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Preparation of Drug-Diluent Hybrid Powders by Dry Processing

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Abstract—New hybrid powders have been produced by the dry processing of six drugs (oxyphenbutazone, prednisolone, theophylline, indomethacin, phenacetin and aspirin), with potato starch used as a core material, by means of an electric mortar and a powder suface reforming system designed to produce hybrid powders. The hybrid powders obtained immediately after production differed in their structure from interactive mixtures. With the hybrid powders the drug was spread on the surface of the core particle by friction and collision that occurred in the dry process, but with interactive mixtures the drug simply adhered as intact particles to the surface of diluent particles. Scanning electron microscopy and powder X-ray diffractometry indicated that the mechanochemical phenomenon was essential for the production of the hybrid powders. With time, a shape change in the adhering drug was observed as a relaxation process took place, with recrystallization resulting from the release of accumulated energy. The change with time might depend upon the method of producing powders and the physical properties of the drug used, e.g. the smooth layer of indomethacin produced by the powder surface reforming system reverted to fine particles tightly adhering to the starch surface, though no change was observed with prednisolone.

The concept of 'particulate design', which treats a particle as a unit, has attained considerable importance in the manufacture of solid pharmaceuticals. The addition of this new function to a particle has been thought necessary to augment the quality of solid pharmaceuticals. Although the wet process is the one mainly used in the manufacture of solid pharmaceuticals, it requires supplementary equipment to dry products and to recover solvents, this increases overheads and solvent residues may be present. Therefore, the dry process is to be preferred to the wet process, where possible.

In the production of a new functional particle for the purpose of augmenting the quality of solid pharmaceuticals, phenomena observed in the dry processing of a drug, diluent, lubricant and other pharmaceutical powders are important. For instance, specific mixed states produced by dry mixing of fine and coarse particles have been reported by Hersey (1975). He found that when large differences in particle size and particle interaction exist between the two types of paticles, the fine particles adhered to the surfaces of coarse particles, to give specific mixed states which he called an 'ordered mixture' or for which the form 'interactive mixture' has been preferred by Egermann (1983). The interactive mixture was suggested as having potential advantages for producing high-quality pharmaceutical powders. McGinity et al (1985) and Nyström & Westerberg (1986) reported that interactive mixtures prepared by the mixing of a less-soluble drug and other large particles gave high dissolution rates. Improvement of drug dissolution rate by the formation of interactive mixtures was proved to be caused by an increase in the surface area exposed to the dissolution medium (Nyström & Westerberg 1986). Westerberg et al (1986) also reported that the drug release rate from interactive mixtures was dependent on the wettability and the solubility of carrier particles. Powder segregation, which may occur during handling, is a serious problem in a situation where even minor changes in the degree of powder mixing could have a significant influence on the bioavailability of pharmaceuticals. Interactive mixtures, where fine drug particles adhere to larger particles with an interparticle force strong enough to prevent the breakdown of interactive units, showed no significant segregation tendency.

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However, the intensity of the interparticle force necessary to attain interactive mixing depends on the physical and physicochemical properties of fine and coarse particles (Staniforth & Rees 1982). Consequently, a hybrid powder composed of carrier particles and a drug adhering to them needs to be produced. We have reported on hybrid powders produced from aspirin and potato starch by dry processing with a centrifugal rotating mixer and found that the hybridization accelerated aspirin dissolution (Ishizaka et al 1988).

We now describe hybrid powders produced from six drugs and a diluent by dry processing using two other devices.

Materials and Methods

Materials

Potato starch was used as a core material. Six drugs (oxyphenbutazone, prednisolone, theophylline, indomethacin, phenacetin and aspirin) were used for hybridization. The particle size of theophylline, phenacetin, and aspirin was reduced to less than 100 μm by pulverizing with an electric mortar (Model ANM-1000, Nitto Kagaku Co. Ltd., Nagoya, Japan). Micronized fractions of oxyphenbutazone, prednisolone, and indomethacin were used without further pulverization.

A thermal analysis system which consisted of a thermal analysis station (Model SSC-5000, Seiko Instrument Co. Ltd., Tokyo, Japan) and a differential scanning calorimeter

unit (Model DSC-100, Seiko Instrument Co. Ltd., Tokyo, Japan) was used to measure the thermal properties of drugs. DSC experiments were carried out over a temperature range from 50°C below to 50°C above the melting point of the drug, with a heating rate of 2°C min^{-1}. The DSC experiment for each drug was performed more than three times, and mean values were reported. The melting points and the heats of fusion of the drugs were reproduced within $\pm 1{\cdot}1\%$ and $\pm 3{\cdot}0\%$, respectively, for different samples.

