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Improvement of solubility and dissolution rate of poorly water-soluble salicylic acid by a spray-drying technique

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Spray drying techniques have been applied to improve the solubility and dissolution rate of poorly water-soluble salicylic acid. Spray drying of the acid dispersed in acacia solutions resulted in as much as a 50% improvement in the solubility of the product. Solubility improvement was closely related not only to the concentration of acacia but also the amount of amorphous material in the spray-dried products. The heat of solution was inversely related to these parameters. The dissolution rate of spray-dried product was almost instantaneous being about 60 times faster than that of the original powder. A great improvement in the wettability of the spray-dried material seemed to be mainly responsible for the increase of dissolution rate.

Spray drying has been used pharmaceutically not only as a drying technique but also for preparing free-flowing granules for tableting (Raff, Robinson & Svedres, 1961; Scott, Robinson & others, 1964). It has also been applied to the preparation of micro encapsulated agglomerates (Kawashima, Matsuda & Takenaka, 1972a, b), the manufacture of a sustained action tablet (Kornblum, 1969) and the production of finely divided powders from coarse particles after dissolution (Kornblum & Hirschorn, 1970).

Improvement of dissolution rate may be achieved by mechanical particle size reduction such as grinding, air attrition and ball milling; by the use of solid solutions or eutectic mixtures (Goldberg, Gibaldi & Kanig, 1966; Chiou & Niazi, 1971) and by using solid dispersions in polyethylene glycol 6000 (Chiou & Riegelman, 1971). Kawashima & others (1972) showed that spray drying causes changes in the crystal form of salicylic acid and sodium salicylate, in addition to changes in parameters such as angle of repose and cohesive forces. I have investigated the applicability of the spray-drying technique as a means of improving the solubility and dissolution rate of salicylic acid.

METHODS

Preparation of spray-dried products of salicylic acid

Aqueous solutions in various concentrations of acacia were prepared (500 ml). To these was added slowly finely powdered salicylic acid (subliming at about 75°), a homomixer having a jet type rotator being used until uniform smooth slurries were formed (Table 1). Spray-drying techniques were those described previously

Table 1. *Particle properties and physicochemical constants of spray-dried salicylic acid.*

Composition of the slurries								
Salicylic acid (g)		75	75	150	150	300	300	
Acacia (g)		50	100	50	10	10	50	
Water (ml)		500	500	500	500	500	500	
Particle properties*								
S_w (cm² g⁻¹) × 10⁻³		9·29	6·66	6·41	4·70	4·87	10·79	2·88†
D_{sp} (μm)		4·34	6·59	6·15	8·83	8·39	3·68	14·4
σ (g cm⁻³)		1·49	1·37	1·52	1·44	1·47	1·51	1·44
Amorphous content (%)		46	20	15	0	0	22	
Physicochemical constants‡								
S × 10³	17°	2·26	2·42	1·88	1·29	1·22	1·83	1·26§
(mol dl⁻¹)	27°	2·64	2·87	2·26	1·67	1·66	2·28	1·75
	37°	3·49	3·62	2·99	2·22	2·14	3·05	2·46
	47°	4·61	5·27	3·46	4·32	3·33	4·66	3·58
H (kcal mol⁻¹)		4·44	4·73	5·11	5·95	6·01	5·69	5·42

* S_w, specific surface area by permeability method; D_{sp}, specific surface area mean diameter; σ true density.
† Particle properties of original salicylic acid.
‡ S, solubility; H, heat of solution.
§ Physicochemical constants of original salicylic acid.

(Kawashima & others, 1972a, b). The slurry was atomized at the rate of 50 ml min^{-1} by a centrifugal atomizing wheel driven at 40 000 rev min^{-1} into the drying chamber at 140 $\pm$ 10°.

Measurement of properties of dried products

True density was measured using a Beckman air comparison pycnometer. Specific surface area was determined by the air permeability method (Suito, Arakawa & Takahashi, 1956) and the specific surface area diameter was calculated. X-ray diffraction patterns of dried products were obtained using a diffractometer Model JDX (Nihon Denshi) and 1·5418Å radiation. X-ray diffraction analysis was made using calcium carbonate as an internal standard on the (211) plane. The amorphous content of salicylic acid in the dried particles was determined by subtracting the crystallinity levels obtained by X-ray diffraction analysis from those obtained by chemical analysis.

