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Physicochemical properties of spray-dried agglomerated particles of salicylic acid and sodium salicylate

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Aqueous slurries of salicylic acid and sodium salicylate, containing various kinds of binder, namely gum arabic, gelatin, polyvinyl alcohol, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, tragacanth and sodium alginate, were spray dried using a centrifugal wheel atomizer. Almost all the spherical dried products were free flowing microgranules, although formulations including gelatin or polyvinyl alcohol proved to be difficult due to agglomeration. Particle properties such as diameter, true density, sphericity and surface area were measured, all of these being strongly influenced by the concentrations of sodium salicylate and binder. The surface topography of the products was studied with a scanning electron microscope. Granules bound with gum arabic and polyvinylpyrrolidone had smooth surfaces without holes or craters. Analysis of the X-ray diffraction patterns and the infrared absorption spectrum of products showed that these granules still contained both salicylic acid and sodium salicylate, in contrast to granules prepared using other binders, where only sodium salicylate remained, the salicylic acid having sublimed. They are microcapsules containing salicylic acid and sodium salicylate of grain size of about 20–80 and 13–17 nm respectively, and amorphous contents of about 50–80%. The thickness of the encapsulating film was 1–3 μm. The change in appearance of a drying slurry droplet is discussed and two typical drying processes are described.

Spray drying is useful for agglomerating and improving the flow properties of pharmaceutical powders as well as a drying process. The application of spray drying techniques to the preparation of granules has been reported by Robinson, Raff & Svedres (1961) and to tabletting of dried powders by Kornblum (1969) and Gunsel & Lachman (1963). The preparation of granules of magnesium carbonate or synthetic aluminium silicate by spray drying has been studied by Takenaka, Kawashima & others (1971) with a view to improving the fluidity of the resultant solids for tabletting. Although the spray drying agglomeration of pharmaceutical organic compounds (Asker & Becker, 1966) and the encapsulation of volatile flavour oil (Saka, 1961; Metcalfe, 1956) has been reported, no work on the spray drying agglomeration or encapsulation of volatile organic medicaments has to our knowledge appeared.

If the binders included in formulations for spray drying are capable of forming films over the surface of drying droplets, thus hindering the sublimation of volatile materials, one would expect that such formulations could be agglomerated or encapsulated by spray drying. To test this, formulations including salicylic acid (subliming at about 75°), sodium salicylate and a binder were spray dried and gave free flowing agglomerated powders. Some of the products proved to be encapsulated; the parameters which largely governed encapsulation were determined.

METHODS

Preparation of slurries and spray drying technique

Aqueous solutions of gum arabic, gelatin, polyvinyl alcohol, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, tragacanth and sodium alginate in various concentrations were prepared. Finely powdered salicylic acid and sodium salicylate were added slowly to 500 ml of each of the binder solutions using a homomixer having a jet type rotator until uniform smooth slurries were obtained. The compositions of the slurries are listed in Table 1.

Table 1. *Composition of the slurries for spray drying.*

	Binder*							
	GA	PVP	CMC	MC	A-Na	TG	PVA	G
Salicylic acid (g)	300	75	75	75	75	75	75	100
Sodium salicylate (g)	500	100	300	100	100	300	100	300
Binder (g)	10	5	5	5	5	5	5	10
Water (ml)	500	500	500	500	500	500	500	500

* GA, gum arabic; PVP, polyvinylpyrrolidone; G, gelatin; CMC, carboxymethylcellulose; MC, methylcellulose; A-Na, sodium alginate; TG, tragacanth; PVA, polyvinyl alcohol.

The slurry was atomized at 50 ml/min by a centrifugal atomizing wheel driven at about 40 000 rev/min, and fed into the drying chamber at $150 \pm 10°$. The centrifugal wheel atomizer was a Kestner type rotating disk plate of 4 cm diameter. The height and the diameter of the drying chamber were 1·5 m and 95 cm respectively. A cyclone collector was used to collect the agglomerated powder.

