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Application of Calcium Silicate for Medicinal Preparation. I. Solid Preparation Adsorbing an Oily Medicine to Calcium Silicate[1)]

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Calcium silicate (Florite® RE, FLR), a fine porous powder, was recently approved as a medicinal additive. In this study we sought to make a solid preparation by adsorbing an oily medicine to FLR; tocopheryl nicotinate (TN) was used as the oily medicine.

TN adsorbed to FLR powder (TN-PO) was prepared by adsorbing TN ethanol solution to FLR and granulating with hydroxypropylcellulose (HPC) in order to improve the flowability. The results were as follows.

FLR showed an excellent liquid holding ability compared with other excipients, and this was attributed to the high capillarity of the pores. In the adsorbing process, FLR particles were granulated with TN overflowing from the pores or adhering to the particle surface. The angle of repose was decreased with increasing TN content, which was attributed to the process of granulation, and the angle of repose of the granules with a binder (TN-GR) was below 40° at any TN content.

These results show that FLR is an useful additive for the solid preparation of an oily medicine.

Keywords solid preparation; calcium silicate; tocopheryl nicotinate; oily medicine

Oily medicines such as vitamin E, clofibrate, gefarnate and ethyl icosapentate, and slightly water soluble medicines dissolved in oleic acid as an oil have generally been produced and sold in the soft capsule form.[2)] In this paper, to improve the compliance and utility for patients and reduce production cost,[3—6)] the solid preparation of an oily medicine was attempted.

Calcium silicate (Florite® RE, FLR), which has a characteristic porous structure,[7—9)] was recently approved as a medicinal additive. So we studied the solid preparation of tocopheryl nicotinate as an oily medicine using FLR which has pore capillarity.

First, we attempted the transformation of tocopheryl nicotinate to powder, and then we granulated it to improve the flowability.

Experimental

Materials Tocopheryl nicotinate (TN) was supplied by Sagami Kasei Co., Ltd. The melting point and density at 38 °C and 0.999, respectively. Porous calcium silicate (Florite® RE, FLR, Eisai Co., Ltd.) was used as a carrier of adsorbing liquid. Colloidal silica (Aerosil® 200, Nippon Aerosil Co., Ltd.), magnesium aluminometasilicate (Kyowa Kagaku Sangyo Co., Ltd.), synthetic aluminum silicate (Fuji Kagaku Sangyo Co., Ltd.), crystalline cellulose (Avicel® PH-101, Asahi Kasei Kogyo Co., Ltd.), cornstarch (Nippon Cornstarch Co., Ltd.), lactose (DMV Co., Ltd.) and dibasic calcium silicate (Taihei Kagaku Sangyo Co., Ltd.) were used to compare the properties with FLR. HPC (L-grade, density = 1.21) was obtained from Nippon Soda Co., Ltd. Tween 80 was purchased from Kanto Kagaku Co., Ltd.

Measurement of the Property of Excipients The density and angle of repose of each excipient were measured using an air comparison pycnometer (Toshiba-Beckman Co., Ltd., Model 930) and a Konishi angle of repose meter (Konishi Seisakusho Co., Ltd., Model FK), respectively. The specific surface area was measured by the air permeability method, employing a specific surface area meter (Shimazu Seisakusho Co., Ltd., Type SS-100), and the particle diameter was determined by the following equation,

$$Sw=6/\partial\cdot D$$

where Sw is specific surface area, ∂ is density and D is particle diameter. The obtained values are shown in Table I. The liquid holding ability of each excipient was measured by the JIS K-6220 method[10)] using dibutyl phthalate as an oily material. The pore size distribution of each excipient was measured by mercury intrusion porosimetry, employing a mercury porosimeter (Quanta Chrome Co., Autoscan-33). The contact angle of mercury with the samples and the surface tension of mercury were regarded as 140° and 480 dyn/cm, respectively.[11)]

Observation of Surface of FLR Particles A scanning electron microscope (SEM, Hitachi Seisakusho Co., Ltd., Type S-2250N) was used to observe the surface of FLR.

