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The effect of cohesive and non-cohesive ternary components on the homogeneity and stability of a prednisolone interactive mixture

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Summary

Micronized prednisolone (1%) was mixed with lactose–starch granules (425–850 μm) to produce an interactive mix of satisfactory homogeneity (CV = 3.0%) and good stability under segregating conditions. The addition of talc (1 and 5%) to the preformed prednisolone–granule mix had little effect on drug homogeneity with mixing time. The talc was cohesive and interacted with the prednisolone–granule particles to form ternary adhesion units; the prednisolone remained associated with the larger granule fractions. Only under harsh segregating conditions did some slight prednisolone segregation occur in the 5% talc ternary system. The presence of starch (1–20%) showed marked drug segregation tendencies within the ternary system. The starch behaved less cohesively than talc; its presence caused a major redistribution of prednisolone from the granule to the starch particle at all concentration levels and provided a mixed system of prednisolone–granule and prednisolone–starch particle adhesion units of sufficiently different sizes to promote substantial adhesion unit segregation. The redistribution is clearly seen in the ternary mixing profile.

Introduction

The effect of ternary components on the drug homogeneity and stability of preformed interactive mixes is not only of interest theoretically but also is of great

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practical application in pharmaceutical processing. In previous studies, Staniforth et al. (1982) used the ultracentrifuge method to assess the interparticulate adhesion characteristics in binary and ternary interactive mixes containing salicyclic acid and lactose or sucrose carriers. Composite adhesion profiles were obtained for ternary systems containing magnesium stearate and starch. The proportion of weakly bound drug particles was found to increase as the magnesium stearate concentration increased while starch produced some stabilization of the interactive system. The addition of talc produced a single-curve profile and showed significant stabilization of the drug. This stabilization was attributed to its electrostatic properties and capacity to fill interparticulate void spaces. In contrast, the addition of magnesium stearate, in concentrations above and below the theoretical monolayer saturation, to a prednisone–lactose granule interactive system had little effect on the drug homogeneity or on the stability of the system to vibratory segregation conditions (Stewart, 1981). Generally few studies have addressed ternary interactive systems and the purpose to this research is to establish the mechanism of drug segregation or stabilization when both cohesive and non cohesive materials are added to a preformed prednisolone interactive mix.

Materials and Methods

Materials

Prednisolone (Sigma) was micronized by fluid energy milling (Chrispro Jetmill model 75P, compressed air 5.8 atm at 12.7 litres $\cdot s^{-1}$; $d_{vn} = 4.0\ \mu m$). The carrier was lactose–starch granules (2 : 1, prepared by wet granulation using starch paste as the binder). A 425–850 μm fraction was obtained by sieve classification. Maize starch ($d_{vn} = 10.9\ \mu m$) and talc ($d_{vn} = 6.9\ \mu m$) were the ternary components.

Methods

Mixing was performed in an Erweka Cube Mixer (20 rpm; 100–200 g load). Twenty 100 mg samples were removed randomly for assay to evaluate homogeneity. The samples were removed using a thief to minimize any disturbance to the mix. Prednisolone was assayed spectrophotometrically by dissolving the prednisolone in the sample in methanol, adjusting to 100 ml and centrifuging to remove insoluble particles. The absorbance was measured using a Cary 219 UV-visible spectrophotometer at 243 nm. A Beer's Law calibration for prednisolone over the concentration range 0.004–0.020 mg $\cdot$ ml^{-1} showed no significant deviation from linearity and the prednisolone concentrations were obtained by inverse prediction. Preliminary experiments showed complete recovery of the prednisolone from the granules. Particle size analyses were performed by sieving (BS410, 20 min) and microscopy (Olympus BH2). Scanning electron micrographs were produced on a Phillips model 505 SEM. Segregation studies were performed using a Pascall Sieve Shaker containing Endecott test sieves (425, 355, 250, 150 μm). Samples of the mix were placed on the 425 μm sieve and shaken for 5, 30 and 90 min. Both the particle weight and prednisolone distribution were determined. For sieves below 425 μm, the whole of the sample was

used in the prednisolone analysis; for the bulk of the mix on the 425 μm sieve, 5×100 mg samples were combined and used for the analysis.