Measurement of properties of agglomerated products

The size distribution of the agglomerated powders was determined by a photographic counting procedure. Representative samples were photographed at convenient magnification. About 1000 particles for each sample were counted and the particle diameter determined using a Fairs' figure (Fairs, 1943). True density was measured using a Beckman air comparison pycnometer. Specific surface area was measured by the BET adsorption method and also by air permeability (Suito & Arakawa, 1956). Electron photomicrographs of some representative samples were taken with a scanning electron microscope Model JSM-2 (Nihon Denshi); specimens were gold-coated and magnifications of 300 and 3000 were used. X-ray diffraction patterns of the agglomerated products were obtained using a diffractometer Model JDX (Nihon Denshi) and 1·5418 Å radiation. The salicylic acid and sodium salicylate contents of the products were determined by the internal standard method of X-ray diffraction analysis using calcium carbonate as an internal standard on the (211) plane. Supplementary analyses were also made. Binder, moisture, salicylic acid and sodium salicylate contents were determined by gravimetric analysis, by the Karl Fischer method, by neutralization titration and by ultraviolet absorption at 298 nm.

RESULTS

Almost all of the agglomerated products were fine granules having a diameter of 15–100 μm, compared with 1–8 μm for the original salicylic acid, and were fairly

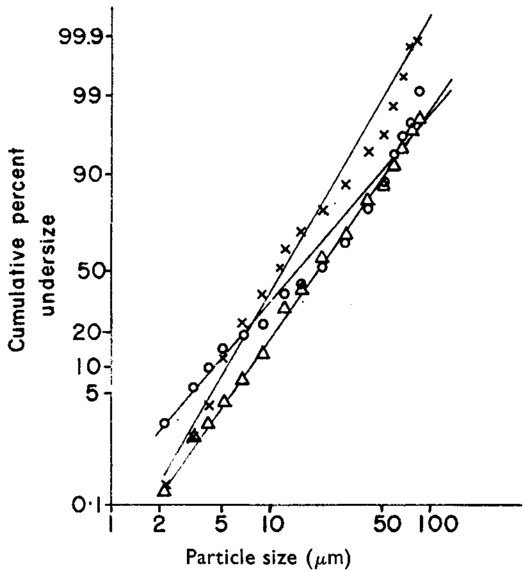

FIG. 1. Particle size distributions, by number, of spray-dried agglomerates. ○, gum arabic; ×, sodium alginate; △, carboxymethylcellulose.

Table 2. *Particle properties of agglomerated products.*

Binders	D_g (μm)	σ_g	Micromeritic parameters* D_{vs}(μm)	ρ (g/cm³)	S_{wb}(cm²/g)	S_{wp}(cm²/g)
GA	17·0	0·425	62·0	1·40	6644	6287
PVP	14·5	0·320	42·9	1·44	10321	4906
CMC ..	22·0	0·368	69·5	1·32	21343	13513
MC	22·2	0·334	61·0	1·32	10608	17157
A-Na ..	12·7	0·317	46·4	1·45	11294	3864
TG	16·3	0·307	47·3	1·54	9811	5418
Mg-CMC† ..	35·0	0·254	59·7	2·21	211000	10600
Al-CMC† ..	28·0	0·273	53·5	3·10	2810000	9630

* D_g, geometric mean diameter; σ_g, geometric standard deviation; D_{vs}, volume surface mean diameter; ρ, true density; S_{wb}, specific surface area by BET method; S_{wp}, specific surface area by permeability method.

† Mg-CMC, magnesium carbonate products using CMC and Al-CMC, synthetic aluminium silicate products using CMC (cited from Takenaka, Kawashima & others, 1971, for comparison).

free flowing, polyvinylpyrrolidone and gum arabic products especially so. In contrast, slurry containing gelatin or polyvinyl alcohol proved to be difficult to agglomerate and these products were very bulky and cohesive. The spray-dried products had log normal size distributions (Fig. 1).

The volume surface mean diameter was about 40–70 μm, the true density was 1·32–1·54 g/cm³, and the specific surface areas were 6600–21 300 cm²/g by the BET method, and 3800–14 000 cm²/g by the air permeability method. Unexpectedly, there was little difference between the values of surafce area obtained by the two methods. This may be contrasted with the magnesium carbonate and synthetic aluminium silicate products (Table 2). The spray-dried products thus appear to have fairly smooth surfaces.

The infrared absorption spectra of gum arabic and polyvinylpyrrolidone products showed the characteristic absorption bands of salicylic acid and sodium salicylate at 1650 cm^{-1} (carbonyl of salicylic acid) and 1570–1590 cm^{-1} (carboxylate). However, the spectra of the products made with other binders did not have the stretching vibration absorption band of the carbonyl of salicylic acid so that these products contain only sodium salicylate and binders.

