International Journal of Pharmaceutics, 78 (1992) 95–102

IJP 02593

Research Papers

Mechanism of caking of granules containing oily materials

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(Received 28 March 1991)
(Modified version received 28 June 1991)
(Accepted 10 July 1991)

Key words: Caking; Oily material; Fracture strength; Heat treatment; Solidification; Penetration; Granule surface

Summary

Caking of granules containing oily materials was studied. It was found that caking occurred on storage below the melting point of the oily materials and that it was particularly marked for granules with fresh surfaces. However, the caking tendency diminished or disappeared on heat treatment, even in the case of granules with fresh surfaces. The dependence of the penetration rate of oily materials on temperature and the amount of oily materials on the fresh surfaces of granules with or without heat treatment was determined. Direct observation of these surfaces under a stereoscopic microscope was further conducted. Based on these results, a schematic model of the caking of granules containing oily materials was presented: oily materials are present in thick layers on the fresh surfaces immediately after the crushing process, however, heat treatment increases the fluidity of the oily materials and facilitates their penetration into wedges between carrier particles. Thus, heat treatment shows an effective anti-caking action.

Introduction

In most pharmaceutical manufacturing processes, powders or granules are handled in a non-compressed state. Even in this state, some powders or granules tend to undergo caking during storage, which causes several problems in pharmaceutical manufacturing processes.

The influence of environmental humidity or water during storage on their cohesion (Fukuoka et al., 1983; Heng and Staniforth, 1988; Kulvanich and Stewart, 1988), caking (Sauchelli, 1960; Masuzawa, 1970; Down and McMullen, 1985), and anti-caking (Noguchi, 1988) has been reported. Most workers who studied the caking of powders reported it to depend on water content. However, others stated that the cohesive or adhesive force is influenced by temperature (Pilpel and Britten, 1979; Danjo et al., 1982; Malamataris and Pilpel, 1982), showing a maximum at a homologous temperature (ratio of treatment temperature to the melting point) of about 0.9.

On the other hand, the number of pharmaceutical products containing oily materials is growing with increase in many new bioactive substances currently under development such as vitamins, prostaglandins, hormones, etc. However, there have been no reports on the caking of powders or granules containing oily materials. Only Heng

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and Wan (1987) have described a study simply on the physical properties of granules containing polysorbate 80 which is oily but not bioactive.

In the present study, therefore, the effect of temperature on the caking of granules containing oily materials and their mechanism of caking were investigated.

Materials and Methods

Materials

Table 1 lists the physical properties of the oily materials used, which were dl-α-tocopherol (Hoffmann-La Roche Co.), d-α-tocopherol acetate and palmitate (Ajinomoto Co.), castor oil (Kozakai Seiyaku Co.), coconut oil (R. Nagai Co.), polyethylene glycol 400 (PEG 400, Iwai Kagaku Yakuhin Co.) and polysorbate 65 (Kao-Atlas Co.). Lactose (JP-XI grade) that had been passed through an 80 mesh sieve was used. Sucrose (JP-XI grade) that had been pulverized with an atomizer (model A2-W, Fuji Paudal Co.) and passed through a 30 mesh sieve was used. Glass beads were purchased from Toshiba Ballotini Co., and sieved. The fraction of 500–840 μm was used.

Preparation and treatment of granules

After premixing 360 g of both lactose and sucrose for 1 min in a Henschel mixer (model FM-10B, Mitsui Miike Kakoki Co.), 80 g of oily material in the liquid state was poured into the mixer with stirring, and the mixing process then continued for 1 min. Next, 40 g of distilled water was added with stirring and the mixing process continued for another 1 min. The wet mass obtained was extruded through a 1000 μm (preparation A) or 500 μm (preparation B) screen with a basket extruder (model RG-5M, Kikusui Seisaku-sho Co.) and dried at 60 ° C for 60 min in an air through tray drier (Nihon Drying Machinery). The dried granules thus obtained were sieved to obtain granules larger than 840 μm (sample 1A) or 500 μm (sample 1B). Samples 1A and 1B, respectively, then were forced through an 840 μm screen and sieved by a 500 μm screen to obtain the 500–840 μm fraction (samples 2A and 2B). A part of each 500–840 μm fraction was abraded by friction treatment using a twin-shell blender (samples 3A and 3B). Another part of each 500–840 μm fraction was heat treated by warming at 60 ° C for 60 min (samples 4A and 4B).