Results

Mixing studies

Prednisolone (1%) was mixed with the lactose–starch granules. The mixing profile of coefficient of variation (CV) of the prednisolone content versus time (Fig. 1) indicated a satisfactory degree of homogeneity even after 5 min mixing. The criteria for effective mixing has been previously discussed (Cook and Hersey, 1974; Crooks and Ho, 1976) with coefficients of variation of less than 5% being satisfactory. The CVs of 3.4, 3.0 and 3.0% at 5, 10 and 20 min included variance due to analytical method and sampling and therefore indicated excellent prednisolone homogeneity within the mix. A microscopic examination of the mix revealed that a true interactive system existed with the micronized drug particles adhering to the larger carrier granules.

The ternary components, talc and starch were mixed with the prednisolone–granule interactive mix and samples taken using a sampling thief at 5, 10 and 30 min for homogeneity evaluation. Two concentrations of talc (1 and 5%) were used. These concentrations were chosen as they are both realistic in terms of lubricant concentrations and represent amounts which are, at least theoretically, below and above the monolayer saturation of the granule surface (Table 1). While the ternary mixing profile for added talc (Fig. 2) showed a slight decrease in homogeneity between the 5 and 30 min mixing times (i.e. F-test; $P = 0.05$–0.02), there was little difference between the homogeneity of the initial prednisolone–granule mix and the final ternary mix (F-test; $P = 0.05$). In addition, the CVs were always below 5%.

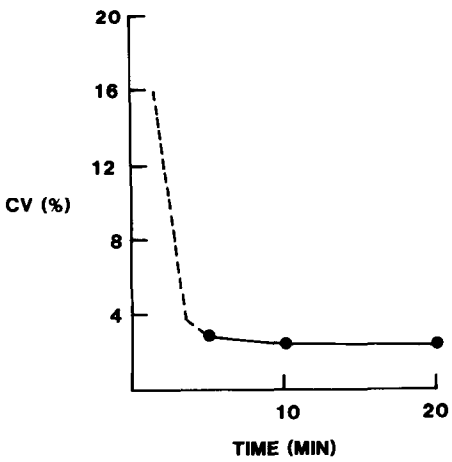

Fig. 1. The mixing profile for micronized prednisolone (1%) and lactose–starch granules (425–850 μm).

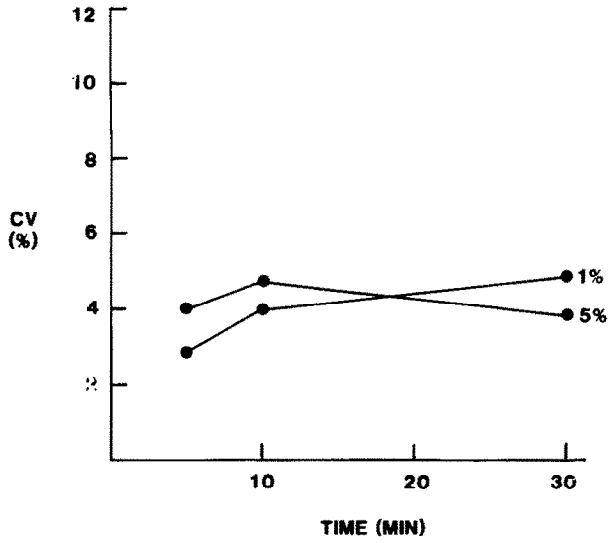

Fig. 2. The effect of added talc on the homogeneity of the prednisolone–granule interactive mix.

Four concentrations of starch were added between 1 and 20%. The concentrations of starch were chosen to allow comparison with the added talc (1 and 5%) and also to be realistic in terms of an added disintegrant (10 and 20%). The ternary mixing profile for added starch (Fig. 3) exhibited different behaviour depending on concentration. The addition of 1% starch caused an increased CV with time (CV = 7.1%

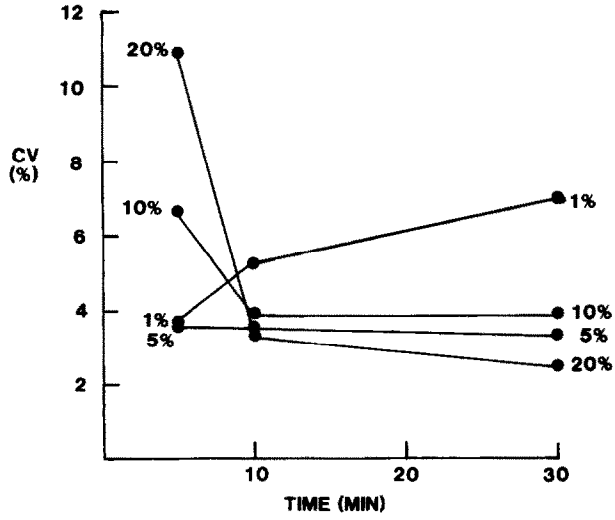

Fig. 3. The effect of added starch on the homogeneity of the prednisolone–granule interactive mix.

