medicines have been replaced by new medicines, but NGD powder (hospital formulation) which is composed of diastase, sodium bicarbonate and powdered gentian has been known for a long time and is still in common use today. NGD powder is prescribed for gastric irritation caused by other agents, and also to many patients for other epigastric symptoms[1-3]. This medicine has a simple formula and is rated highly by both patients and clinicians, because it is composed of safe and cheap drugs. However, many patients, regardless of age or sex, complain of difficulty in taking NGD powder because of its fine powder form. In particular, aged patients complain about its bitter taste and

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dustiness[4]. Moreover, it has disadvantages such as difficulty in handling and poor hygroscopic stability, because of its powder form[2,5]. Therefore, we have attempted to reformulate NGD as tablets, and investigate the optimum conditions for the preparation of NGD tablets.

Materials and Method

1. Materials

Sodium bicarbonate(Asahi Glass), powdered gentian(Maruisi Seiyaku), diastase(Maruisi Seiyaku), magnesium oxide(Astra Japan, trade name, magnesium oxide VFG) and crystalline cellulose (Asahi Kasei, Avicel PH-301) were used as constituents for the preparation of tablets. All were Japanese Pharmacopoeia grade. The other reagents used were analytical grade.

2. Preparation of NGD powder

NGD powder is composed of sodium bicarbonate 2.0 g, powdered gentian 0.3 g, diastase 0.5 g, magnesium oxide 0.2 g, and is taken three times daily. Sodium bicarbonate and powdered gentian were screened using GYRO SIFTER (Tokuju Kosakusho Co., Tokyo, Japan) with 50-mesh sieves. Diastase and magnesium oxide were then added to these drugs and mixed in a MIX WELL BLENDER (Tokuju Kosakusho Co., Tokyo, Japan) at 30 rpm for 10 minutes.

3. Tabletting

A tablet-hitting pressure displacement measuring system (Sratt Press, Model N-20 E, Okada-Seiko Co., Tokyo, Japan) equipped with punches (diameter,10 mm ; concave shape, 14 R) was used as a single-punch tabletting machine. Microcrystalline cellulose (MCC) was added to NGD powder as a disintegrating and binding agent, in amounts of 20% (Tablet A), 30% (Tablet B), or 40% (Tablet C). Each of these was compressed using a force of 0.5, 1.0, 1.5 or 2.0 ton/cm^2. The formula of NGD tablets prepared in this study are shown in **Table** 1 . These tablets were tested in the following experiments.

Table 1. Formulations of NGD Powder and NGD Tablets

Formula	Total weight	Constituents (g)				
		Sodium bicarbonate	Powdered gentian	Diastase	Magnesium oxide	MCC
NGD powder	3.000	2.000	0.300	0.500	0.200	-
Tablet A	0.625	0.333	0.050	0.083	0.033	0.125
Tablet B	0.710	0.333	0.050	0.083	0.033	0.210
Tablet C	0.830	0.333	0.050	0.083	0.033	0.330

NGD powder ; Stomachic Powder,taken three times daily after meals.

4. Measurement of Physicochemical characteristics

a. Weight variation

The weight variation test was performed according to the method described in Japanese Pharmacopoeia (JP) XIII.

b. Crushing strength

The Crushing strength, (the force required to break a tablet by compression) was measured using a rheometer (Model RT-3005 D, Rheotech Co. Ltd., Tokyo, Japan) using at a pressing speed of 60 mm/min.

c. Friability

The friability test was performed on forty tablets using a friabilator (Kayagaki Irikakogyo Co. Ltd., Tokyo, Japan)[6].

d. Disintegration time

The disintegration time was determined using a disintegration apparatus (T 2-H, Toyama Sangyo Co. Ltd., Osaka, Japan), according to the method described in JP XIII, with purified water.