TABLE 1

Physical characteristics of oily materials

Oily material	Melting point (° C)	Viscosity (cP)			
		15 ° C	30 ° C	40 ° C	60 ° C
dl-α-Tocopherol	below 0	9000			90
d-α-Tocopherol acetate	26–27	15000			120
d-α-Tocopherol palmitate	39–43			240	110
Castor oil	− 20 to − 18	1470			70
Coconut oil	20–28		34		14
PEG 400	4–8	180			20
Polysorbate 65	27–31			123	42

Observation of caking of granules containing d-α-tocopherol acetate

25 g of samples 1A, 1B, 2A, 2B, 3A, 3B, 4A, and 4B were placed in glass bottles and stored overnight at 15 ° C. On the following day, granules were inspected for signs of caking.

Determination of fracture strength for caking of granules

The measurement of fracture strength of granules (preparation A) was carried out using the apparatus shown in Fig. 1. It consists of a handmade 25 mm cube sectional vessel (Fig. 1A). After 5 g of the sample 1A, 2A, 3A, or 4A, had been placed in the vessel, all sides of the vessel were closed by a rubber band. Next, each granule preparation was stored overnight at several temperatures under a constant load of 40 g (Fig. 1B). Caked granules at the base of the vessel were obtained by removing the constant load and opening the sectional vessel. The cake obtained was placed in a petri dish on ice or dry ice to maintain the storage temperature. Subsequently, weights were placed on the cake with the load being increased continuously by 20 g increments (Fig. 1C). The total load with which the cake was fractured was taken as the fracture strength for caking of granules.

Measurement of oily material concentration in cross-section of the glass bead mass

20 g of glass beads (590–840 μm) were mixed with 1 g of oily material containing 2% Sudan III as an indicator in a 50 ml beaker, and 0.5 ml of a 10% aqueous solution of sucrose was added as binder under continuous mixing.

The wet mass, 8.0 g, was placed in the 2.5 cm cube vessel (Fig. 1A) under constant load (40 g) for 10 min and dried at 60 ° C for 60 min in a hot air oven (model DH-41, Yamato Kagaku Co.). After removal of the load, the dried mass was divided into two parts with a razor blade to expose fresh surfaces. One part was cooled for 30 min in a refrigerator (2 ° C) and the other was warmed for 60 min in the oven (60 ° C) before cooling in a refrigerator. The former is a model of sample 2A, and the latter is that of sample 4A.

Then, the first layer (590–840 μm thickness) of the glass bead mass was scraped off from the freshly divided surface of each part treated as described above. The concentrations of Sudan III in the scraped fractions thus obtained were measured spectrophotometrically at 515 nm after dissolved in 10 or 20 ml ethanol.

Observation of cross-sections of glass bead mass

Samples were prepared in a similar manner to the measurement of the concentration of oily material and their cross-sectional characteristics were observed under a stereoscopic microscope (model SMZ-10, Nihon Kogaku Kogyo Co.).

Penetration of oily materials into tapped powder

Penetration of oily materials into tapped powder was determined according to the method proposed by Buckton et al. (1985): 6.6 g of powder (lactose : sucrose = 1 : 1) was placed in a glass test tube and tapped to a pre-determined porosity (0.5). A filter paper disc of suitable diameter was placed on the powder bed. After oily materials containing 2% Sudan III and powder bed had attained each testing temperature (15, 30, 40 and 60 ° C), 0.5 g of an oily material containing 2% Sudan III was poured on the powder bed. The above temperatures were maintained during penetration. The distance of penetration of oily materials was measured using slide calipers after 15, 30, 45, and 60 min.

Determination of viscosities of oily materials

The viscosity of each oily material was determined on a BL viscosimeter (Tokyo Keiki Seizosho Co.) at 15, 30, 40 and 60 ° C.