Preparation of the Powder Adsorbing TN Using FLR TN solutions of 10—60% concentrations were prepared by dissolving 10, 20, 30, 40, 50 and 60 g of TN in ethanol (100 ml) and their viscosity was measured with a digital viscometer (Kyowa Scientific Co., Ltd., DV-II+). FLR was dried at 80 °C for 3 h *in vacuo*. While agitating 15 g of FLR by an

TABLE I. Particle Diameters, Densities and Angle of Repose of Used Powder

	Particle diameter (μm)	Density (g/cm^3)	Angle of repose (°)
Florite® RE	0.535±0.005 (26.1[a)])	2.27±0.07	46.7±1.2
Aerosil® 200	0.383±0.003	2.56±0.04	38.3±0.5
Magnesium aluminometasilicate	1.113±0.006	2.97±0.07	33.0±1.2
Synthetic aluminum silicate	0.834±0.006	2.06±0.07	48.7±0.8
Crystalline cellulose	11.962±0.017	1.29±0.04	42.8±0.6
Cornstarch	16.837±0.009	1.32±0.06	46.6±1.0
Lactose	19.013±0.021	1.38±0.04	48.9±0.6
Dibasic calcium phosphate	7.274±0.011	1.94±0.06	42.1±1.1

Data represent means±S.D. (n=3). *a*) This data was measured by the coulter counter method.

TABLE II. Viscosity of Each TN Solution and TN Contents in the FLR Powders Adsorbing TN Solution

	TN solution conc. (%)					
	10	20	30	40	50	60
Viscosity (mPa·s)	1.5	2.4	4.1	7.2	14.9	34.8
TN content (%)[a)]	39±1[b)]	73±6	120±2	163±3	206±4	245±9

a) Percent of TN to FLR. *b*) Data represent means±S.D. (n=5).

agitator at 500 rpm in a 500 ml beaker, TN solution of each concentration was dropped by a micro tube pump at 2.5—2.8 ml/min. When a certain volume (±about 1 ml) of each concentration of TN solution was dropped, FLR particles crawled up on the wall of a beaker and could not be agitated because of the liquid bridge among them. This amount was then regarded as the maximum of liquid adsorption. After drying *in vacuo*, the powder which adsorbed each quantity of TN (TN-PO) was obtained. The viscosities of the six concentrations of TN solution and the TN contents in the produced TN-PO are shown in Table II.

Granulation of TN-PO While agitating TN-PO of six TN concentrations at 500 rpm in a 500 ml beaker, 10% HPC solution was dropped by micro tube pump at 2.5—2.8 ml/min as a binder. In a manner similar to that of adsorbing TN, the crawling up of particles on the wall of the beaker was regarded as the end of granulation. After drying *in vacuo*, granules of TN-PO of each TN concentration (TN-GR) were obtained.

Dissolution Study It is difficult to estimate the releasing property of TN by the method using the first fluid, because TN is a water-insoluble material.[12,13] So in this paper the dissolution profiles of TN from TN-PO and TN-GR were observed by the paddle method (J.P. XII) using the first fluid added with a surface active agent. Tween 80 (9 g) was dissolved in 900 ml of the first fluid and this solution was used as a dissolution medium. TN-PO and TN-GR having diameters below 125 μm and 212—300 μm, respectively, were employed. Each sample which contained 360 mg of TN was put into the above mentioned dissolution medium at 37±0.5 °C with a rotating paddle at 100 rpm. Then a 10 ml aliquot of the sample solution was taken out, filtered through a disposable filter (0.45 μm, Toyo Roshi Kaisha, Ltd.) at appropriate intervals, and 6 ml of ethanol was added to 2 ml of the sample solution. The concentration of TN was determined spectrophotometrically by the absorbance at 264 nm.

Results and Discussion

Liquid Holding Ability and Particle Structure of FLR and Other Excipients Figure 1 shows the liquid holding ability of FLR and some other kinds of excipients. FLR showed adsorbing liquid volume about 7 times the empty weight, and about 4—14 times that of other excipients except Aerosil® 200.