e. Neutralizing capacity

The neutralizing capacity was measured using a dissolution test device that was used for the method described in JP XIII. The dissolution test (paddle method) apparatus (Toyama Sangyo Co. Ltd., Osaka, Japan) and 900 ml (37.0±0.5℃) of the first fluid for the disintegration test (JP XIII) were used. The sample amount was fixed at 6 times the usual dose because gastric juice is generally secreted at 50～150 ml/h[7]. The rotating speed of the paddle was set at 200 rpm. The pH variation of the solution after an addition of the sample was continuously measured using a pH meter (Toa Electronics HM-20 S). The mean dissolution time (MDT) was calculated from the pH profile by moment analysis[8].

f. Digestive activity

The digestive activity of the tablets was determined according to its amylum digestive activity in measurement of amylosaccharifying activity in JP XIII.

g. Stability

The preparation was stored in a box (Nagano Seiki Co., Ltd.) for 30 days under the following conditions ; temperature, 25℃ and relative humidity (RH), 75%[9], and at predetermined times, the tablets were weighed and tested for crushing strength. Furthermore, the digestive activity of NGD powder and the tablets prepared by the addition of 30% MCC and using a compression force of 1.0 ton/cm^2 were tested immediately and 15 months after preparation.

h. Multiple regression analysis

The characteristics of the tablets were analyzed by multiple regression analysis[10] with respect to compression force (X1) and mixing ratio of MCC (X2), and the prediction equations obtained from the multiple regression analysis were illustrated three-dimensionally.

Statistical analysis was performed by the Student's t-test. Values were expressed as mean±S.D..

Results and Discussion

The disintegration time, neutralizing capacity and long-term stability of digestive activity were important considerations for the preparation of NGD tablets. The tablet formulation has been determined to make as simple as the powder formulation by choosing a binding agent. NGD tablets could not be prepared when 20% MCC was added or when a compression force of 0.5 or 1.0 ton/cm^2 was used. But the other conditions of preparation were successful (**Fig.** 1 , 2 , 3). Every tablet conformed to the standard of the weight variation test in JP XIII. No lubricant was needed because the mixtures of MCC and NGD powder exhibited sufficient fluidity and did not adhere to the punches during compression. As the compression force and MCC amount were increased, the crushing strength of the tablets tended to increase (Fig.1). Generally, a crushing strength of 3～7 kg is considered appropriate[11]. Tablets prepared by the addition of 20% MCC using a compression force of 1.5 ton/cm^2, 30% MCC using a compression force of 0.5 ton/cm^2 or 40% MCC using a compression force of 0.5 ton/cm^2, showed a friability of 22～85%(**Table** 2). However as the

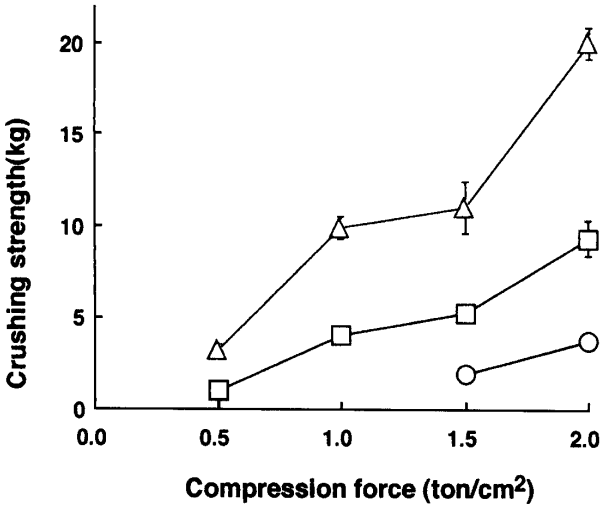

Fig. 1. Relationship between Compression Force and Crushing Strengh.
Each point represents the mean±S.D. (n=10)
○ : Tablet A (20% MCC), □ : Tablet B (30% MCC), △ : Tablet C (40% MCC)