X-ray diffraction patterns of the products were obtained and compared with salicylic acid and sodium salicylate patterns. All products gave fairly sharp patterns, which confirmed that salicylic acid was present only in the gum arabic and polyvinylpyrrolidone products (Fig. 2). The intensities of the characteristic peaks of salicylic acid and sodium salicylate which appeared in the product patterns were compared with those of the original salicylic acid and sodium salicylate crystals. The relative intensities of product to original crystal are low; this may be the result of conversion to an amorphous or disordered-crystalline form, due to the rapid drying of the slurry droplets.

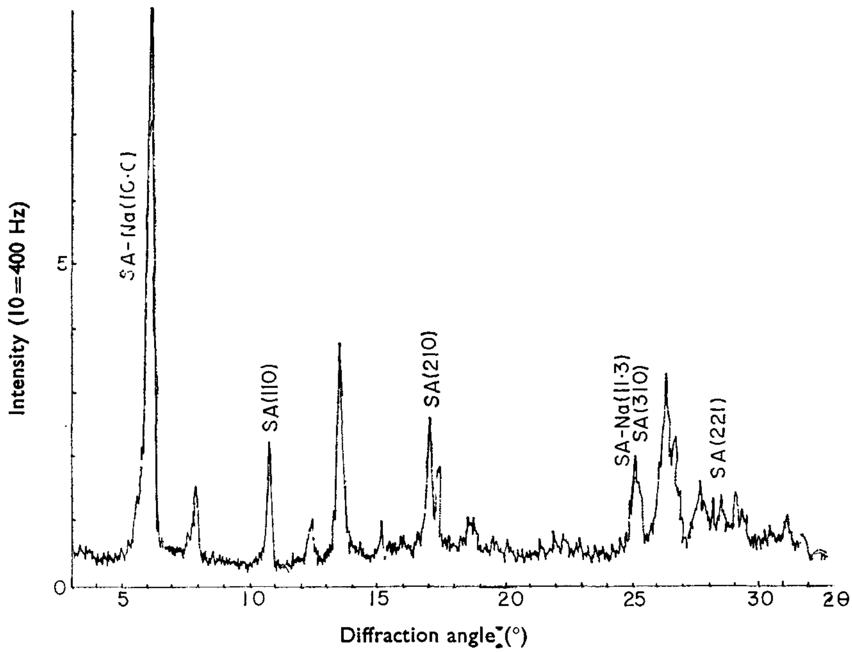

FIG. 2. X-ray diffraction pattern of polyvinylpyrrolidone products at 1·5418 Å wavelength. Abscissa is diffraction angle (degrees) and ordinate is intensity (Hz). 10 = 400 Hz.

Effect of slurry composition for gum arabic products

To investigate the change of product characteristics with slurry composition, 36 slurries were prepared in the possible combinations of gum arabic (10, 50, 100 g), salicylic acid (75, 150, 300 g) and sodium salicylate (0, 100, 300, 500 g) in 500 ml of water. Experimental results are shown in Fig. 3(A) and (B).

As the concentration of gum arabic and sodium salicylate in the slurries increased, the volume surface mean diameter of particles increased. In Fig. 3(B), the effect of the variation in the concentration of salicylic acid on the diameter is shown. The effects of gum arabic and sodium salicylate concentration were significant at the 1 %

level by analysis of variance. The interaction of salicylic acid and sodium salicylate is significant at the 5% level. The degree of sphericity defined as D_{sp}/D_s, where D_{sp} is $6/\rho S_{wp}$ (S_{wp} = specific surface area by the permeability method) and D_s is mean surface diameter, is greatest at the lowest concentration of sodium salicylate; analysis of variance showed this to be significant at the 1% level. The specific surface area is affected mainly by the concentration of gum arabic and sodium salicylate, though that of salicylic acid is of some importance.