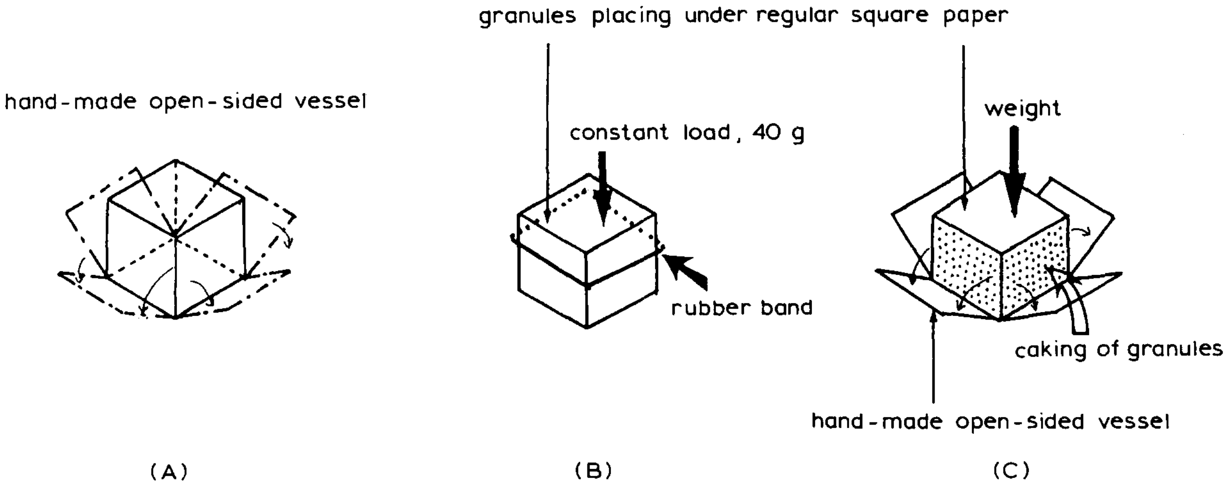

Fig. 1. Apparatus for measuring fracture strength for caking of granules.

Results

Effects of preparation conditions and treatment of granules on caking of granules

The caking tendency of granules (eight samples) containing 10% d-α-tocopherol acetate after overnight storage at 15 °C is listed in Table 2. Parent granules (samples 1A and 1B) did not exhibit caking. Significant caking occurred for granules that had undergone crushing or friction treatment (samples 2A, 3A, and 3B). However, caking was not observed with samples 4A and 4B, which had been heat-treated. Samples 1A and 1B were treated similarly to samples 4A and 4B, the drying process being conducted at 60 °C for 60 min. Thus, heat-treated granules did not exhibit caking.

Samples 2A and 2B displayed marked differences in caking: sample 2A (extruded through 1000 μm) exhibited caking whereas sample 2B (extruded through 500 μm) did not. These samples were obtained by crushing (forcing through) with a 840 μm screen. Preparation A was extruded through a 1000 μm screen, i.e. larger than the screen size (840 μm); therefore, a dried granule may be crushed into many smaller granules and produce several fresh surfaces on crushing (forcing through a 840 μm screen) (sample 2A). However, preparation B was extruded through a 500 μm screen, i.e. smaller than the screen size (840 μm); a dried granule may mostly be passed through a screen and produce a small extent of fresh surface by crushing (forcing through a 840 μm screen).

On the other hand, samples 3A and 3B exhibited caking. The granule surfaces may be scraped and given a fresh surface by friction treatment with a twin-shell blender. These results may indicate that granules having fresh surfaces exhibit caking.

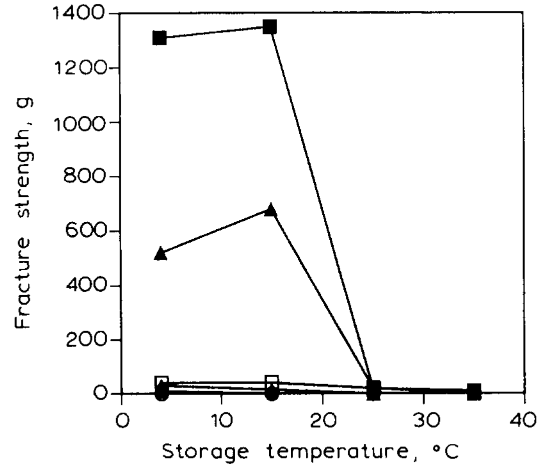

Fig. 2. Fracture strength for caking of granules containing 5% (circles), 10% (triangles), and 15% (squares) d-α-tocopherol acetate. Closed symbols, sample 2A; open symbols, sample 4A.