Figure 2 shows the pore size distribution of FLR, Aerosil® 200, magnesium aluminometasilicate and synthetic aluminum silicate used to examine the difference in the liquid holding ability in terms of particle structure. FLR showed many pores with diameters of about 12 and 0.15 μm, which were considered to be interparticles pores and intraparticle pores, respectively. FLR also has much more pore volume than the others. Figure 3 shows the SEM photographs of FLR particles. FLR appears as a petal structure because of the scaly crystals of calcium silicate which form many pores. FLR is believed to have a good liquid-holding ability because of the high capillarity of these pores. On the other hand, Aerosil® 200 also could adsorb a large quantity of liquid in spite of its smaller pore volume. It is though that, because of its small particle diameter and the large specific surface area, a liquid bridge is believed formed by dibutyl phthalate between Aerosil® 200 particles. This powder adsorbing TN may, however, have formed the slurry state with the exposed liquid

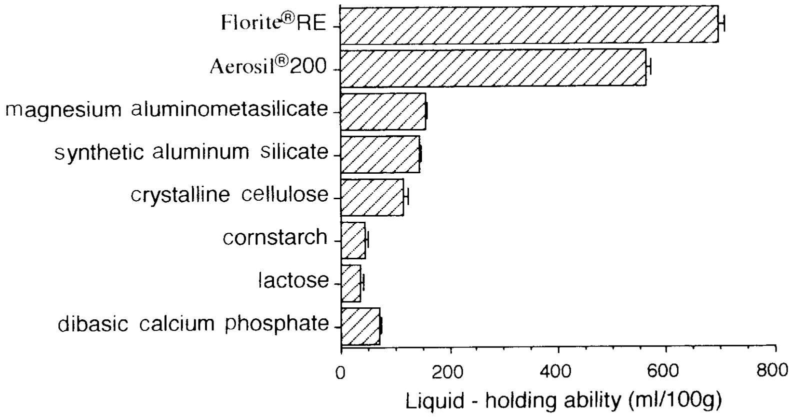

Fig. 1. Liquid Holding Ability of Florite® RE and Some Kinds of Excipients

All tests were performed by the JIS K-6220 method using dibutyl phthalate as an oily material.

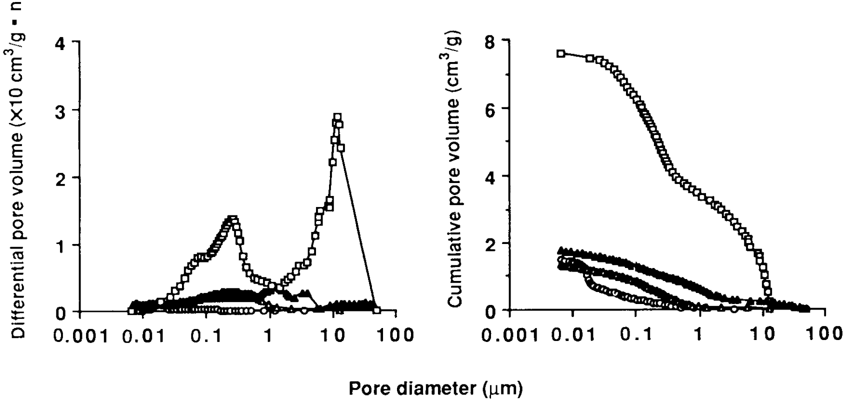

Fig. 2. Pore Size Distributions of Florite® RE and Some Kinds of Excipients

□, Florite® RE; ○, Aerosil® 200; △, magnesium aluminometasilicate; ▲, synthetic aluminum silicate.