Encapsulation

Because gum arabic and polyvinylpyrrolidone particles retained salicylic acid, and had no holes or craters in their surface (Fig. 5), they must be encapsulated

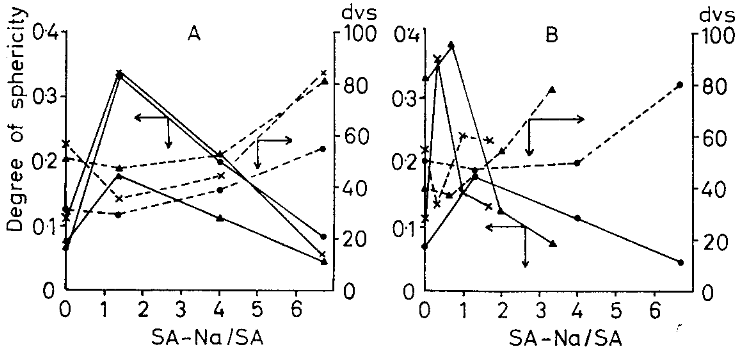

FIG. 3. Correlation between the concentration ratio of sodium salicylate to salicylic acid in slurry, volume surface mean diameter (D_{vs}), and degree of sphericity. (A) each slurry contains 75 g of salicylic acid and ○, 10 g; △, 50 g; ×, 100 g of gum arabic. (B) each slurry contains 50 g of gum arabic and ○, 75 g; △, 150 g; ×, 300 g of salicylic acid. Dotted lines, D_{vs}; solid lines, degree of sphericity.

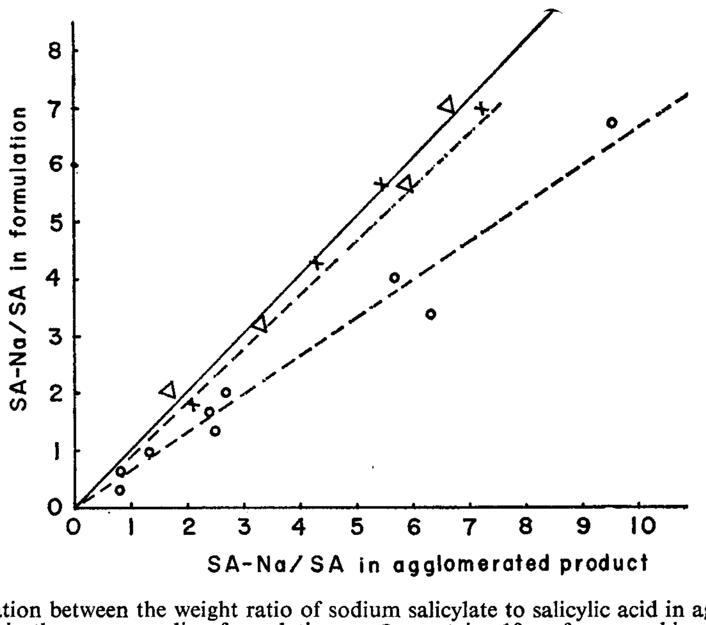

FIG. 4. Relation between the weight ratio of sodium salicylate to salicylic acid in agglomerated products and in the corresponding formulations. ○, contains 10 g of gum arabic; △, contains 50 g of gum arabic; ×, contains 100 g of gum arabic.

Table 3. *Grain size and crystalline forms of salicylic acid and sodium salicylate in agglomerated particle.*

Binder	Grain size Å	Content (%) Chemical analysis	X-ray diffraction analysis	Amorphous content (%)* or another crystalline form (β + amorphous) content (%)	Original crystalline form content (%)
PVP	216	25·2	13·0	48·3*	51·7
GA	802	27·7	5·6	79·8*	20·2
PVP	133	37·8	6·8	82·0	18·0
GA	133	65·3	6·5	90·0	10·0
TG	145	90·1	2·2	97·6	2·4
A-Na	145	85·4	6·0	92·9	7·1
CMC	177	88·8	10·7	87·9	12·1
MC	133	76·5	8·4	89·0	11·0

particles. The weight ratio of sodium salicylate and salicylic acid in such encapsulated particles is compared with the original ratio in the slurry in Fig. 4.

As the concentration of gum arabic in the slurry increases, these two ratios tend to become equal, showing that the sublimation of salicylic acid is hindered. The thickness of the coating film is estimated to be 1–3 μm by the equation (1), if all the gum arabic were on the outside.

$$2l = D_{vs}\,(1 - \sqrt[3]{1 - (C_a\rho/\rho_a)}) \qquad \text{eqn 1}$$

where l is film thickness, C_a is gum arabic content, ρ is particle density and ρ_a is true density of gum arabic.