Measurement of dissolution rates and diffusion coefficients

Experiments on dissolution rate were made in the standard vessel containing 2·3 litres distilled water or 0·1% solutions of Tween 80 held at 17°, 27°, 37° or 47°.

Sample powder (5 g) was introduced into the dissolution medium which was agitated at 146, 380, 620 or 1100 rev min^{-1} using a turbine impeller. Solubilities of dried salicylic acids in water were obtained at the same temperature as in the dissolution rate studies. Samples withdrawn from the aqueous solutions were diluted with the required medium and were assayed photometrically at 298 nm using a Hitachi 139 spectrophotometer.

Diffusion coefficients of salicylic acid in water and aqueous solution of 0·1% Tween 80 were determined by a diaphragm method (Okada & Kawashima, 1968;

Nakagaki, Koga & Iwata, 1962) using salicylic acid solutions of 0·002M made from untreated powder. The measured diffusion coefficients were:

At	17°	27°	37°	47°
	$3{\cdot}36 \times 10^{-6}$	$4{\cdot}01 \times 10^{-6}$	$4{\cdot}59 \times 10^{-6}$	$5{\cdot}88 \times 10^{-6}$
			$4{\cdot}2 \times 10^{-6}$*	
			$9{\cdot}67 \times 10^{-6}$†	

RESULTS AND DISCUSSION

Particle properties of spray-dried products

Spray dried particles made from formulations having lower weight ratios of salicylic acid to acacia were fairly spherical and seemed to be amorphous under the optical microscope. In contrast, formulations having higher ratios produced a mixture of amorphous and crystalline products. Other properties are given in Table 1. The true density of spray-dried products ranged from 1·37 to 1·52 g cm^{-3}, specific surface areas ranged from 4·70 to 10·79 $\times$ 10^{3} cm^{2} g^{-1}, larger than those of the original powder, while the mean specific surface area diameters were 3·68 to 8·83 μm.

The X-ray diffraction patterns of spray-dried products coincided with those of the original salicylic acid but the diffraction intensities of the spray-dried products were rather low. X-ray analysis showed the crystallinity of salicylic acid in spray-dried products to be 50–100%. As the weight ratio of salicylic acid to acacia in the formulations increased, the crystallinity increased as shown in Fig. 1. If the weight ratio is too high so that the binder concentration in a formulation is too low to encase a

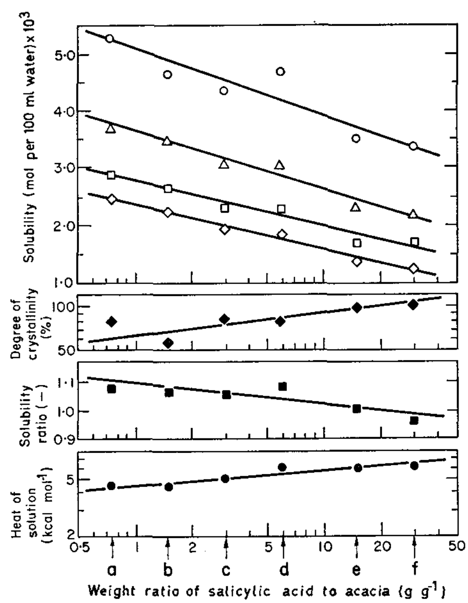

FIG. 1. Relation between solubility, degree of crystallinity and heat of solution, and weight ratio (g g^{-1}) of salicylic acid to acacia in slurries for spray drying. Weight ratio of salicylic acid to acacia is a, 75/100; b, 75/50; c, 150/50; d, 300/50; e, 150/10; f, 300/10. Solubility is at ○, 47° △, 37°; □, 27°; ◇, 17°

* Collett, Rees & Dickinson, 1972.
† Diffusion coefficient in 0·1% solution of Tween 80.

drying droplet, sublimation of the salicylic acid in the drying chamber and recrystallization of salicylic acid vapour in the cyclone collector may occur, resulting in an increase of crystallinity. When the binder concentration is optimum, salicylic acid may be dried and encapsulated rapidly to a high amorphous content without sublimation.

