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SOME PHYSICOCHEMICAL CHARACTERISTICS OF AGGLOMERATES AND MICROCAPSULES OF SULFISOMIDINE SPRAY-DRIED FROM AQUEOUS SLURRIES AND AMMONIUM SOLUTIONS*

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ABSTRACT

Aqueous slurries or ammonium solutions of sulfisomidine containing various kinds of binder, i.e. acacia, gelatin, carboxymethylcellulose, methylcellulose or polyvinylpyrrolidone were spray dried using a centrifugal wheel atomizer. The spray-dried products were found by scanning electron microscopy observation to be agglomerated or encapsulated. The products prepared from the aqueous slurries were microcapsules coated with a smooth film, whilst the products from ammonium solutions were agglomerates with porous agglomerating crusts on their

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surfaces. Micromeritic properties such as, particle diameter, flow and packing properties, etc. were investigated. Infrared absorption spectra confirmed that the spray-dried ammonium sulfisomidine was converted to the non-salt form during drying. X-ray diffraction patterns were obtained to investigate the crystalline forms and to determine the degree of crystallinity of spray-dried sulfisomidine. Solubilities of the products were measured in distilled water and the disintegration test solutions I and II (J.P.) at 37 °C and were correlated with the degree of crystallinity of the spray-dried sulfisomidine.

INTRODUCTION

Spray-dried products are principally free flowing microspheres which can easily be fed into a die for tabletting. Rapid evaporation of solvent from a droplet containing medicaments may prevent their medicinal activities from decreasing by over-heating. Owing to these advantages, the spray drying technique has been widely applied in the pharmaceutical field as an agglomeration method as well as a drying process. Raff et al.[1] proved that spray drying is a rapid and an inexpensive process for tablet granulation. Kornblum[2] prepared a sustained action tablet by compressing spray-dried granules.

When a suitable binder, which is capable of forming a film over the surface of a spray droplet is added to

the formulations, it may be possible to encapsulate the dried particles. Kawashima et al. made microcapsules of magnesium carbonate[3] and salicylic acid[4] employing this process.

Higuchi et al.[5] spray dried some insoluble weakly acidic pharmaceuticals from their ammonium salt solutions and obtained products in the non-salt form. Little is known of the effect of drastic evaporation of ammonia gas neither on the film formation over the surface of the dried paricles, nor on the physicochemical properties of the resultant particles. To elucidate this effect, aqueous slurries or ammonium solutions of sulfisomidine (J.P.) were spray dried and the micromeritic and physicochemical properties of both resultant spray-dried products were investigated.

EXPERIMENTAL

Spray Drying Technique

Aqueous and ammonium hydroxide (2 %) solutions containing various kinds of binder i.e. acacia, polyvinylpyrrolidone, carboxymethylcellulose, methylcellulose and gelatin were prepared in concentrations of 2 % and 1 % respectively. Finely powdered sulfisomidine (J.P.) of 6.8 μm mean diameter was added to slowly to each binder solutions using a jet type homomixer until a uniform slurry or solution was obtained. The formulations for spray drying are seen in Table 1.

TABLE 1
Formulations for Spray Drying

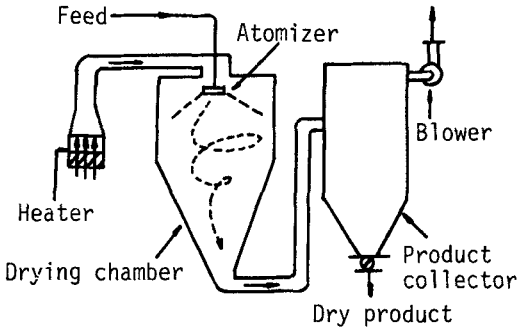
Binder*						
Aqueous slurry						
Sulfisomidine	(g)	75	75	75	75	75
Binder	(g)	10 or 100	10	10	10	10
Water	(ml)	500	500	500	500	500
Ammonium solution						
Sulfisomidine	(g)	75	75	75	75	75
Binder	(g)	10 or 100	10	10	10	10
Ammonium hydroxide solution 2 %	(ml)	1000	1000	1000	1000	1000