Fracture strengths for caking of granules

The fracture strengths for caking of samples 2A and 4A containing 5, 10, and 15% d-α-tocopherol acetate are shown in Fig. 2 as a function of storage temperature. The greater the d-α-tocopherol acetate content, the stronger was the fracture strength. The fracture strengths of sample 2A were much greater than those of sample 4A after overnight storage at 2 and 15 °C. However, in the case of storage at 25 and 35 °C, no samples showed caking. With respect to toco-

TABLE 2

Preparation, treatment, and caking tendency of granules containing d-α-tocopherol acetate

	Sample							
	1A	1B	2A	2B	3A	3B	4A	4B
Screen size of extruder (μm)	1 000	500	1 000	500	1 000	500	1 000	500
Size of granules (μm)	> 840	> 500	500 -840	500 -840	500 -840	500 -840	500 -840	500 -840
Treatment			Crush	Crush	Friction	Friction	Heat	Heat
Caking tendency	−	−	+	−	+	+	−	−

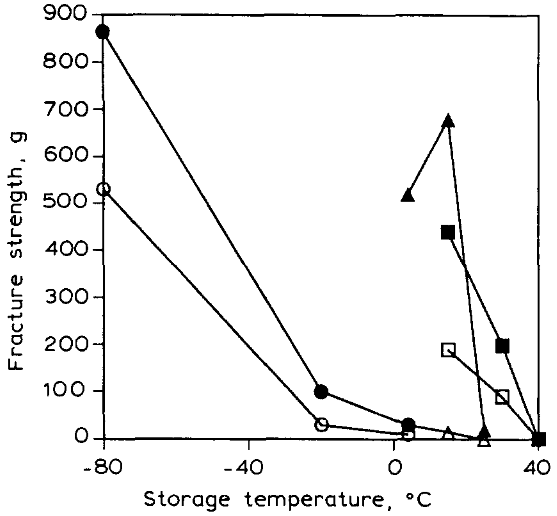

Fig. 3. Fracture strength for caking of granules containing 10% dl-α-tocopherol (circles), d-α-tocopherol acetate (triangles), and d-α-tocopherol palmitate (squares). Closed symbols, sample 2A; open symbols, sample 4A.

pherols, vegetable oils, and surfactants, the fracture strengths of sample 2A were also greater than those of sample 4A (Figs 3–5). None of the samples which had been stored at temperatures higher than the respective melting points of their oily materials (Table 1) exhibited caking. Moreover, in the case of coconut oil, the fracture strengths for caking of granules were weak (Fig. 4).

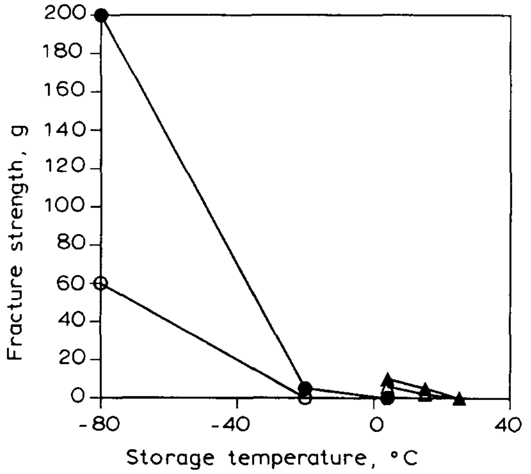

Fig. 4. Fracture strength for caking of granules containing 10% castor oil (circles) and coconut oil (triangles). Closed symbols, sample 2A; open symbols, sample 4A.