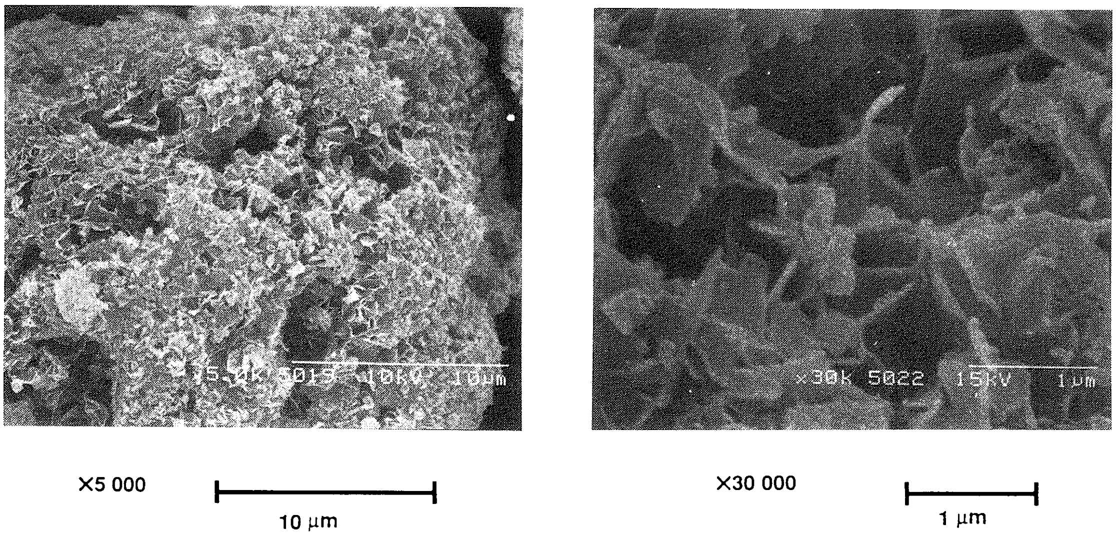

Fig. 3. Scanning Electron Micrographs of FLR Particle

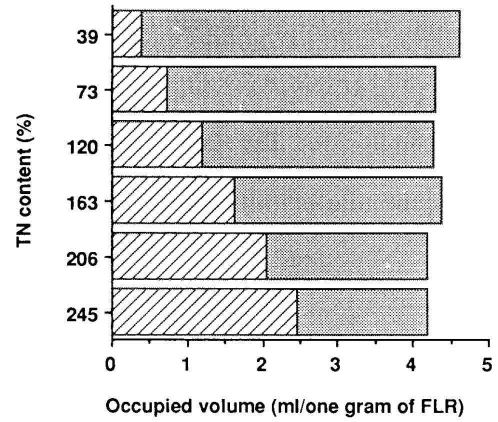

Fig. 4. Volume Occupied by TN and HPC Solution in 1 g of FLR

▨, TN; ■, HPC solution.

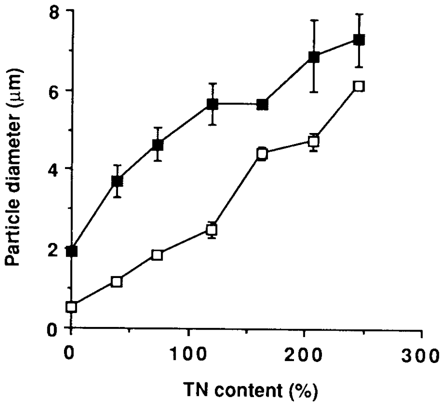

Fig. 5. Effect on TN Content on Particle Diameter of TN-PO and TN-GR

□, TN-PO; ■, TN-GR.

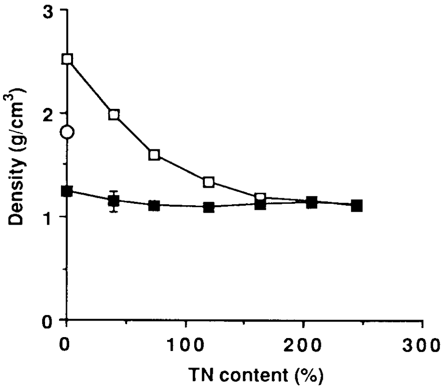

Fig. 6. Effect of TN Content on Density of TN-PO and TN-GR

□, TN-PO; ■, TN-GR; ○, true density of granule composed of HPC and FLR calculated with these densities.

retained on the surface of the particles. Thus it may easily adhere to the inner wall of a pharmaceutical machine such as a hopper or feeder of a tabletting machine in the manufacturing process. FLR was therefore used as a TN adsorbing carrier in the following experiments.