* GA, acacia PVP, polyvinylpyrrolidone CMC, carboxymethylcellulose GE, gelatin MC, methylcellulose

The aqueous slurries or ammonium solutions were atomized into a drying chamber at a feed rate of 50 ml/min by a centrifugal wheel atomizer rotating at 40,000 rpm. The temperature of the drying chamber was maintained at 140 ± 10 °C. The dried products were collected by a cyclone collector. A diagram of the spray drying equipment is seen in Fig.1.

Measurement of Micromeritic Properties of the Spray-dried Products

Particle size and size distribution were measured by a photographic counting method using a particle size analyzer (Model TGZ 3, Carl Zeiss). An air permeametry apparatus (Model SS-100, Shimadzu) based on Arakawa and Suito's method[6] was used to measure the specific surface areas. Flow and packing properties were assesed as angle of repose and tapped density measured by a pouring powder method and a tapping powder method respectively. Spray-dried particles were coated with a gold



Drying chamber	
Diameter	95 cm
Height	150 cm
Temperature	140±10 °c
Atomizer: Centrifugal wheel	
Diameter	4 cm
Rotation speed	40000 rpm

Fig. 1 Spray Drying Equipment.

and their surfaces were observed by a scanning electron microscope (Model JSM-S1, Nihon Denshi) at magnifications of 1000 to 3000.

Measurement of Physicochemical Properties of the Spray-Dried Products

X-ray diffraction patterns were obtained by an X-ray diffractometer (Model JDX, Nihon Denshi) with 1.5418 A° radiation. X-ray diffraction analysis was made using calcium carbonate as an internal standard on the (211) plane. The proportions of amorphous crystals in the spray-dried products were determined by subtracting values of the contents by X-ray diffraction analysis from those obtained by the colorimetric analysis method of Tsuda and Matsunaga[7]. Infrared absorption spectra were obtained by an infrared spectrometer (Model DS-403

G, Nihon Bunko). Solubilities were measured in distilled water, the disintegration test solutions I and II (J.P.) at 37 °C. The disintegration test solutions I and II were made by adding sodium chloride and dibasic sodium phosphate respectively to dilute hydrochloric acid solutions. The pH values of the test solutions I and II were 1.2 and 7.5 respectively.

RESULTS AND DISCUSSION

Micromeritic Properties of Spray-dried Sulfisomidine

Spray-dried sulfisomidine from both aqueous slurries and ammonium solutions comprised fairly spherical particles, when examined under an optical microscope, having a diameter of 5 to 80 μm. The volume surface mean diameter of the particles was 22 to 54 μm and the size distribution was log-normal with a geometric standard deviation of 1.47 to 1.86. The particles from ammonium solutions had a smaller mean diameter than those from aqueous slurries as seen in Table 2.

As expected from the data of the volume surface mean diameter, specific surface areas of the products from ammonium solutions were larger than those of the products from aqueous slurries (Table 2).

Flow properties of the original sulfisomidine were somewhat improved by means of spray drying as sugested in the results of angle of repose measurements. Spray-dried products showed a lower angle of repose than that of the original sulfisomidine (Table 2).