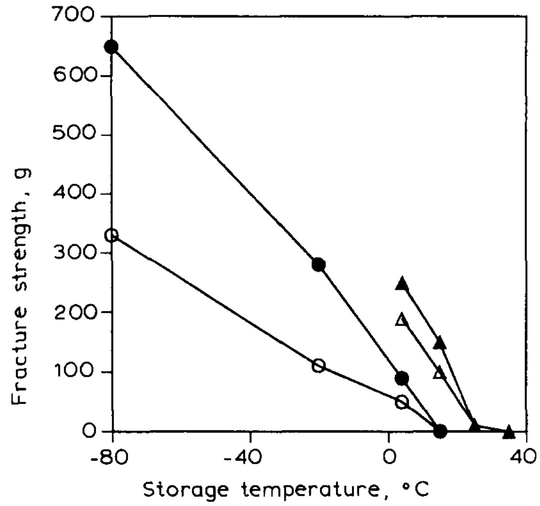

Fig. 5. Fracture strength for caking of granules containing 10% PEG 400 (circles) and polysorbate 65 (triangles). Closed symbols, sample 2A; open symbols, sample 4A.

These results suggest that the caking of granules containing an oily material is correlated with the solidification temperature; this occurs in the case where storage temperature is lower than the melting point of the oily material. The cohesion force of granules is due to such solidification.

Effect of heat treatment on oily material concentration at granule surface

Stereoscopic photomicrographs of cross-sections of a glass bead mass containing 5% d-α-tocopherol palmitate are shown in Fig. 6. Before heating, d-α-tocopherol palmitate remained as a thick layer on the surface of the cross-section of the glass bead mass. In contrast, very little d-α-tocopherol palmitate was observed on the surface after heating and was found mainly in a layer wedged between the glass beads.

Fig. 7 shows the effect of heat treatment on the concentration of Sudan III, which indicates the amount of oily materials in the first layer of glass beads of the divided surface of the mass. The concentrations of Sudan III before heating were higher than those after heating with respect to all oily materials tested. It is therefore evident that the oily materials are present on the surfaces