Change in the Properties of FLR by Adsorbing Liquid and Subsequent Granulation Figure 4 shows the total amount of the HPC solution volume required for granulation of TN-PO and the TN content in TN-PO, whose weight was converted into volume. When TN content was increased, HPC solution volume for granulation was decreased. Moreover, in all cases, the total amount of TN and HPC was nearly the same, ranging from 4.2 to 4.7 ml per 1 g of FLR.

Figure 5 shows the particle diameter of TN-PO and TN-GR with various TN contents. The diameter of TN-GR was increased because of granulation with a binder, while the particle diameter of TN-PO was increased with increasing TN content though no binder was used. It suggests that FLR particles were granulated with TN overflowing from the pores or adhering to the particle surface. Moreover, when the TN content was increased, the concentration and viscosity of the used TN solution rose as shown Table II, and the apparent contact angle of TN solution to the pore on the FLR particle became larger because of the lower shear rate. The TN solution with higher concentration and viscosity was therefore easy to retain on FLR particles and acted as a binder.

Figure 6 shows the density of TN-PO and TN-GR at various TN contents. The density of TN-PO was decreased with increasing TN content, while the density of TN-GR did not change with increasing TN content. The density of 0% of TN content in TN-GR shows the density of the sample adsorbing HPC solution only, and the value was 1.25. However, the true density of this TN-GR (open circle in Fig. 6) was calculated at 1.81 and was different from the measured value. The difference was thought to be due to the air included in the sample, so the amount of included air was calculated, and regarded as the difference between the theoretical volume and the measured volume of the sample.

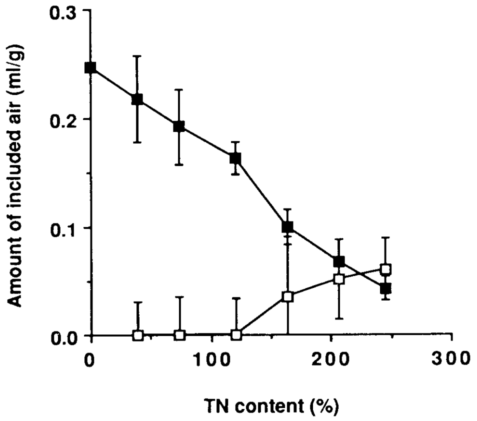

Fig. 7. Effect of TN Content on Amount of Included Air in TN-PO and TN-GR
□, TN-PO; ■, TN-GR.

Figure 7 shows the amounts of included air in TN-PO and TN-GR at various TN contents. At 0% TN content in TN-GR air was calculated at about 0.25 ml per 1 g of FLR. It increased in TN-PO and decreased in TN-GR with increasing TN content. In consideration of this result and the increasing difficulty of permeation into the pores with greater viscosity, the formation models for TN-PO and TN-GR shown in Fig. 8 be considered. At 0% TN content in TN-GR, because the viscosity of HPC solution is extremely high, it may be adsorbed by covering the pores of FLR as shown in [1]-A. After drying, the sorption of HPC may occur including much air in the pores of FLR as shown in [1]-B. When TN solution of a low concentration and viscosity is adsorbed, the solution may permeate deeper into the pores as shown in [2]-A. After drying, the sorption of TN includes less air in the pores as shown in [2]-B. Moreover, the state after granulation with HPC solution and drying may be like [2]-D.