TABLE 2

Micromeritic Properties of Spray-dried Agglomerates

Micromeritic parameter*		D_{vs}(μ)	ρ_t(g/cm^3)	S_w(cm^2/g)	Angle of repose (degree)	Packing properties ρ_l(g/cm^3)	ρ_c(g/cm^3)	Kawakita's eq. Constants a	Kawakita's eq. Constants b x 10^2
Agglomerated product from slurry	GA-10	52.7	1.49	3939	55	0.46	0.79	0.41	10.4
	GA-100	51.6	0.94	3330	61	0.36	0.61	0.38	7.5
	PVP	53.6	1.34	4937	56	0.33	0.74	0.46	3.8
	MC	29.3	1.05	9039	48	0.21	0.34	0.50	2.7
	CMC	40.4	1.33	3670	52	0.47	0.73	0.37	7.4
	GE	50.5	1.41	8816	58	0.28	0.45	0.46	3.7
from ammonium solution	GA-10	22.3	1.34	9083	56	0.24	0.40	0.49	6.0
	GA-100	36.5	1.12	13495	48	0.17	0.32	0.41	2.7
	PVP	22.8	1.32	6657	54	0.21	0.49	0.51	3.2
	MC	34.8	0.92	9589	51	0.20	0.35	0.39	10.4
	CMC	38.1	1.22	5883	52	0.26	0.51	0.44	6.6
	GE	22.1	1.29	6574	58	0.28	0.58	0.49	2.0
Original powder		48.4	1.40	3407	66	0.41	0.74	0.59	6.5

Micromeritic parameter* D_{vs}, volume surface mean diameter S_w, specific surface area by permeability method ρ_c, closest packing density ρ_l, loosest packing density ρ_t, true density

The loosest packing volume of powder in a measuring cylinder was measured and subsequently the cylinder was tapped until the closest packing was obtained. During tapping, the volumes of powder were measured at an adequate interval to test Kawakita's equation[8] for describing the packing process. Kawakita's equation is represented as eqn. 1.

$$\frac{n}{c} = \frac{1}{ab} + \frac{n}{a} \qquad \text{Eqn. 1}$$

$$a = \frac{V_0 - V_\infty}{V_0}, \qquad c = \frac{V_0 - V_n}{V_0}$$

where b is the constant, n is the tapped number, V_0 is the volume of powder in a measuring cylinder at the loosest packing, V_n is the volume after the n-th tapping and V_∞ is the volume at the closest packing. Plots of n/c against n showed linear relationships which confirmed that the packing process can be represented by Kawakita's equation. As seen in the eqn. 1, a is defined as the reciprocal of the slope and b is calculated from the intercept of the straight line. For the constants a and b, non-significant differences were found between the original and spray-dried sulfisomidine. This indicates that the proportion of consolidation of both powders by tapping was almost the same. Unexpectedly the loosest and the closest packing densities of the spray-dried products were lower than those of the original sulfisomidine.

Due to the poor packing properties, it was still difficult to make a uniform tablet using the spray-dried products alone as well as the original sulfisomidine, even though the flowabilities of the spray-dried products were somewhat improved.

Surface Topography of Spray-dried Sulfisomidine

Scanning electron microscopy photographs of the spray-dried products were taken to investigate the surface topography of the spray-dried products. The surfaces of the particles prepared from aqueous slurries were coated with a smooth surface film e.g. the acacia product in Fig. 2(B),(D), whilst the surfaces of the particles from ammonium solutions as seen in Fig. 2(A), (C), were composed of a characteristic agglomerating crust. The interstices of the agglomerating crust form pores resulting in increasing surface areas. This was confirmed by the specific surface area data of the products from ammonium solutions which were larger than those from aqueous slurries. Drastic evaporation of ammonia from a spray droplet might decrease the film forming ability of the binder. This resulted in the characteristic surface topography of the products from ammonium solutions.

Crystalline Form of the Spray-dried Sulfisomidine

Infrared absorption(I.R.) spectra of original and spray-dried sulfisomidine were obtained as seen in Fig.