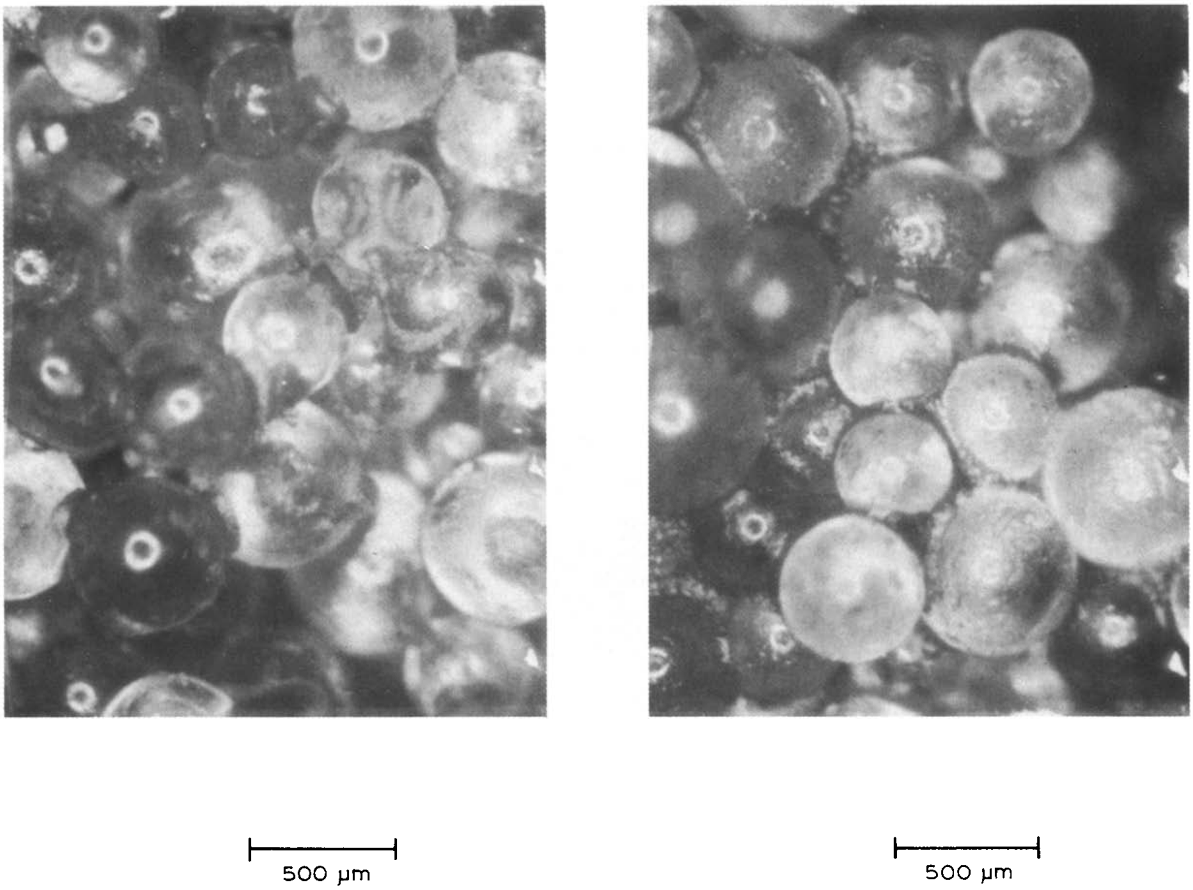

Fig. 6. Stereoscopic photomicrographs of cross-section glass bead mass containing 5% d-α-tocopherol palmitate before (left) and after (right) heating.

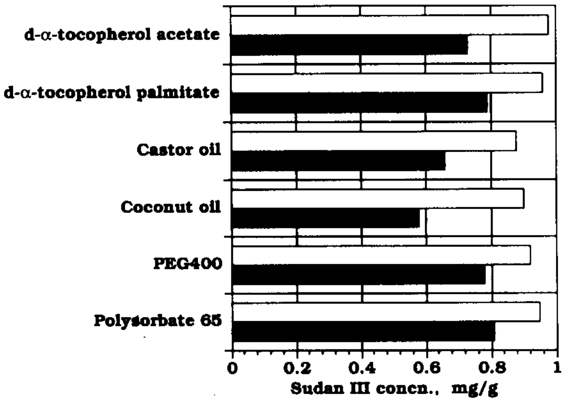

Fig. 7. Sudan III concentration on cross-section of glass bead mass containing 5% oily material before (open bars) and after (filled bars) heating.

of granules in thick layers after being forced through a screen (before heating), and that heat treatment decreases the amount of oily materials on the surface.

The effect of temperature on the penetration of tocopherols, castor oil, coconut oil, PEG 400, and polysorbate 65 is shown in Fig. 8. It is clear that the higher the temperature, the more rapid was the extent of penetration. These results suggest that the penetration rate (amount of penetration) of oily material increases on heat treatment and that the amount of oily material decreases at the granule surface on penetration into granules.

Discussion

The present results indicate the following schematic model with granules containing oily material in preparation A (Fig. 9). Oily materials exist predominantly in layers wedged between carrier particles after the drying process in the wet granulation method (sample 1A), i.e., oily materials are scarcely present as thick layers on the surface of granules. In sample 2A, immediately after crushing (forced through a 840 μm screen whose size is smaller than the extruded

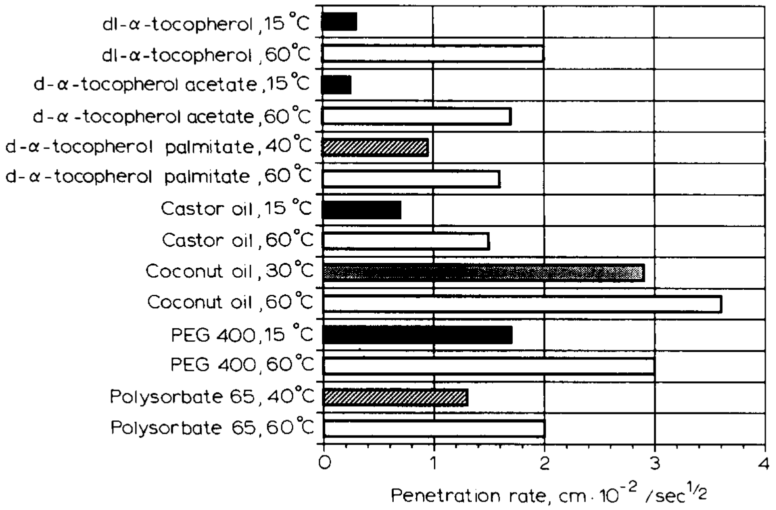

Fig. 8. Penetration rates of oily materials into tapped powder (porosity = 0.5) at 15, 30, 40, and 60 ° C.