Hybridization of drug with potato starch

A 5% (w/w) mixture of drug in potato starch was gently made in a beaker and 20 g was processed for 60 min in the electric mortar (Method I). Two powder surface reforming systems (Nara Hybridization System Models NHS-0 & NSH-1, Nara Machinery Co. Ltd., Tokyo, Japan) which were designed for producing hybrid powers were also used for hybridization (Method II). A schematic diagram of the machines is shown in Fig. 1. The powder mixture from the powder inlet is carried on an air stream generated by the blades rotating at high speed, and circulates in the machine through the cycle tube. In the machine, particles collide with other particles, the blades, and the inner surface of the machine. The temperature in the machine is measured with a thermometer in the cycle tube. The inner surface of the hybridization chamber is cooled by a jacket through which cold water is circulated. Twenty grams and 100 g of the drug-starch mixtures were processed for 5 min with NHS-0 and NHS-1, respectively, with outer edges of the blades rotating at 80 ms^{-1}, except for oxyphenbutazone, when the rotation was 60 ms^{-1}. The resultant hybrid powders were kept in a sealed container and protected from light.

The surface appearance of the resultant powders was observed with a scanning electron microscope (Model JSM-T20, JEOL, Tokyo, Japan). The extent of the crystallization of the drugs in the resultant powders was evaluated with an X-ray diffractometer (Model Gigerflex-2012, Rigaku Denki Co. Ltd., Tokyo, Japan). Physical mixtures were used for comparison with the hybrid powders and were prepared by gentle mixing of known quantities of a drug, potato starch and 10% lithium fluoride as an internal standard. They were evaluated by X-ray diffractometry, and a calibration curve was obtained by plotting the ratio of the main peak area of drug to that of lithium fluoride against the weight fraction of drug. Each experiment was performed in triplicate, and mean values were used. Reproducibility was adequate. The correlation coefficient of the calibration curve was 0·998. The extent of drug cystallization was calculated using this calibration curve.

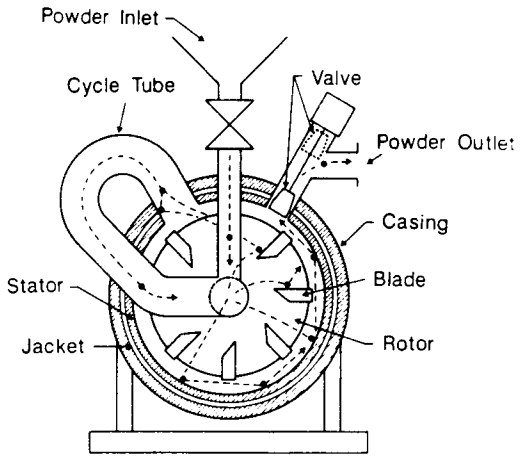

FIG. 1. A schematic diagram of the machine used for Method II.

Results and Discussion

Scanning electron micrographs of hybrid powders obtained immediately after producing by Method I are shown in Fig. 2. The drugs were fixed on the surface of the starch core by applying physical force with the automatic mortar. The resultant hybrid powders differed from one another in surface appearance. Oxyphenbutazone, prednisolone, theophylline, and indomethacin coated potato starch particles in a layer. The layers of prednisolone, theophylline and indomethacin had sandy surfaces and seemed to be composed of micronized particles and crushed particles, but, the surface of the oxyphenbutazone layer was smooth. As for phenacetin and aspirin, the layers were not found and crushed particles were sparsely observed on the smooth surfaces of starch. Dry processing by Method II also produced hybrid powders in which the drug spread over the starch surface in a layer. Surface appearances of the hybrid powders obtained immediately after being produced are shown in Fig. 3. Though some crushed particles were found on the surfaces, oxyphenbutazone, prednisolone, indomethacin and phenacetin had formed smooth drug layers. A smooth layer and innumerable microvilli-like projections protruding from its surface were observed after the dry processing of theophylline with potato starch. Aspirin formed a sandy layer.

