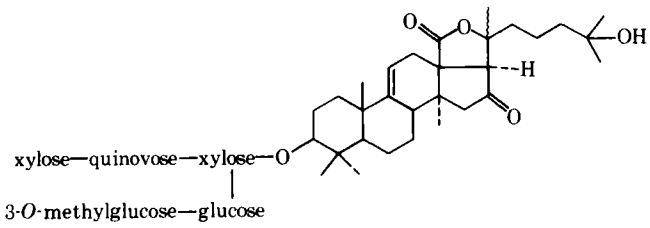

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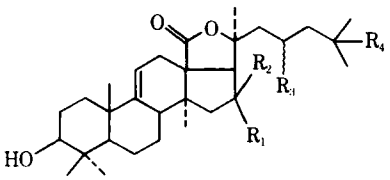
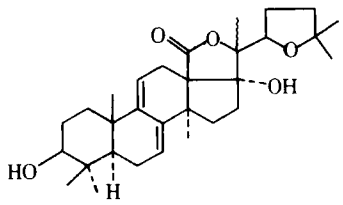


IIa: $R_1 = R_2 = O, R_3 = H, R_4 = OH$
IIb: $R_1 = R_2 = O, R_3 = H, R_4 = OCH_3$
IIc: $R_1 = OH, R_2 = H, R_3 = OCOCH_3, R_4 = H$



III

ently available evidence strongly indicates that such sea cucumber saponins have potentially useful and interesting biological properties. The inhibition of cell growth by the three tetracyclic triterpene saponins described in this report may be due to the ability of certain sea cucumber saponins to inhibit protein synthesis (rat bone marrow tissue culture) and RNA synthesis (yeast cell culture) (13).

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For Part XLIV of this series, see G. R. Pettit, *China Q.*, in press.

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Starch Paste Granulations: Factors Causing Binder Dilution Effects on Granulations and Tablets

Keyphrases □ Starch paste granulations—effect of mixing time, speed, and binder dilution on physical properties of tablets □ Granulations, starch paste—effect of mixing time, speed, and binder dilution on physical properties of tablets □ Dosage forms—tablets, effect of mixing time, speed, and binder dilution on physical properties of tablets

To the Editor:

In a recent communication (1), the dilution factor of starch paste binder and its effects on granulations and tablets were reported. The conventional wet granulation process was used to prepare granulations in a small

Table I—Starch Paste Dilutions

	Formulation A	Formulation B	Formulation C
Lactose, g	860	860	860
Starch (in dry mix), g	47	47	47
Starch (in paste), g	26	26	26
Water (for paste), ml	100	130	160
Water (used to *qs*), ml	100	70	40

Table II—Sieve Analysis of the Three Formulations

Formulation	Percent Remaining on Corresponding Screens after Dry Granulation Step							Percent Remaining on Corresponding Screens following Attrition at 500 Revolutions						
	20 Mesh	40 Mesh	60 Mesh	80 Mesh	120 Mesh	140 Mesh	Pan	20 Mesh	40 Mesh	60 Mesh	80 Mesh	120 Mesh	140 Mesh	Pan
A	9.0	56.6	16.6	6.9	6.5	2.4	2.0	7.0	39.4	16.9	6.7	7.8	3.3	18.9
B	13.3	53.9	18.6	6.4	4.7	1.8	1.3	12.8	46.4	16.9	5.4	5.0	2.0	11.5
C	10.3	56.7	16.8	6.9	5.8	2.3	1.2	5.9	40.7	15.1	7.1	6.5	3.3	21.4

planetary-type mixer. The three formulations tested are given in Table I. The lactose and starch were dry mixed in the mixer bowl for 5 min. The amount of water used to make the starch paste was varied from a 4:1 to a 6:1 water to starch ratio. The total amount of water used in each experiment was kept constant by varying the amount of water added to the mass after the starch paste had been mixed with the lactose–starch mixture for 1 min.

The total mixing time was kept constant at 5 min. The wet mass was passed through a 6-mesh screen, dried at 50° to a moisture content of 1%, and then passed through a 16-mesh screen. These granules were evaluated for friability and compressibility. It was reported that the friability and compressibility of the granules improved with increasing starch paste dilution. Disintegration time increased slightly with each dilution of the starch paste.