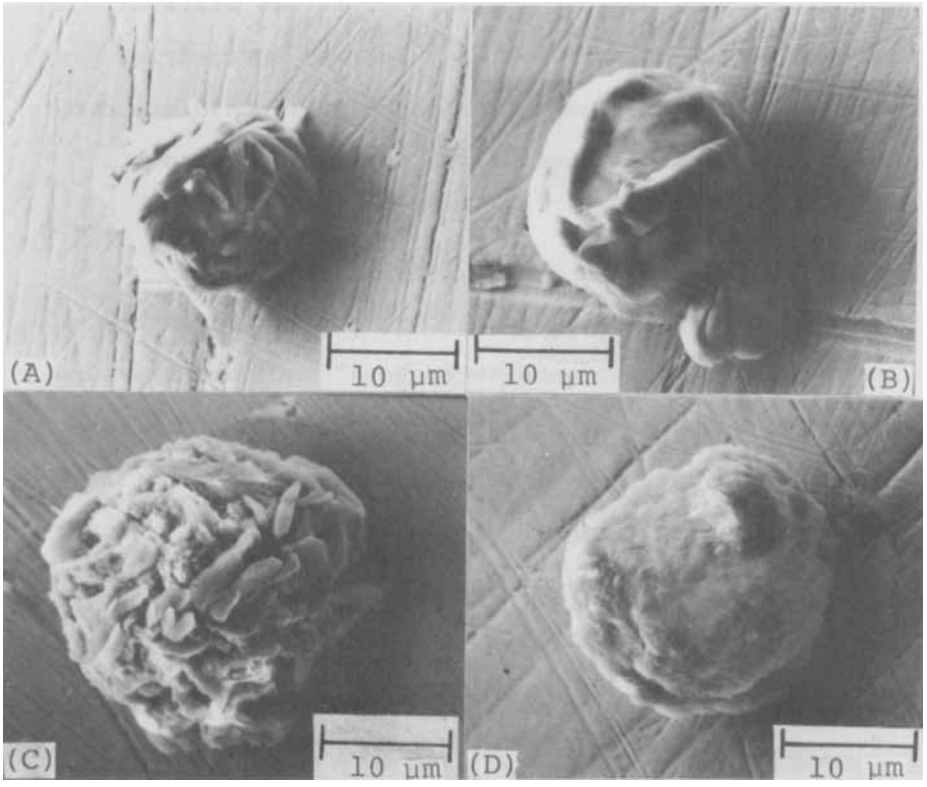


Fig. 2 Scanning Electron Microscopy Photograph of Spray-Dried Product.
Feeding liquid: (A),(C), ammonium solution
(B),(D), aqueous slurry
Binder: (A),(B), gelatin (C), acacia
(D), methylcellulose

3. The I.R. spectra of the product from ammonium solutions in Fig. 3(B), at the range of 2800 to 3000 cm^{-1} and 1000 to 1100 cm^{-1} were rather broad compared with those of the original sulfisomidine (Fig. 3(A)). This difference was attributed to the effect of the acacia and the water included in the spray-dried products. It

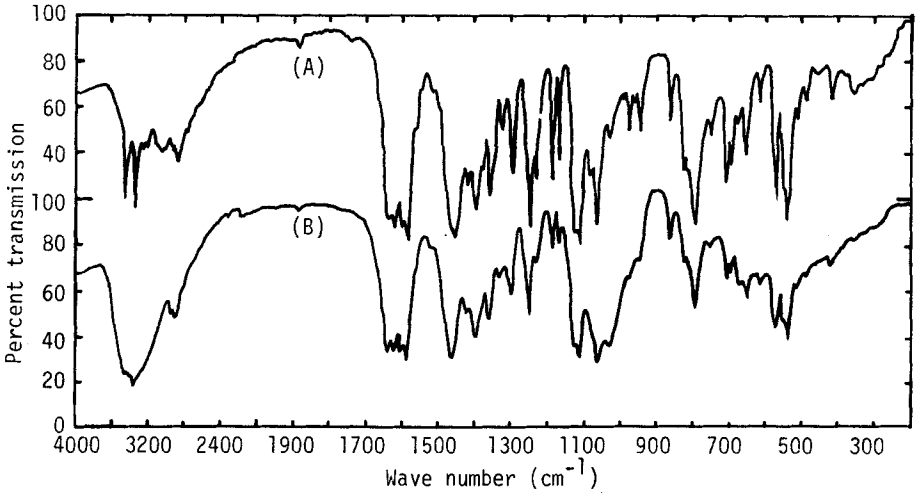


Fig. 3 Infrared Absorption Spectra of Sulfisomidine.
(A), original sulfisomidine
(B), product bound with acacia from ammonium solution

was concluded that the I.R. spectra of the products from ammonium solutions were essentially the same as that of the original sulfisomidine. This confirmed that the ammonia of the ammonium salt of sulfisomidine was released completely during spray-drying leaving the free sulfisomidine in non-salt form.