The characteristics of spray-dried materials can differ according to the conditions of drying (Crosby & Marshall, 1958). In addition to micromeritic variations such as shape, size, surface area and porosity, differences can also occur in the crystal form of spray-dried materials owing to the rapid drying of the slurry droplets. Fell & Newton (1970) produced spray-dried lactose which was a mixture of the three forms α-monohydrate, α-anhydrous and β-lactose. Normally crystallized lactose contains 100% α-monohydrate. Gunsel & Lachman (1963) showed that spray-dried lactose contains about 8% of amorphous material. In the present work, the proportions of amorphous salicylic acid and sodium salicylate were determined by subtracting the values of contents obtained by X-ray diffraction analysis from those obtained by chemical analysis. Sodium salicylate is estimated to be about 80–97% amorphous, and salicylic acid in the polyvinylpyrrolidone and gum arabic products contains 50 and 80% respectively. The amorphous contents of >90% in sodium salicylate seem improbable because of the fairly sharp appearance of peaks in Fig. 2. In addition, several new diffraction peaks at diffraction angles of 13·5, 17·4, 26·0, 26·2 and 28·3 degrees, which do not appear in the X-ray patterns of the original sodium salicylate or the original and spray-dried salicylic acid, appear in those of all of the spray-dried products in this study. Therefore, the sodium salicylate in the spray-dried products must be polymorphic composed of the normal crystals, another crystalline form, provisionally named β, and an amorphous form (Table 3). The width of the diffraction peaks on the (10·0) plane of sodium salicylate and the (110) and (210) planes of salicylic acid were measured and the grain sizes (t) of both compounds in the particles were calculated by the Scherrer equation,

$$t = 0{\cdot}9\lambda/B\cos\theta_B \qquad \text{eqn 2}$$

where λ = 1·5418 Å, B is the width of the diffraction peak (degrees), and θ_B is the diffraction angle (degrees). The grain sizes of salicylic acid crystals are larger than those of sodium salicylate, and the grain size of the latter is fairly constant.