The hybridized state of the drugs could be divided into three groups: (1) that with a layer having a smooth surface, (2) that with a layer having a sandy surface which seemed to be composed of micronized and crushed particles and (3) that in which the crushed particles adhered to the starch surface. When prepared by Method I, oxyphenbutazone was in group 1, prednisolone, theophylline and indomethacin in group 2, and the other drugs in group 3. Ampolsuk et al (1974) reported that digoxin and hydrocortisone could be spread over the surface of lactose particles by frictional pressure. Digoxin and hydrocortisone are certainly in either group 1 or 2. When prepared by Method II, oxyphenbutazone, prednisolone, indomethacin, theophylline and phenacetin were in group 1 and aspirin in group 2.

Judging from the hybridized state of the drugs, they were undoubtedly micronized, fixed to the starch surface and changed into a layer by mechanical forces such as shear stress and impact force during dry processing. Therefore, the hybridized state was probably dependent on the physical properties of the drugs. First, the melting point seemed to play a role in hybridization. In this system, the temperature is increased by a conversion of mechanical energy to thermal energy during hybridization. Oxyphenbutazone, which formed the smooth layer by hybridization, has the lowest melting point. Maximum temperature during the dry processing of the powder surface reforming system, melting point and heat of fusion of each of the drugs are listed in Tables 1 and 2. However, assuming that the hybridized state indicated