TABLE 1

DEGREE OF SURFACE SATURATION OF THE CARRIER FOR THE PREDNISOLONE–GRANULE AND PREDNISOLONE–GRANULE–TALC INTERACTIVE SYSTEMS

Material adsorbed	Degree of surface saturation [a] (%)	
	alone	ternary mix
prednisolone	39	–
talc 1%	22	61
talc 5%	110	149

[a] Calculated from a knowledge of the particle number, $6/\pi\, d_{vn}^3 \rho$, of each component in the mix and the theoretical number of particles per granule for each material to cause surface saturation [$4d_g^2/d_p^2$, where d_g = granule diameter and d_p = adsorbed particle diameter (Hersey, 1975)].

at 30 min mixing); the addition of 5% starch caused little change in CV with time, while the addition of the higher percentages of starch (10 and 20%) both showed poor initial homogeneity which improved with time to give satisfactory homogeneity. At the end of the mixing period (i.e. 30 min), only the homogeneity of the 1% ternary starch mix was significantly different from the original homogeneity of the prednisolone granule mix (F-test; $P < 0.001$).

Segregation studies

The mixes were subjected to segregation conditions by vibrating the powder mixes using the Pascall sieve-shaker. The method allowed the determination of the weight and prednisolone content of powders in several sieve fractions below 425 μm. The conditions experienced by the powders during segregation were considered to be harsh with the low frequency of vibration (200 Hz approx.) and high acceleration (of the order of 100 $m \cdot s^{-2}$) being conditions known to cause severe segregation (Staniforth and Rees, 1982; Staniforth and Rees, 1983).

The results of the segregation studies of the prednisolone–granule, prednisolone–granule–talc and prednisolone–granule–starch mixes are shown in Tables 2 and 3. The prednisolone–granule interactive mix showed good stability to the segregating conditions. Little constituent segregation was evident with only 0.6% of prednisolone being detected in the < 150 μm fraction after 90 min of segregation. A reduction in prednisolone associated with the granule fraction (> 425 μm) occurred with time, i.e. 96.9–92.8% after 90 min of segregation. During the segregation studies carrier comminution occurred (Table 2) with subsequent loss of prednisolone from the larger granule fraction. However, the prednisolone still remained associated with the comminuted carrier particles.

The addition of talc to the preformed ordered mix caused some decrease in prednisolone of the > 425 μm granule fraction during segregation, e.g. for 1% and 5% added talc the prednisolone content associated with this particle size fraction decreased to 88.8 and 79.2%, respectively, in comparison with 92.8% for the prednisolone–granule mix after 90 min segregation. Careful examination of the drug distribution in the prednisolone–granule and talc–prednisolone–granule ternary

TABLE 2

PREDNISOLONE AND WEIGHT DISTRIBUTION [a] OF POWDER IN THE SUB-GRANULE SIZE RANGE DURING SEGREGATION OF THE PREDNISOLONE–GRANULE AND PREDNISOLONE–GRANULE–TALC MIXES

Sieve fraction (μm)	Prednisolone–granule			Prednisolone–granule–talc					
				1%			5%		
	5 min [b]	30 min	90 min	5 min	30 min	90 min	5 min	30 min	90 min
> 425	96.9(97.7)	95.7(96.7)	92.8(96.1)	95.8(97.4)	91.2(94.2)	88.8(94.2)	91.9(93.9)	91.4(93.8)	79.2(86.3)
355	2.6(1.9)	3.0(2.4)	4.7(2.6)	2.0(1.4)	5.3(3.9)	7.6(4.4)	3.8(2.9)	5.4(4.2)	11.8(8.1)
250	0.4(0.3)	0.4(0.4)	1.4(0.8)	1.3(0.8)	2.0(1.2)	2.0(1.0)	2.3(1.8)	1.9(1.4)	4.5(2.9)
150	0(0.1)	0.3(0.3)	0.5(0.3)	0.4(0.2)	0.8(0.5)	0.9(0.5)	1.4(1.0)	0.3(0.2)	1.8(1.1)
< 150	0(0)	0.6(0.3)	0.6(0.3)	0.5(0.1)	0.7(0.3)	0.7(0.3)	0.6(0.5)	1.0(0.4)	2.7(1.6)

[a] Weight distribution shown in brackets.