The drying process for a slurry droplet

Charlesworth & Marshall (1960) investigated the evaporation of suspended drops

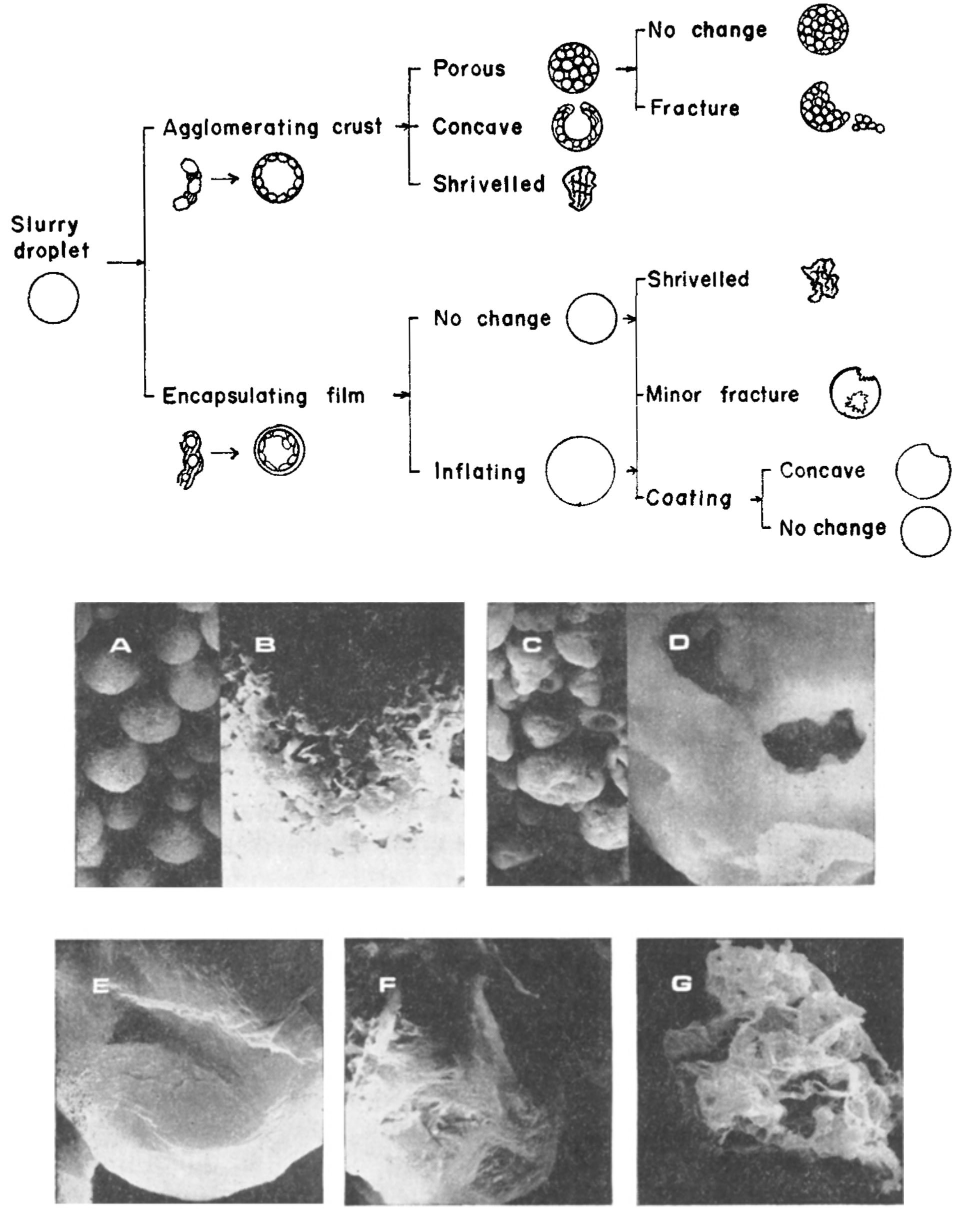

FIG. 5. Classification of appearance changes in drying slurry droplet and scanning electron microscopy photographs of agglomerated products. (A), (B), magnesium carbonate magnified at ×150, ×1500 respectively; (C), (D), aluminium silicate magnified at ×150, ×1500 respectively; (E), gum arabic magnified at ×1500; (F), tragacanth magnified at× 1500; (G), gum arabic containing no sodium salicylate magnified at ×1500. At a magnification of ×150, 1 cm = 23 μm; at ×1500, 1 cm = 2·3 μm. (A), (B), (C), and (D) from Takenaka & others (1971) for comparison.

containing dissolved solids and observed the appearance changes of the droplets during drying. The appearance changes of slurry droplets including binders can be obtained from the scanning electron microphotographs of the various agglomerated products (Fig. 5). Such changes may be divided into two types according to the behaviour of the binder solution. When the surface concentration reaches the saturation point, crusts will form, and the slurry will enter the funicular or pendular state. At this point, if the contact angle of the binder solution is high, the solid will be agglomerated and an agglomerated crust will form. If the contact angle is low, a pliable film encasing the materials will form. If the crust is porous, its appearance does not change with further drying. An example of such behaviour is the drying of a slurry containing magnesium carbonate. In Fig. 5(A) and (B) magnesium carbonate products show well rounded spheres and a number of micropores on their surface. Their surface seems to consist of a large number of thin crusts of 4–6·5 μm and small pores of 0·5–1·3 μm are very dark; indicating that they are deep. If the crust is not very porous, it fractures resulting in the formation of craters or shrivelled particles due to the stresses set up by the further solid phase growth. Aluminium silicate products show these hollow craters of about 15–20 μm in Fig. 5(C), which are very deep and large in Fig. 5(D). If the encapsulating film is sufficiently permeable to allow passage of the liquid, there is no change in the appearance and the dried particles are microcapsules like gum arabic or polyvinylpyrrolidone products. In Fig. 5(E) the shape of gum arabic products is almost spherical, with a slightly distorted surface. If the passage of liquid through the film is not easy, pressure builds up within the particle, and it fractures or inflates resulting in the formation of craters or a shrivelled and dimpled surface. The surface of tragacanth products had holes and large craters of about 5–10 μm diameter as shown in Fig. 5(F). Gum arabic products from the formulation without sodium salicylate show very characteristic dimples and wrinkles in Fig. 5(G), and a large difference between this product and the others was observed.

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