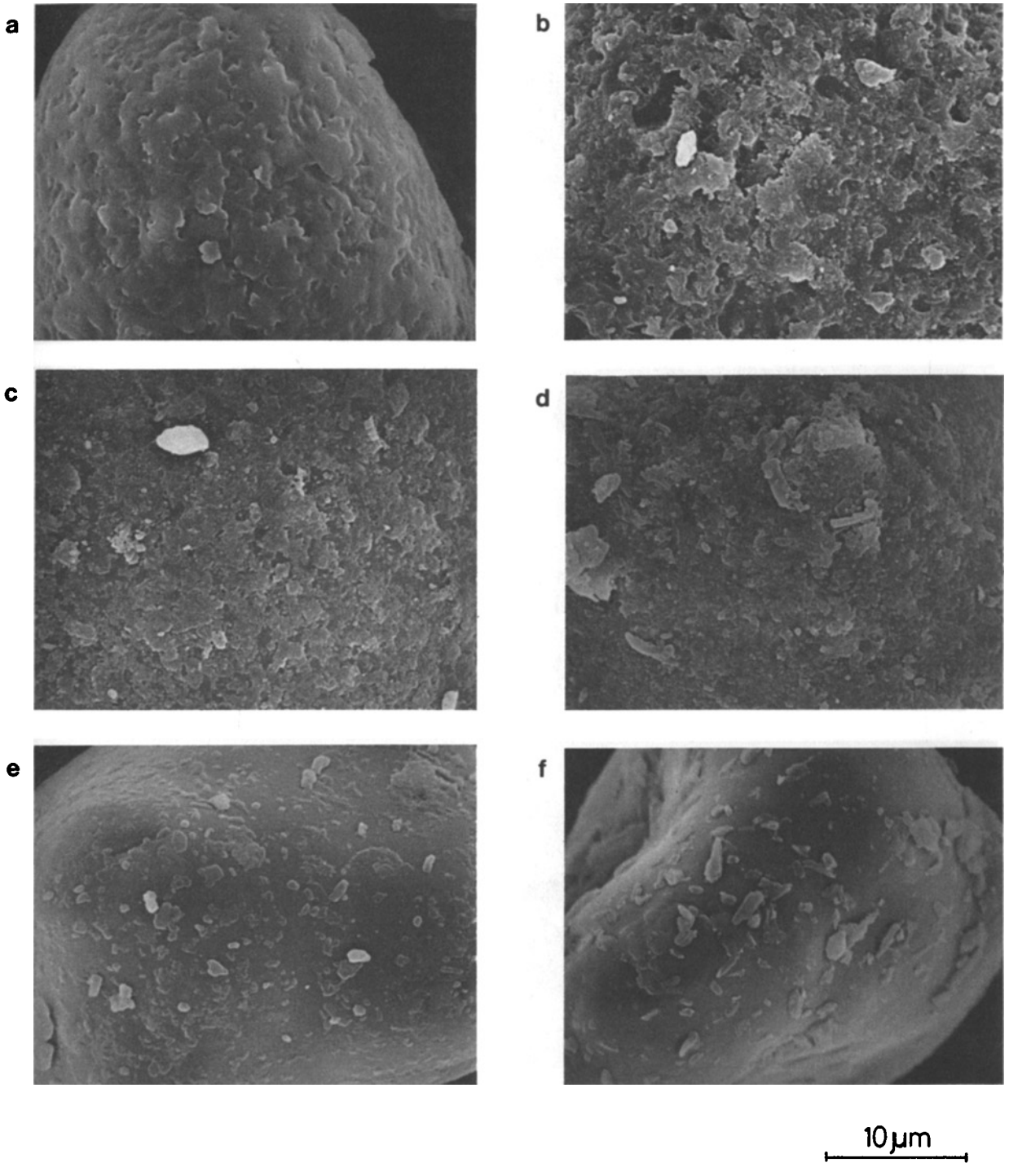

FIG. 2. Scanning electron micrographs of hybrid powders obtained immediately after producing by Method I. a, oxyphenbutazone; b, prednisolone; c, indomethacin; d, theophylline; e, phenacetin; f, aspirin.

how easy a drug could be hybridized with potato starch, and that the intensity of the mechanical force to give a constant weight of each drug was constant, the heat of fusion in mJ mg^{-1} seemed to be related to the hybridized state rather than to the melting point, because the maximum temperatures attained in the process by Method II did not reach the melting points of the drugs. Besides, prednisolone, indomethacin and theophylline, which formed the layers when they were processed by Method I, have melting points higher than those of phenacetin and aspirin which did not form the layers. The order of the drugs in heat of fusion in mJ mg^{-1} was probably the same as that of the hybridized state seen immediately after producing the hybrid powders. A complete, smooth layer must have been obtained when mechanical energy sufficient to disturb the crystal lattice of the drug completely, was imparted to the micronized drug particles on