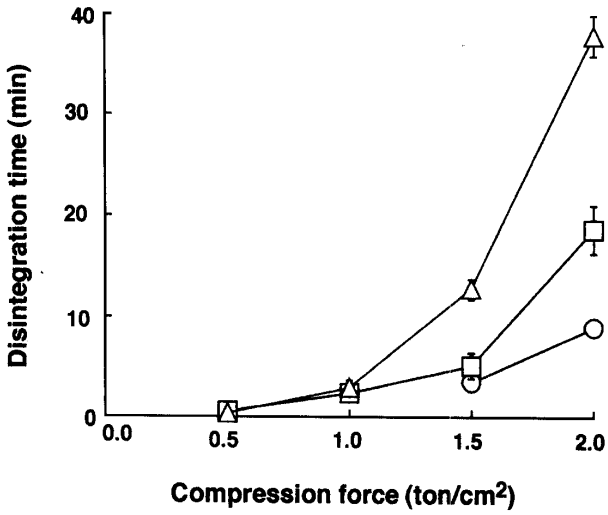

Fig. 2. Relationship between Compression Force and Disintegration Time of Tablets.
Each point represents the mean±S.D. (n=6)
○ : Tablet A (20% MCC), □ : Tablet B (30% MCC), △ : Tablet C (40% MCC)

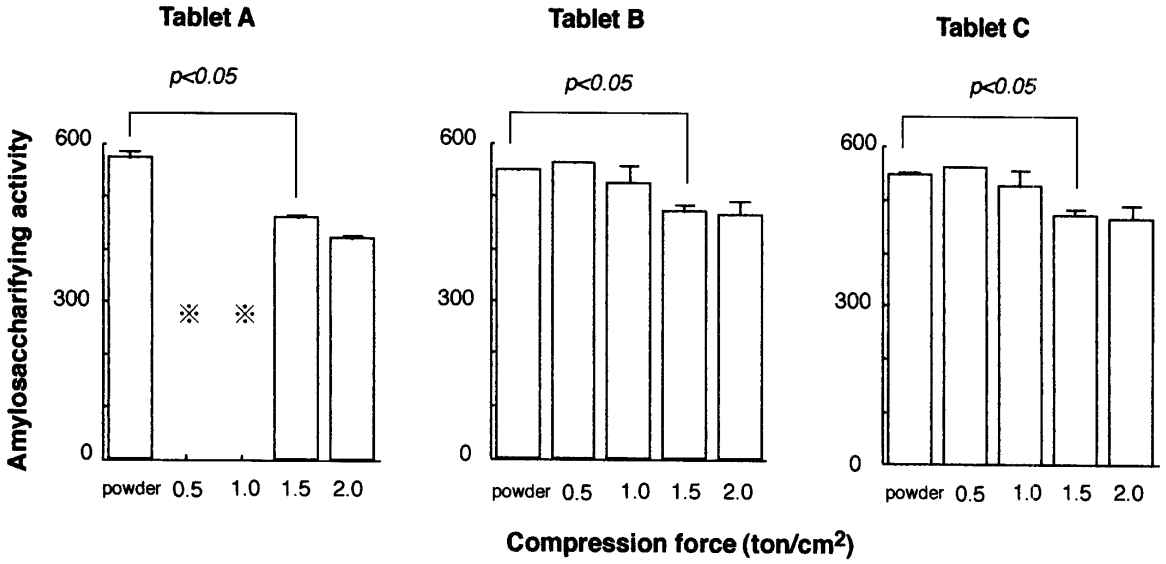

Fig. 3. Amylosaccharifying Activity of NGD Tablets Prepared under Various Compression Forces
Each point represents the mean±S.D. (n=3)
※ ; Not able to prepared.