[b] Segregation time.

TABLE 3

PREDNISOLONE AND WEIGHT DISTRIBUTION [a] OF POWDER IN THE SUB-GRANULE SIZE RANGE DURING SEGREGATION OF THE PREDNISOLONE–GRANULE–STARCH MIXES

Sieve fraction (μm)	Prednisolone–granule–starch											
	1%			5%			10%			20%		
	5 min [b]	30 min	90 min	5 min	30 min	90 min	5 min	30 min	90 min	5 min	30 min	90 min
> 425	93.7(97.5)	93.3(95.7)	84.6(92.4)	90.6(95.5)	81.4(90.0)	78.4(90.3)	83.0(91.1)	75.5(87.6)	62.9(80.3)	61.7(79.0)	53.1(73.6)	50.4(71.0)
355	1.8(1.4)	4.8(3.4)	6.3(4.4)	3.0(2.3)	7.1(5.8)	6.1(4.9)	4.4(3.6)	5.7(4.9)	8.3(7.4)	3.3(3.2)	4.5(4.7)	5.1(5.4)
250	1.1(0.8)	1.0(0.7)	2.5(1.5)	1.2(0.9)	2.7(2.0)	2.2(1.5)	2.1(1.6)	2.2(1.8)	4.8(4.1)	1.5(1.5)	1.9(1.8)	2.3(2.2)
150	0.2(0.1)	0(0.1)	1.7(1.0)	0.3(0.3)	0.5(0.4)	0.6(0.3)	1.1(0.8)	1.2(0.8)	2.3(1.7)	1.3(1.0)	1.4(1.2)	1.9(1.6)
< 150	3.2(0.3)	1.0(0.1)	4.9(0.8)	4.9(1.1)	8.3(1.8)	12.7(2.9)	9.4(3.0)	15.4(4.8)	21.7(6.5)	32.2(15.3)	39.1(18.7)	40.4(19.8)

[a] Weight distribution shown in brackets.

[b] Segregation time.

systems revealed that, only in the 5% talc ternary system and only after harsh segregation conditions (i.e. 90 min segregation) did any significant amount of prednisolone occur in the lower particle size granule fractions. For example, 2.7% of prednisolone was found in the granule fraction < 150 μm after 90 min of segregation compared with between 0 and 1% for every other segregating condition in Table 2. While some displacement of the prednisolone occurred from the > 425 μm granule fraction with the addition of talc, the displaced prednisolone, for most conditions in Table 2, was associated with the higher particle size fractions, e.g. the prednisolone content of the granules greater than 250 μm varied between 98.0 and 100% for all mixes with the exception of 5% talc ternary mix which had decreased to 95.5% after 90 min of segregation.

The addition of starch to the preformed prednisolone–granule mixes produced segregation behaviour which differed markedly to that of the talc ternary mixes (Table 3). The presence of even small amounts of starch caused both significant decreases in prednisolone content in the > 425 μm fraction and increased the prednisolone in the fine fraction (< 150 μm) even under mild segregation conditions. For example, after 5 min segregation, the addition of 5% starch reduced the prednisolone content to 90.6% in the > 425 μm fraction and increased the prednisolone in the fine fraction (< 150 μm) to 4.9%; the addition of 20% starch under the same conditions caused almost a 40% prednisolone loss from the original granules with over 30% being associated with the fine particle size range. Harsher segregation conditions produced even more pronounced effects on all the starch ternary mixes. Table 3 shows that the degree of segregation obtained at each time increases with increased starch concentration.

The weight distribution data obtained during the segregation studies (Tables 2 and 3) reinforced the different behaviour of the ternary mixes. The starch ternary system (1 and 5%) under all conditions of segregation produced distributions richer in fine material, e.g. the amount of material in the < 150 μm fraction was between 2 and 3 times greater for the starch ternary system than for that of talc.