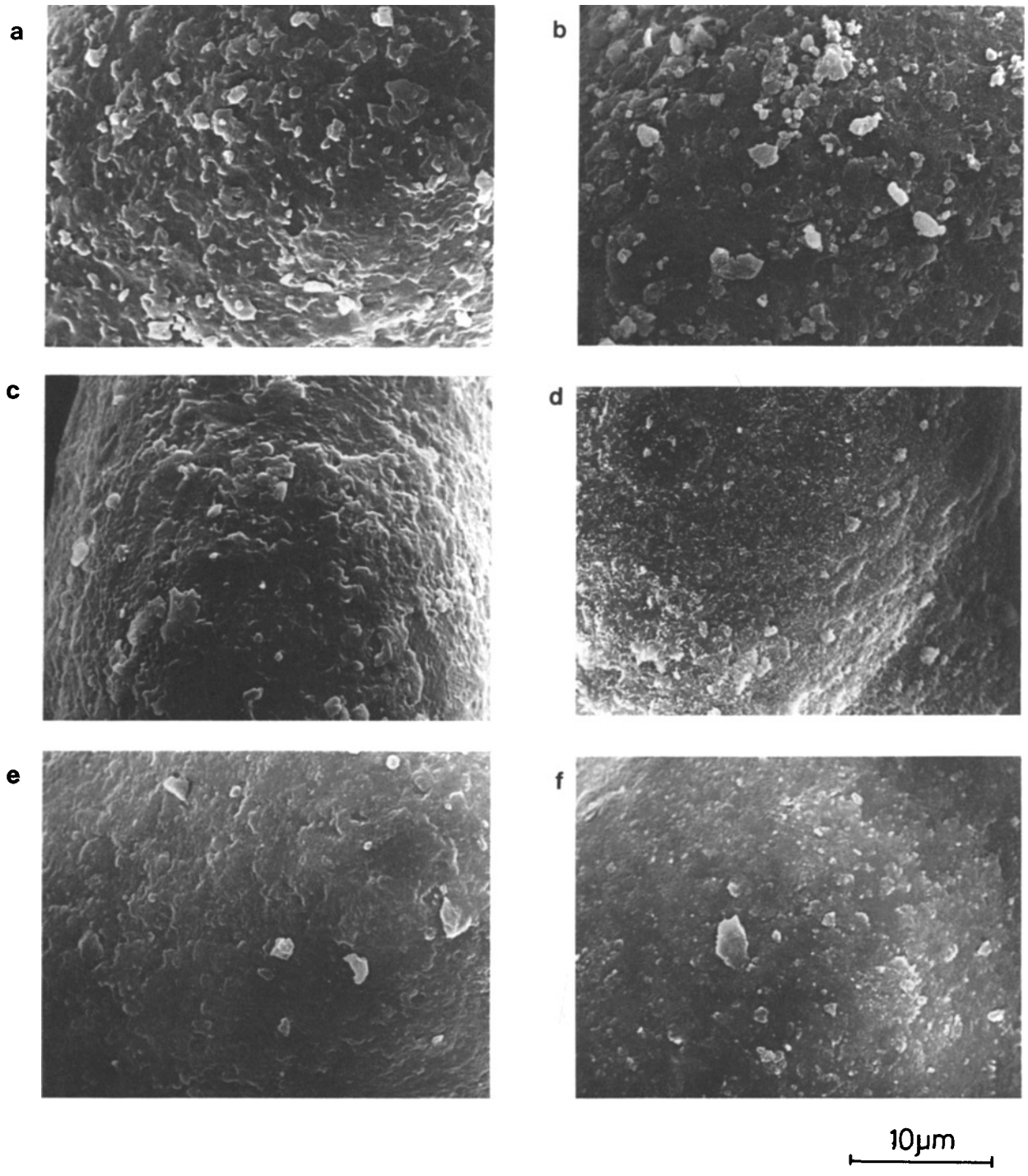

FIG. 3. Scanning electron micrographs of hybrid powders obtained immediately after producing by Method II. a, oxyphenbutazone; b, prednisolone; c, indomethacin; d, theophylline; e, phenacetin; f, aspirin.

the starch surface. Mechanochemical phenomena might have occurred in the hybridization process of drug with potato starch.

A change in surface appearance of some of the hybrid powders was seen by electron microscopy. The hybrid powders kept for 105–108 days are shown in Figs 4, 5. Although the hybrid powder of oxyphenbutazone initially had a smooth layer after being produced by Method I, many particles of approximately 1 μm in diameter were found on the drug layer after 4 days. Thereafter, the number and size of the particles increased with time. The time course of the change depended upon the method used. The smooth layer of oxyphenbutazone produced by Method II split into many pieces over the surface of core particles, these then grew into leaf-like particles. But, after about 100 days, no difference existed between the hybrid powders produced by Method I and Method II. With indomethacin, the surface appearance of the hybrid powder produced by Method I changed