Table 2. Friability of Tablets (%)

Compression force (ton/cm^2)	Tablet A	Tablet B	Tablet C
0.5	※	85.2	21.6
1.0	※	4.3	1.5
1.5	51.3	3.6	0.8
2.0	3.3	0.9	0.3

※ : Not to be able to prepared.

compression force and MCC amount were increased, the disintegration time of the tablet was prolonged(Fig.2). A short disintegration time is believed to be desirable for optimum diastase potency[3].

In regard to digestive activity, there was no significant difference between NGD powder and tablets prepared by the addition of 30% (Tablet B) or 40% (Tablet C) MCC using a compression force 1.0 ton/cm^2 However, the activity was significantly decreased ($P<0.05$) in tablets prepared using a compression force of more than 1.5 ton/cm^2 (Fig.3). This phenomenon could probably be attributed to potency deactivation by compression. The time course of pH variation when each preparation was tested with the first fluid for the disintegration test (Jp XIII), is shown in Fig.4. The MDT of NGD powder was determined to be 4.66 minutes by moment analysis. It was higher than that obtained for a mixture of sodium bicarbonate and magnesium oxide (alkaline composition of NGD powder). It is considered that the NGD powder did not disperse in the test solution. The dispersing time for NGD powder in the test solution was calculated as 3.41 minutes because the MDT of NGD powder was 4.66 minutes and that of the alkaline composition of NGD powder was 1.25 minutes. The MDT of NGD tablets increased with increase of compression force and amount of MCC. The preparations that exhibited lower MDT than that of NGD powder were Tablet A, compressed using force of 1.5 ton/cm^2, Tablet B, compressed using force of 1.0 ton/cm^2 and Tablet C, compressed using force of 0.5 ton/cm^2.

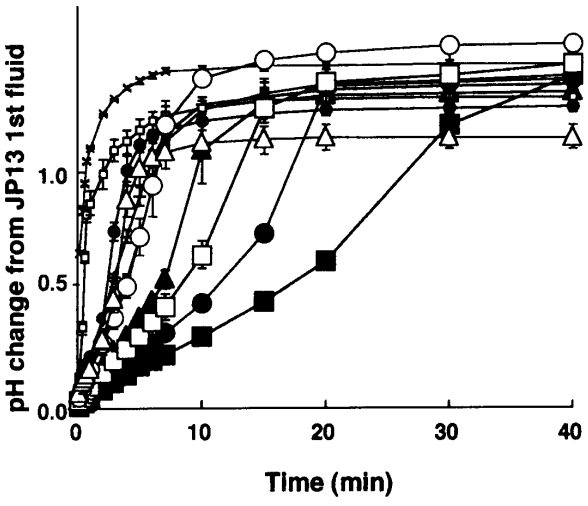

Fig. 4. pH Change Profile of NGD Tablets and NGD Powder in JP XIII 1 st Fluid.(37.0 ±0.5℃, 900 ml)
Each point represents the mean±S.D. (n=3)
× : Alkaline Component of NGD,
＋ : NGD Powder,
△ : Tablet A 1.5 ton/cm^2, ▲ : Tablet A 2 ton/cm^2, ● : Tablet B 1 ton/cm^2, ○ : Tablet B 1.5 ton/cm^2, ● : Tablet B 2 ton/cm^2, □ : Tablet C 0.5 ton/cm^2, ■ : Tablet C 1 ton/cm^2, □ : Tablet C 1.5 ton /cm^2, ■ : Tablet C 2 ton/cm^2

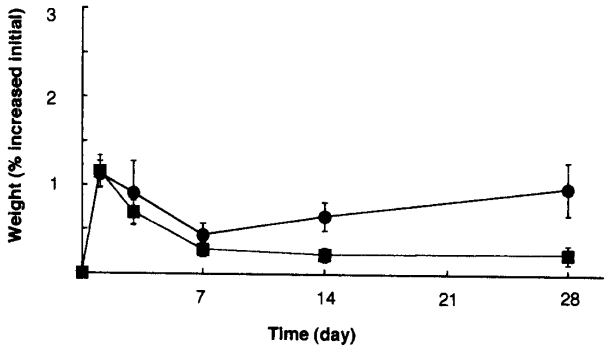

Fig. 5. Time Course of Weights of Tablets Stored at 25℃, 75% RH
Each Point Represents the mean±S.D. (n =10)
●: Tablet B (30% MCC), ■: Tablet C (40% MCC)