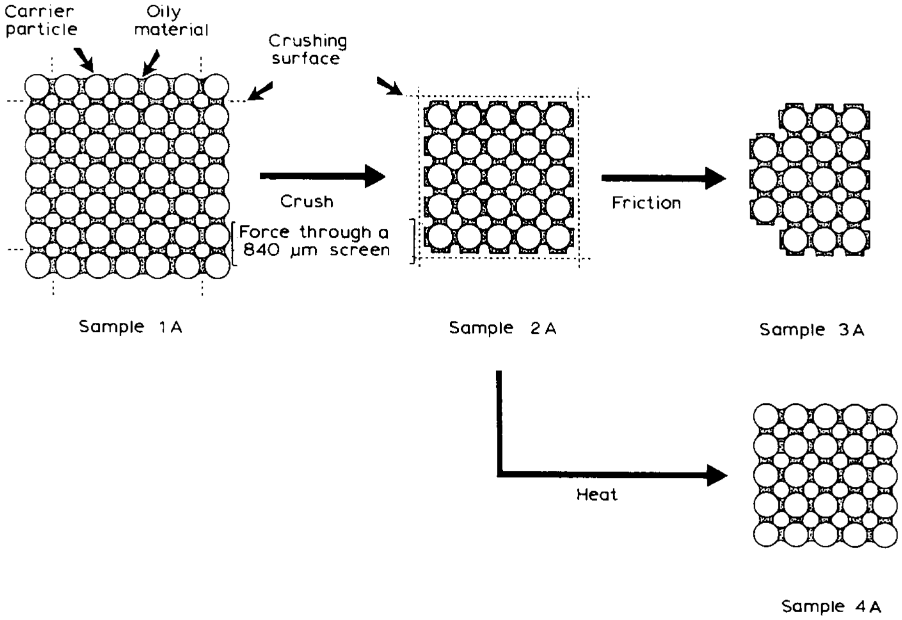

Fig. 9. Schematic model of influence of crushing, friction, and heat treatment on oily material distribution in a granule (preparation A).

size), oily materials which are particularly highly viscous and of low fluidity remain in thick layers on the fresh surface of a granule. They exhibit caking of granules after storage at temperatures lower than the respective melting points of the oily materials due to solidification of the latter (Table 2 and Figs 2–5). However, the oily materials do not solidify and the granules do not cake at temperatures higher than the respective melting points of the oily materials (Figs 2–5). Friction treatment flakes off carrier particles on the surfaces and exposes other fresh surfaces (sample 3A). The amount of oily material on the surface of sample 3A is equal to that of sample 2A. Consequently, caking of granules (samples 2A and 3A) is readily caused by cohesion between granules and solidification of oily material on the surface of granules (Table 2). However, heat treatment increases the fluidity of oily materials on the surface (Fig. 8) and enables them to penetrate more readily into wedges between particles (sample 4A). Thus, the amount of oily material on the granule surface decreases (Figs 6 and 7), and heat treatment then shows marked effective anti-caking action (Table 2 and Figs 2–5).

In preparation B, sample 1B also contains granules after the drying process and barely any oily material is found on the surface of granules, similarly to sample 1A. However, the screen size during crushing (forcing through a 840 μm screen) is larger than the extrusion size. Therefore, the crushing process exposes a small amount of fresh surface (sample 2B). Thus, sample 2B exhibits little caking (Table 2). Friction treatment exposes several fresh surfaces which leave thick layers of oily materials by flaking off carrier particles at granule surfaces (sample 3B) and the increasing caking tendency (Table 2). The amount of oily materials on the granule surface and caking tendency of preparation B decrease similarly to the case for preparation A on heat treatment (Table 2).

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