Discussion

The results indicated that the starch and talc ternary systems differed during both the mixing and segregation studies. Talc, added to the preformed interactive mix, behaved cohesively, becoming adsorbed on the adhesion unit interface. Confirmation of this behaviour was seen in the scanning electron micrograph of the talc (5%)–ternary system (Fig. 4A and B). Even in these high talc concentrations, the cohesive nature of the talc was evident; the particles were widely distributed as a dense network over the granule surface. The behaviour of the talc in this sytem was similar to that of magnesium stearate in a prednisone–lactose–granule interactive system (Stewart, 1981). While the prednisolone content of the original carrier fraction became slightly depleted under segregating conditions, the drug still remained associated with the larger carrier fractions. Under harsh segregation and conditions of multilayer talc adsorption, (i.e. 5% added talc), some prednisolone was

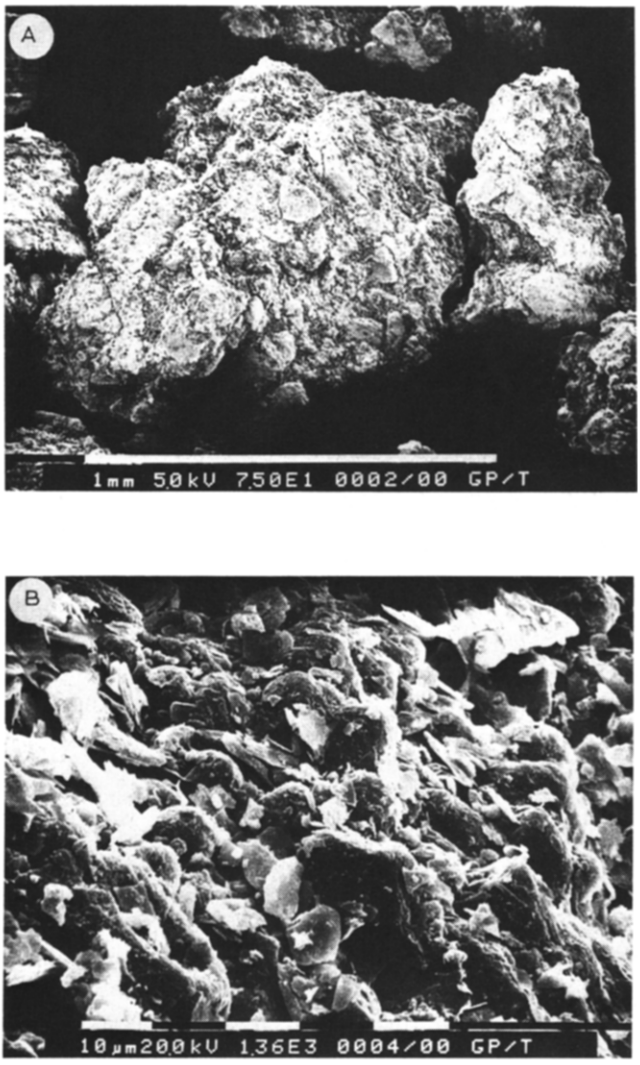

Fig. 4. Scanning electron micrographs of the talc–prednisolone–granule ternary mixture. A: adhesion unit (magnification ×115). B: adhesion unit surface (magnification ×2100). C: dislodged talc aggregate (magnification ×2400).

found in the lower particle fractions. The larger more weakly held talc particles, under these conditions, were dislodged from the granule carrying with them small amounts of prednisolone. Fig. 4C shows such a segregated particle (or aggregate) with what appears to be drug particles attached. It was not possible to identify these small particles adsorbed to the talc aggregate using the electron microprobe since the atomic weight of the elements of prednisolone (C, HandO), was too low; however, chemical analysis during the segregation studies showed prednisolone to be associ-

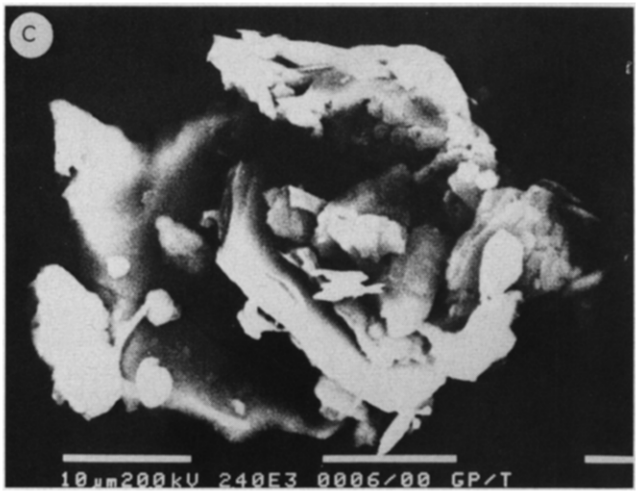

Fig. 4 (continued).

ated with these particle fractions. The cohesive behaviour of the talc with little change in the prednisolone distribution was consistent with the ternary mixing profile (Fig. 2) which showed no significant change in homogeneity in comparison with the homogeneity of the initial prednisolone–granule mix.