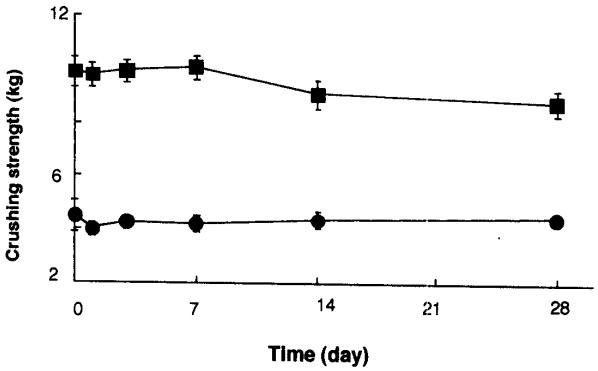

Fig. 6. Time Course of Crushing Strength of Tablets Stored at 25℃, 75% RH
Each Point Represents the mean±S.D. (n =10)
●: Tablet B (30% MCC), ■: Tablet C (40% MCC)

Table 3. Regression Equation for Each Characteristic and Statistical Parameter

	$a(X_1)$	$b(X_2)$	$c(X_1^2)$	$d(X_2^2)$	$e(X_1X_2)$	f	R^2
Y1	-81.3064	14.19970	-	-	2.01421	556.514	0.86792
Y2	-0.63	-46.8364	-	13.29	0.9208	25.7675	0.92543
Y3	-	-	0.00413	-	0.22612	-7.04076	0.9126
Y4	-21.2011	-301.622	0.19313	40.7975	4.74905	608.175	0.55332
Y5	-10.773	-	4.45559	-	0.25352	1.314	0.98827

$Yn=aX_1+bX_2+cX_1^2+dX_2^2+eX_1X_2+f$
Y1:Amylosaccharifying Activity, Y2:Disintegration Time,
Y3:Crushing Strength, Y4:Friability, Y5:MDT
R:Multiple correlation coefficient
X_1:Compression Force(ton/cm^2), X_2:Percent of MCC

In the test for conservation stability, variations in weight and crushing strength were not observed. Generally, it is thought that diastase has strong deliquescence. But the weight and crushing strength of the tablets were stable over a long period (**Fig.** 5, 6). The digestive activity of the tablets immediately and at 15 months after preparation were 500.0 units/g and 526.9 unit/g, respectively, and the difference was not statistically significant.

Table 3 shows the prediction equations from each measured value obtained by multiple regression analysis. The coefficients of determination(R^2) derived from the amylosaccharifying activity equation(Y1) from the friability equation(Y4) were 0.867 and 0.553, respectively. Thus, no significant correlations were noted. Because the amylosaccharifying activity decreased rapidly under 1.5 ton/cm^2 as mentioned above, and the friability increased rapidly with decreasing hardness of tablets, the R^2 in each characteristic value of disintegration time, crushing strength and MDT were 0.936, 0.913 and 0.988 respectively; these were predictable from these equations to a certain extent. Three-dimensional diagrams for each of the characteristic values are shown in Figs.7,8,9. The

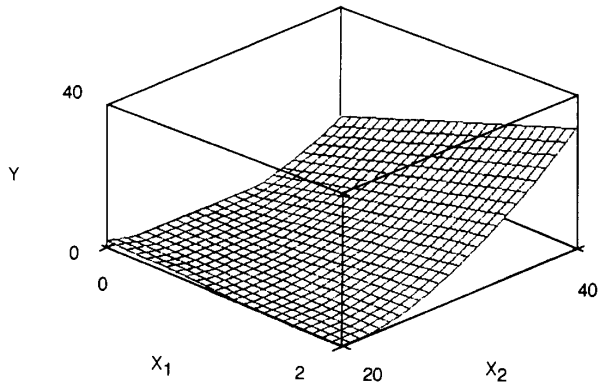

Fig. 7. Three Dimensional Plots of Disintegration Time Against Compression Force and Concentration of MCC Added
Y : Disintegration Time (min), X_1 : Compression Force (ton/cm^2), X_2 : Percent of MCC added