On the other hand, when TN solution of high concentration and viscosity is adsorbed, the solution may permeate more shallowly into the pores compared with [2]-A as shown in [3]-A. After drying, the sorption of a great deal of TN may occur and include much more air in the pores than in [2]-B. The state after granulation with HPC solution and drying may be like [3]-D. Based on these models, the change in the density of TN-GR could be explained as follows. At 0% TN content in TN-GR,

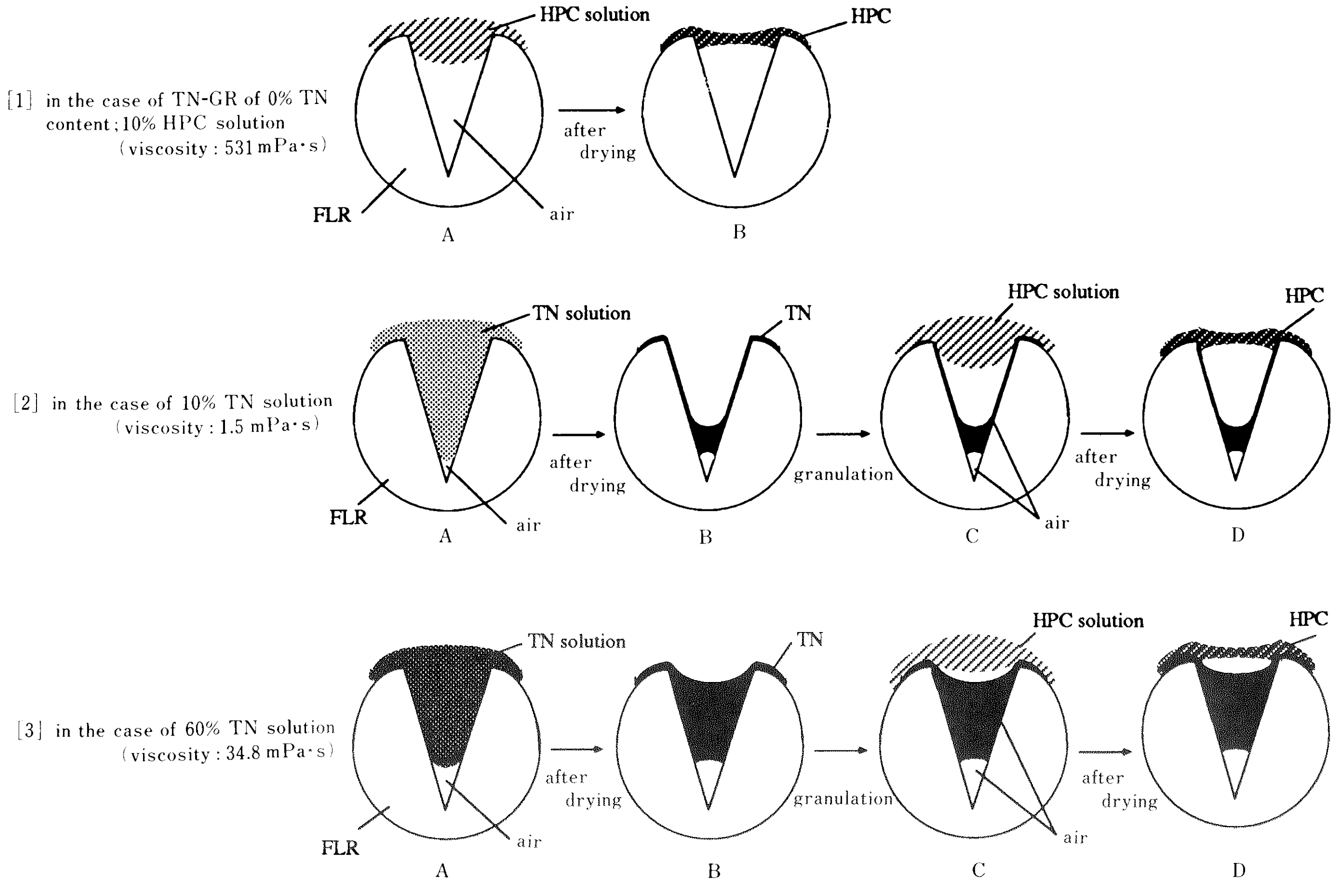

Fig. 8. Model of Formation Process of TN-PO and TN-GR

the measured value was less than the theoretical value, perhaps because the measured volume is extremely large owing to the sorption of HPC with much air in the sample. Each case of TN-GR shows a tendency to increase in density with increasing TN content: that is, with changing from the state of [2]-D to [3]-D, because of the lesser amount of included air; at the same time, it also shows a tendency to decrease in density, because of the decrease in HPC solution used for granulation with greater TN content as shown in Fig. 4. These tendencies might offset each other, and this may be why the density of TN-GR did not change with increasing TN content. We therefore concluded that TN-PO and TN-GR were produced according to these models, because it was possible to explain the change in densities based on Fig. 8.