Starch did not interact with the preformed prednisolone–carrier adhesion units to the same extent as talc. Fig. 5A shows the effect of the addition of 5% starch, some starch particles can be seen on the carrier surface but many were not adsorbed and exist as small aggregates within the mix. The segregation studies illustrated dramatically the ability of the prednisolone to be redistributed from the adhesion units to the fine particle fraction (i.e. < 150 μm). Comparative examination of 1% and 5% ternary systems after 90 min segregation showed that approximately 5–7 times more prednisolone occurred in the fine granule fraction (< 150 μm) for starch than for the talc ternary system. The prednisolone in the fine granule fraction was associated with the starch particle or aggregates (Fig. 5B). The presence in the mix therefore of large prednisolone–carrier and fine prednisolone–starch adhesion units present conditions conducent to severe adhesion unit segregation. Thus, two distinct segregation phases can be seen in the starch ternary mix: (a) redistribution of the prednisolone between the original carrier and the added ternary component during mixing; and (b) adhesion unit segregation of the original carrier–prednisolone and newly formed starch–prednisolone adhesion units under segregation conditions.

The effect of the initial redistribution of prednisolone is seen in the early stages of the starch ternary mixing profile (Fig. 3). The high CVs at 5 min for 10 and 20% added starch reflected the non-homogenous mixture of the added starch and the prednisolone adhesion units. Drug homogeneity increased as the redistribution proceeds. The cause of the significant decrease in homogeneity for 1% added starch was unknown but may reflect the difficulty in the random mixing of the small

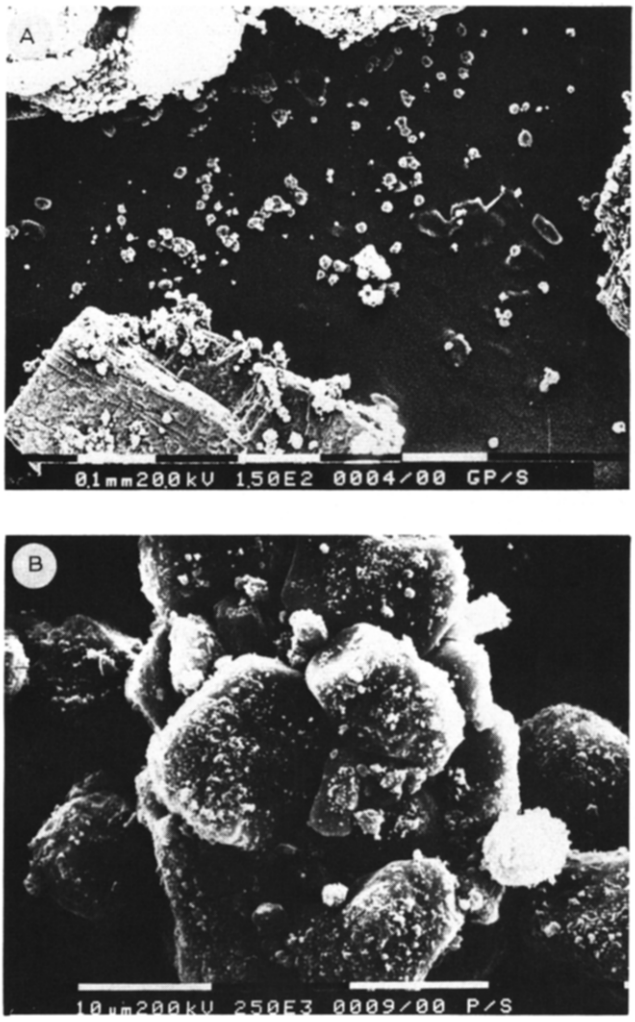

Fig. 5. Scanning electron micrograph of the starch–prednisolone–granule ternary mixture. A: adhesion units and separated starch particles (magnification ×150). B: separated starch aggregate (magnification ×2500).

proportion of starch–prednisolone ordered units with the larger original prednisolone–granule ordered system.

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