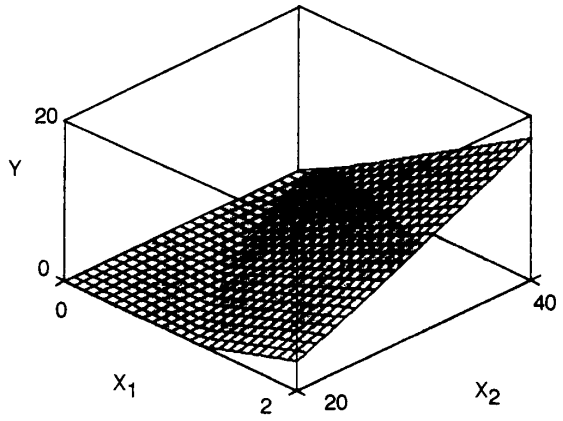

Fig. 8. Three Dimensional Plots of Crushing Strengh Against Compression Force and Concentration of MCC Added
Y : Crushing Strengh (kg), X_1 : Compression Force (ton/cm^2), X_2 : Percent of MCC added

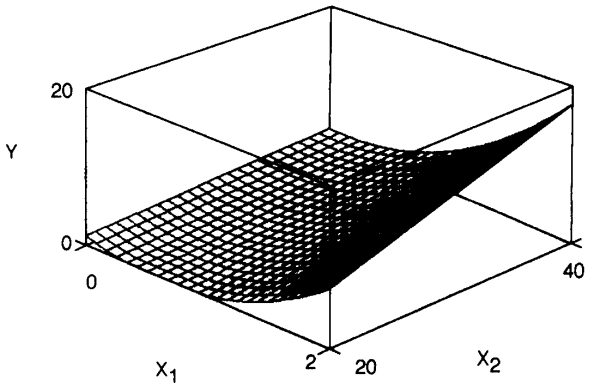

Fig. 9. Three Dimensional Plots of MDT Against Compression Force and Concentration of MCC Added
Y : MDT(min), X_1 : Compression Force (ton/cm^2), X_2 : Percent of MCC added

disintegration time increased with increase in amount of MCC and the compression force used (**Fig.** 7). Since a rapid disintegration time is considered desirable, the optimum values (MCC addition at 30% and compression force at 1.0 ton/cm^2) were observed in the center of the simulation area. Crushing strength (**Fig.** 8) and MDT (**Fig.** 9) increased with increase in compression force and amount of MCC. The correlation matrix was calculated from each of the characteristic values for the tablets (**Table** 4). A correlation between disintegration time and MDT was determined indicated that the neutralizing capacity was affected by disintegration time.

In this study, it is suggested that the addition of 30% MCC NGD powder and a compression force of 1.0 ton/cm^2 were the optimum conditions for preparing NGD tablets. These NGD tablets are stable for 15 months and can be satisfactorily prepared as the hospital formation. These tablets are expected to be applied clinically.

Table 4. Simple Correlation Matrix

	Y1	Y2	Y3	Y4	Y5
Y1	1.0	-0.173384	0.205551	-0.121679	-0.22416
Y2		1.0	0.881592	-0.382546	0.970058
Y3			1.0	-0.535285	0.88437
Y4				1.0	-0.487184
Y5					1.0

Y1:Amylosaccharifying activity, Y2:Disintegration time,
Y3:Crushing strength, Y4:Friability, Y5:MDT

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