Important parameters in the conventional wet granulation process are mixing time and speed of mixing. Mixing time is generally determined by the type and speed of mixing equipment. It is important to reach an appropriate degree of wetting in the powder particles during the wet granulation procedure. The properties of the dried granules with regard to hardness, friability, and compressibility vary with the varying degree of wetting in the wet granulation.

It should be obvious to the formulator that gross changes in the viscosity or thickness of the starch paste binder require changes in the mixing time for reaching a similar degree of wetting during the wet granulation process. Thick starch paste requires a longer time for mixing compared to a thin starch paste. Unless a thick starch paste is mixed for a longer period compared to a thin starch paste, one should expect differences in the degree of wetting of the powder particles. These differences would be reflected in the hardness, friability, and compressibility of the dried granulation. Obviously, Hill (1) optimized the degree of wetting of the lactose–starch mixture in favor of the thin starch paste to show the binder dilution effects.

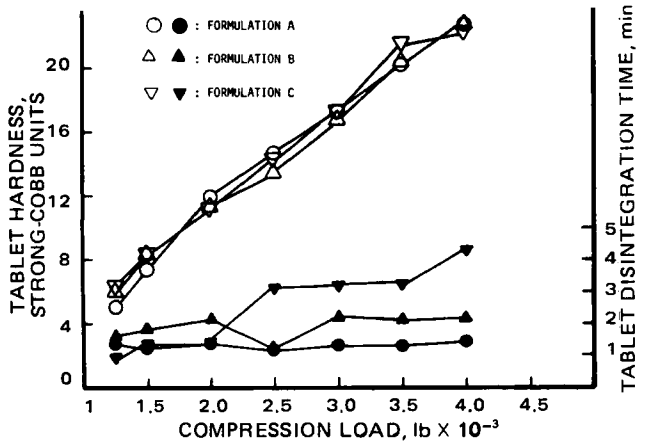

Figure 1—*Tablet hardness–compression load profiles and corresponding disintegration times of the three formulations. Mixing time and mixing speed were 10 min and 60 rpm, respectively. Key:* ○, △, *and* ▽, *tablet hardness; and* ●, ▲, *and* ▼, *tablet disintegration time.*

Careful evaluations should be carried out for any changes in the process, such as dilution of the binder solution, or in the size or type of mixing equipment during the tableting scale-up operations. Mixing time should be adjusted to ensure similar wetness of the powders. In view of these considerations, we consider it important to present data that clearly show that the binder dilution effects on the dry granulation friability and compressibility reported recently (1) are a consequence of improper mixing and are readily eliminated by increasing the mixing time from 5 to 10 min, ensuring a similar degree of wetting of the powders using the thick and thin starch pastes.

Similar procedures (1) were used in the preparation of granules and tablets. The lactose and starch were dry mixed in the mixer bowl for 5 min. The amount of water used to make the paste was varied from a 4:1 to a 6:1 water to starch ratio. The total amount of water used in each experiment was kept constant by varying the amount of water added to the mass after the starch paste had been mixed with the lactose–starch mixture for 1 min. The total amount of mixing time was increased from 5 to 10 min. The mixing speed was constant at 60 rpm. The wet mass was put through a 6-mesh screen by hand, dried at 50° to a moisture content of 1%, and then passed through an oscillator using a 16-mesh screen.

Granulation friability was measured by tumbling 25 g of granulation larger than 150 mesh end to end in a Plexiglas cylinder, 3.81 cm in diameter and 30.49 cm long. Sieve analysis[1] of the granulations before and after attrition was made. The sieve assembly was vibrated and sifted for 5 min at a pulse and sift setting of 7. The granulations were mixed with 0.5% magnesium stearate and 0.5% talc and compressed by an instrumented single-punch machine[2]. The punches and dies were 1.11 cm flat-faced beveled edge. The tablet hardness was determined[3]. The disintegration was carried out by the USP procedure.

The sieve analysis of the three granulations before

[1] Model L3P, Allen Bradley Co., Milwaukee, Wis.
[2] Stokes model E.
[3] Strong Cobb Arner Inc., Cleveland, Ohio.