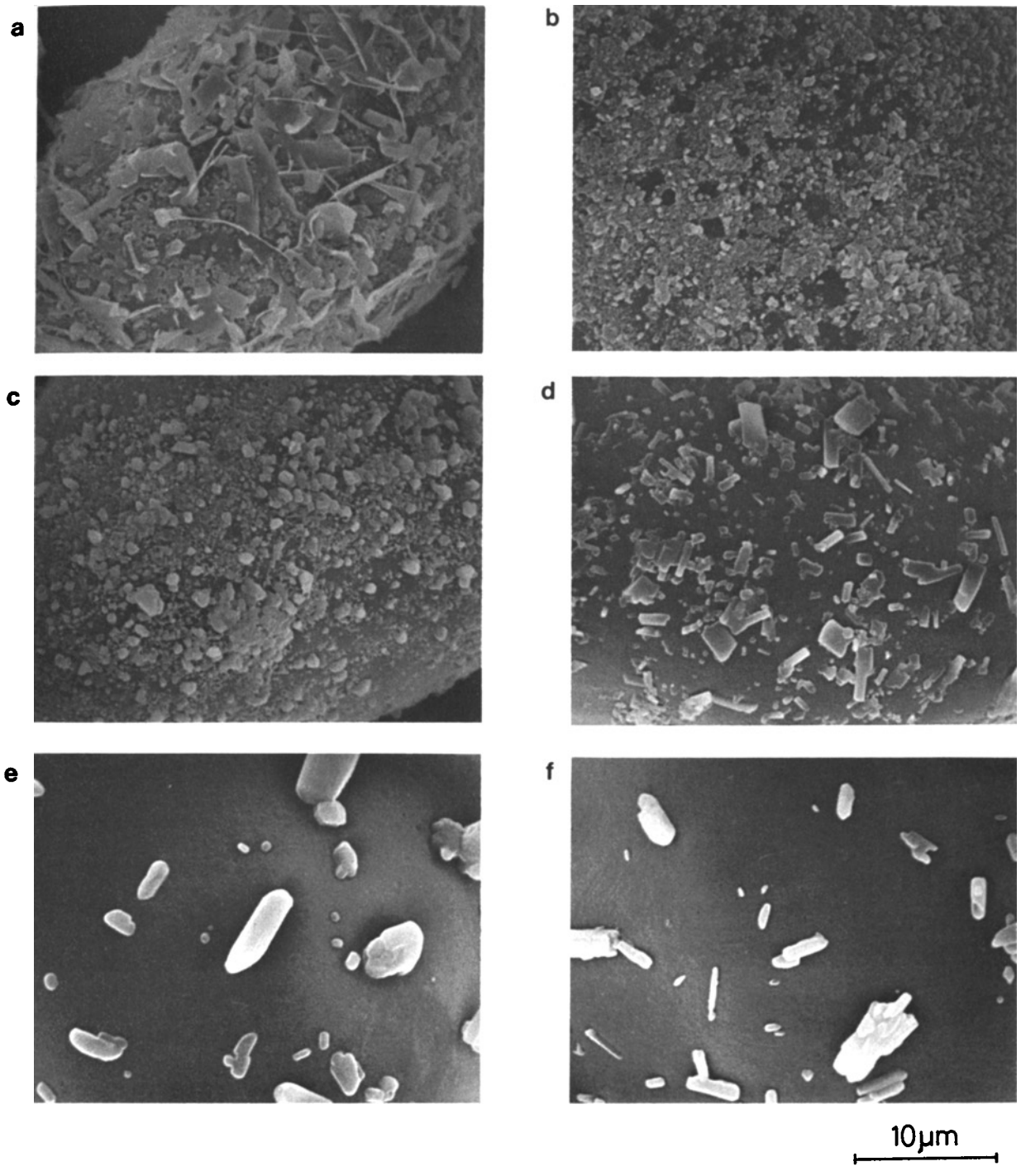

FIG. 4. Scanning electron micrographs of hybrid powders produced by Method I. After 106–108 days. a, oxyphenbutazone (108 days); b, prednisolone (108 days); c, indomethacin (107 days); d, theophylline (107 days); e, phenacetin (106 days); f, aspirin (106 days).

gradually until the 107th day, while with Method II a large number of fine uniform particles had appeared on the surface of the drug layer within 24 h, and the drug layer completely disappeared owing to particle growth after 45 h. The particles grew to be ca 1 μm by the 4th day, and afterwards they did not change. Even when these particles were subjected to vibration by sieving, they could not be detached from the starch surface. The hybrid powder of theophylline produced by Method I, showed a remarkable change. Squarish particles appeared on the drug surface after 3 days and the drug layer had disappeared by the 23rd day. When theophylline was hybridized by Method II, microvilli-like projections, which were seen initially, grew to be needle-like particles, which were quite unlike the squarish particles produced by Method I. The crushed particles of phenacetin and aspirin found in the hybrid powders produced by