Solubility of original and spray-dried salicylic acid in water

Solubility of spray-dried salicylic acid products in water was 2·14 to 3·62 × 10^{-3} mol per 100 ml at 37° which was 1–1·5 times higher than that of the original powder. The relation between the salicylic acid—acacia weight ratio in the formulations and the solubility of the corresponding products was logarithmic. Although solubilities may be closely related to crystallinity as expected from the literature (Allen & Kwan, 1969), solubility increases of up to 50% seemed too large to be due to amorphism effects alone: the acacia concentrations in the dried products also affected solubility. These effects of acacia were demonstrated by increased solubility of the original powder when measured in solutions to which acacia had been added. The solubility improvement due to the net amorphism effect, the solubility ratio, was as much as 10% as shown in Fig. 1.

A relation between the solubility and the reciprocal of absolute temperature existed as expressed in equation (1).

$$S = S_0 \exp\left(\frac{-E_h}{RT}\right) \quad \quad \quad \quad (1)$$

Where S and S_0 are the molal solubilities at the experimental temperature and absolute zero, respectively, E_h is the heat of solution, R is the gas constant and T is the absolute temperature. The heat of solution was calculated to be 4·44–6·01 kcal mol^{-1} (18·58–25·16 kJ mol^{-1}) which was lower than that of the original salicylic acid. As shown in Fig. 1, the heat of solution decreased as the amorphous salicylic acid content in the dried products increased.

Dissolution rate of original and spray-dried salicylic acid in water

Concentration *vs* time curves for the dissolution of spray-dried salicylic acid under

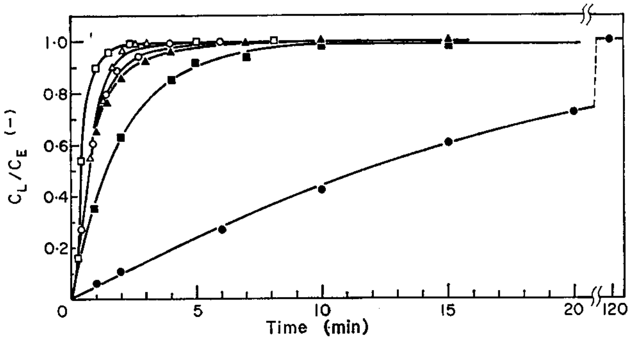

FIG. 2. Concentration of solute in bulk liquid vs time curve at 37° for the dissolution of original salicylic acid and spray-dried salicylic acid prepared from slurries having the weight ratio (g g^{-1} of salicylic acid to acacia of 300 : 50. Dissolution of spray-dried salicylic acid in water at ○, 620 rev min^{-1}; □, 1100 rev min^{-1}; △, 620 rev min^{-1} containing Tween 80. Dissolution of original salicylic acid in water at ●, 620 rev min^{-1}; ■, 1100 rev min^{-1}; ▲, 620 rev min^{-1} containing Tween 80. C_L is the concentration in the bulk at time t and C_E is the equilibrium concentration.

various conditions are compared with the curve for the original salicylic acid in Fig. 2.

The dissolution rate of spray-dried salicylic acid in distilled water at 620 rev min^{-1} and 37° was very fast, more than 60 times the rate for the original acid. Rate of agitation affected the dissolution rate of the original powder much more than the spray-dried material. The addition (0·1%) of a surface-active agent, Tween 80, to the dissolution medium greatly enhanced the dissolution rate of the untreated powder. No significant differences in dissolution rate for spray-dried salicylic acid with and without surface active agents in the dissolution medium were found.

The greatly improved wettability of the spray-dried product may be the main factor improving the dissolution rate, although the specific surface area of the spray-dried material was larger than that of the original salicylic acid. The diffusion coefficient of salicylic acid in the solution of 0·1% Tween 80 at 37° was $9{\cdot}67 \times 10^{-6}$ $cm^2 s^{-1}$, about twice its value in the dissolution medium without surfactant. The improvement of diffusion coefficient through the addition of surface-active agent to the dissolution medium increased the dissolution rate for the original powder.

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