Evaluation of the Flowability and Releasing Property of TN-PO and TN-GR Figure 9 shows the angle of repose of TN-PO and TN-GR at various TN contents. The angle of TN-PO was decreased with increasing TN content and was below 40° at above 100% of TN content. In TN-GR it was also below 40° at various levels of TN content. Below about 40° of the angle of repose is said to be no obstacle to flowability in the various processes for producing medicine.

Figure 10 shows the releasing behaviors of TN-PO and TN-GR. The percent of released TN from TN-PO after 2 h rose with increasing TN content. This result suggests that the specific surface area of the samples was decreased because the samples used in the experiment had 360 mg of TN included in their weight, so their weight for the test was decreased with increasing TN content. On the other hand, the percent of released TN and the rate of release from TN-GR were slightly lower compared with TN-PO. This suggests that the specific surface area was reduced because the particle diameter of TN-GR used for the test was largest than that of TN-PO.

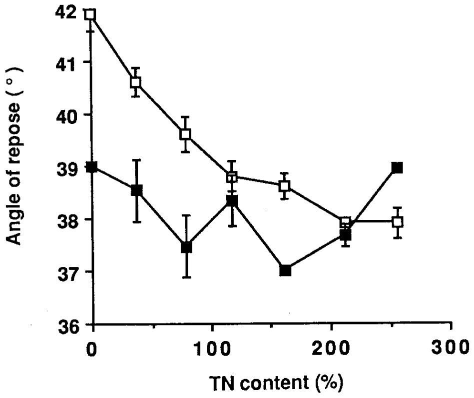

Fig. 9. Effect of TN Content on Angle of Repose of TN-PO and TN-GR

TN-PO; □, TN-GR, Used TN-GR were not sieved. Each point represents the mean ± S.D. obtained from 3 experiments.

Conclusion

FLR showed excellent liquid-holding ability because of the capillarity of its many pores, and a small amount of it was able to hold a large quantity of medicine. Moreover, little of it adheres to the pharmaceutical machines. Therefore, it is possible to transform TN, which is an oily medicine, in a solid preparation using FLR. Furthermore, TN-PO obtained with the granulation process showed a good fluidity and releasing property of TN, suggesting that TN-PO may have potential usefulness for both powder and granule for tableting.

References and Notes

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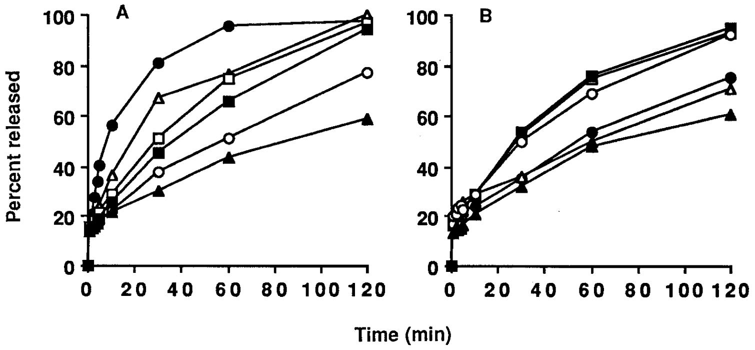

Fig. 10. Effect of TN Content on the Releasing Profile of TN in TN-PO (A) and TN-GR (B) Having Different TN Content

Granules of 70 to 50 mesh fraction were used for the experiment □, 39%; ■, 73%; ○, 120%; ●, 163%; △, 206%; ▲, 245%.