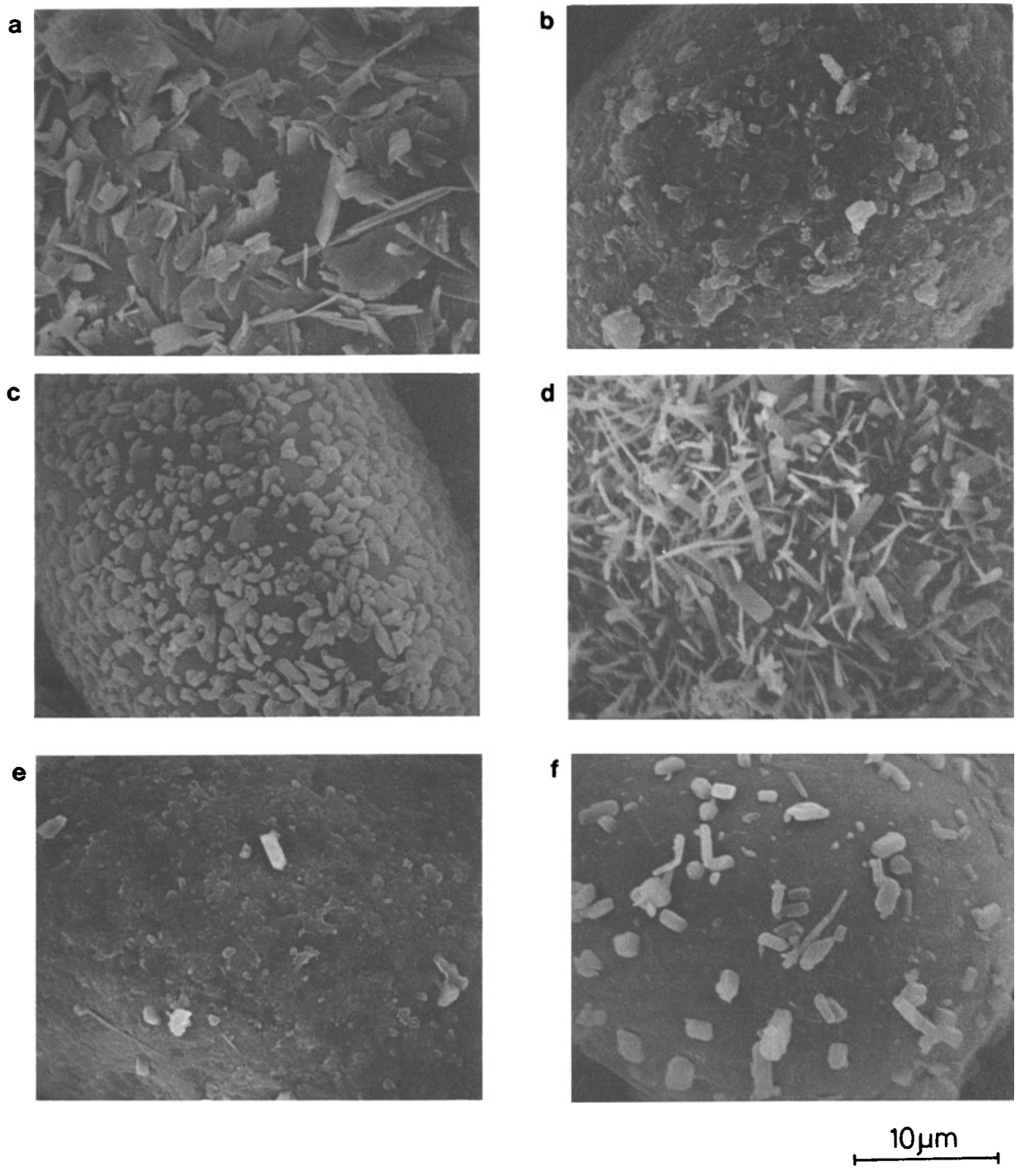

FIG. 5. Scanning electron micrographs of hybrid powders produced by Method II. After 105 days. a, Oxyphenbutazone; b, prednisolone; c, indomethacin; d, theophylline; e, phenacetin; f, aspirin.

Method I grew and returned to their original shapes, they then gradually faded from the starch surface. A phenacetin layer was observed even after 105 days in the hybrid powder produced by Method II, though a small number of rod-like particles had appeared on the 23rd day. Aspirin processed by Method II, showed squarish particles on the drug surface after 22 h, and the drug layer completely disappeared by 40 h. With prednisolone, a part of the drug layer produced by Method I split into fine particles after 105 days, while there was no change in the hybrid powder produced by Method II.

The shape change of the drugs adhering on the starch surface seemed to be evidence that the mechanochemical phenomenon had occurred during the hybridization process. In general, the mechanical energy produced in such processes as mixing, pulverizing and grinding, disturbs the crystal lattice and structure of a solid, and allows it to change from

Table 1. Maximum temperature during hybridization process with the powder surface reforming systems NHS-0 and NHS-1.

Drug	Revolution speed ($m\ s^{-1}$)	Temperature (°C) NHS-0	NHS-1
Phenacetin	80	52	—
Aspirin	80	50	—
Theophylline	80	49	53
Prednisolone	80	46	45
Indomethacin	80	53	58
Oxyphenbutazone	60	29	38

Table 2. Melting point of drugs.