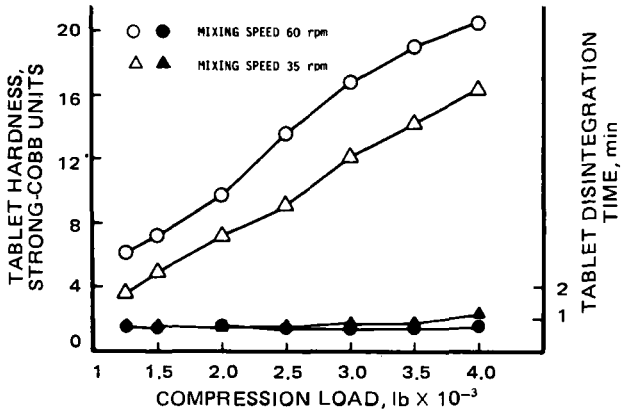

Figure 2—*Tablet hardness–compression load profiles and corresponding disintegration times. Mixing time was 5 min. Key: ○ and △, tablet hardness; and ● and ▲, tablet disintegration time.*

and after attrition is given in Table II. These results indicate no significant differences in the granulation size before and after attrition. Figure 1 gives the results of the tablet hardness–compression load profiles. The compressibility of the three granulations was essentially the same. These data indicate that when the three formulations were mixed for 10 min instead of for 5 min (1), the dilution factor effects on granule hardness and compressibility disappeared. A similar degree of wetting in the powders was reached by adequate mixing, which resulted in no differences in hardness, friability, and compressibility of the dried granules prepared from thick and thin starch pastes. Thus, we have shown clearly that the dilution factor effects on hardness, friability, and compressibility of granules are a consequence of improper mixing during the wet granulation procedure.

Figure 2 also gives the average disintegration times as a function of the compression load for the three formulations given in Table I. At lower compression forces, the differences in the disintegration times of the three formulations are slight and do not appear to follow any definite trend relating to the viscosity of the starch paste. However, at higher compression loads, the differences in the disintegration time might be significant and thus relate to a slightly longer disintegration time for tablets made with thin starch paste compared to thick starch paste.

In the conventional wet granulation procedure, the speed of mixing generally determines the mixing time. The results in Fig. 2 show the effect of mixing speed at a constant mixing time on the tablet hardness–compression load profiles from tablets prepared using Formulation C. The harder tablets at the 60-rpm mixing speed are in agreement with the smaller percentage of fines formed after attrition. The tablet disintegration time was not affected by the change in mixing speed at a constant mixing time.

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Starch Paste Granulations: Factors Causing Binder Dilution Effects on Granulations and Tablets — A Response

Keyphrases□ Starch paste granulations—effect of starch paste viscosity on granule hardness and physical properties of tablets □ Granulations, starch paste—effect of starch paste viscosity on granule hardness and physical properties of tablets □ Dosage forms—tablets, effect of starch paste viscosity on granule hardness and physical properties of tablets

To the Editor:

Granulation mixing time is an important variable, of course. That fact is recognized by often specifying maximum mixing times for the manufacture of granulations. However, the purpose of my communication was to show the unexpected effect of starch paste viscosity on the hardness of the resulting granules. This effect is of interest because the same total amount of water was used in each experiment and it would not be immediately apparent that the paste viscosity would affect the rate of wetting under this circumstance.

A 5-min mixing time was used because the mass appeared to be maximally wet in that time. This is usually the case in the production setting for products made today. The granulating operator has the flexibility to mix until the mass appears granular. It would not be feasible to place a finite limit on mixing time because the actual time required often varies with some physical aspect of the powders such as moisture content, particle size, or shape. The paste dilution study lends support, in fact, to Chowhan and Palagyi's statement that: "Careful evaluations should be carried out for any changes in the process, such as dilution of the binder solution, ..."

The authors also stated that the dilution factor effects disappeared when the three formulations were mixed for 10 min instead of 5 min. This is not entirely true. Even though they showed that the effect on compressibility disappears as shown by similar hardness–pressure profiles, some effect is still reflected in increasing tablet disintegration times. Admittedly, the changes are small and would not be expected to affect tablet acceptability unless a product had a very short disintegration time limit.

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