Drug	m.p. (°C)	Heat of fusion ($mJ\ mg^{-1}$)	($KJ\ mol^{-1}$)
Phenacetin	134·1	173·6	31·1
Aspirin	131·4	159·5	28·7
Theophylline	270·6	140·6	25·3
Prednisolone*	—	—	—
Indomethacin	158·6	100·5	36·0
Oxyphenbutazone	94·3	92·5	31·7

* Decomposed at 235°C (JP XI).

the crystalline to the amorphous state. Accumulation of a part of the mechanical energy in the solid particles increases the internal energy, and most of the accumulated energy is released quickly to give a metastable state. Hence, the drugs adhering to the starch surface forming smooth layers are considered to be in the metastable state. Their changes in surface appearance with time probably means a relaxation process with recrystallization. Fig. 6 shows the X-ray diffraction profiles of oxyphenbutazone as a physical mixture and as the hybrid powder produced by Method II. The

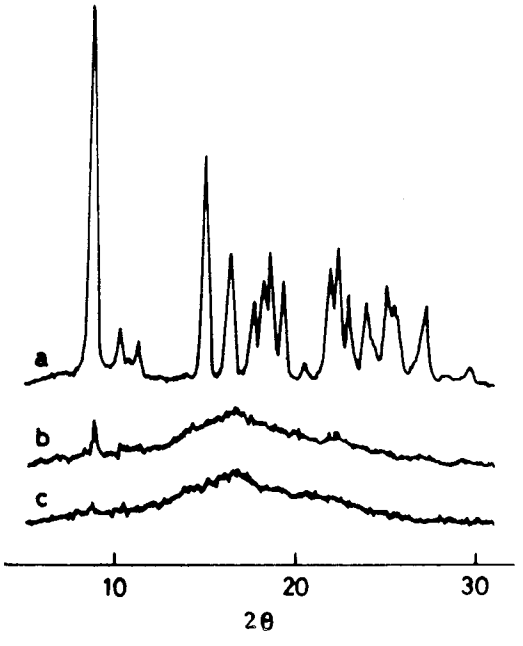

FIG. 6. X-ray diffraction profiles of oxyphenbutazone, a physical mixture, and a hybrid powder. a, oxyphenbutazone; b, a physical mixture (5·0% oxyphenbutazone–potato starch); c, a hybrid powder (8·5% oxyphenbutazone–potato starch).

Table 3. Change in the degree of oxyphenbutazone crystallinity with time.

Time	Degree of crystallinity (%)
4 days	12·8
1 month	18·1
7 months	43·3

profile of oxyphenbutazone was identical with that reported by Matsuda & Kawaguchi (1986), i.e. the oxyphenbutazone was in the monohydrate form. Physical mixing with potato starch made it impossible to detect the peaks of oxyphenbutazone, except the main peak observed at 8·8° (2θ). A broad peak in the region from 10° to 28° is due to potato starch. The main peak was also detected for the hybrid powder (8·5% drug), and its diffraction angle did not shift. Compared with the data reported by Matsuda & Kawaguchi (1986), it was evident that the hybridization did not transform oxyphenbutazone from the monohydrate form to other crystalline forms. But, the intensity of the main peak appearing in the X-ray diffraction profile of the hybrid powder was apparently less than that shown in the profile of the physical mixture (5·0% drug). Similar results were obtained for prednisolone, indomethacin and theophylline. The extent of crystallization of oxyphenbutazone in the hybrid powders was examined (Table 3). A large portion of the drug in the hybrid powder immediately after its production was in the amorphous state, and then the quantity of crystals gradually increased with time. Powder X-ray diffractometry clearly indicated that the shape change of the drug adhering to the starch surface was a relaxation process with recrystallization.

Hybrid powders could be produced by dry processing of a variety of drugs with potato starch, using an electric mortar or a powder surface reforming system. Scanning electron microscopy and powder X-ray diffractometry revealed that the mechanochemical phenomenon was indispensable for the production of hybrid powders. The technique could be useful in the manufacture of pharmaceuticals. Thiel et al (1986) granulated interactive mixtures using an aqueous polymer solution in a fluidized bed to prevent adhesion unit and constituent segregation; they obtained batches of tablets in which the contents of drug were uniform and in good condition. The hybrid powder approach described would seem to have an advantage over the interactive mixture, since a drug adheres to coarse particles more tightly in the hybrid powder. Such powders, immediately after being produced and after a relaxation period appear superior to the interactive mixture. It is possible that the hybrid powder could be applied as an intermediate in the manufacture of pharmaceuticals requiring high homogeneity.

The mechanochemical phenomenon observed has latent possibilities for the manufacture of solid phamaceuticals. For example, indomethacin particles of ca 1 μm in diameter can be easily obtained.

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