A rapid evaporation of solvent from a spray-droplet may change the crystalline form to the disordered form. X-ray diffraction patterns of spray-dried products coincided with those of the original sulfisomidine. However the intensities of the peaks which appeared on the pattern were weaker than those from the original sulfisomidine. This phenomenon appeared strongly in the

patterns of the products from ammonium solutions, some of which had no peaks in the pattern as seen in Fig. 4. The same phenomenon as this was observed also in spray-drying of sodium sulfisomidine. The degree of crystallinity of the spray-dried product from ammonium solutions showed values of 0 to 20 %, compared with 25 to 70 % for the products from aqueous slurries(Table 3). As descri-

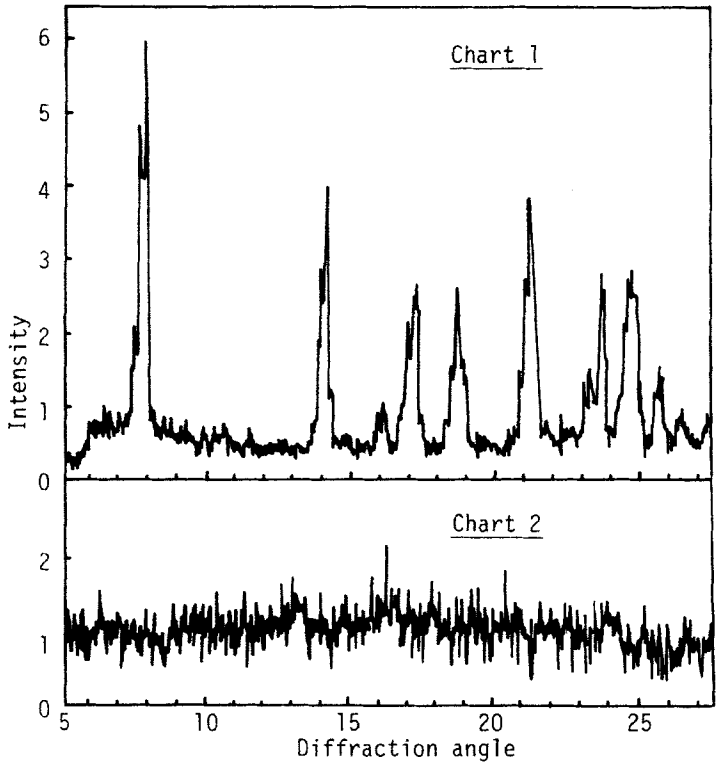


Fig. 4

X-ray Diffraction Pattern of Spray-dried and Original Sulfisomidine.
Chart 1, original sulfisomidine, Intensity: 1=40 Hz
Chart 2, spray-dried sulfisomidine with acacia from ammonium solution, Intensity: 1=10 Hz

TABLE 3

Solubility at 37 °C and Degree of Crystallinity of Spray-dried Products

Agglomerated product	Solvent	Solubility (mg/100ml) Water[a)]		Acid solution		Alkaline solution		Degree of crystallinity (%)
from Aqueous slurry	GA	265	211*	1364	1065*	440	274*	33
	CMC	200	182*	1342	1142*	338	317*	36
	GE	216	181*	1459	1223*	424	291*	69
	MC	228	180*	1516	1031*	377	259*	26
from Ammonium solution	GA	286	220*	1527	1075*	485	238*	0
	CMC	245	215*	1289	1187*	387	285*	17
	GE	236	199*	1596	1336*	436	260*	19
	MC	246	179*	1644	1364*	391	292*	17

* Solubility of mixture comprised of original sulfisomidine and spray-dried binder

† Solubility of original sulfisomidine (mg/100 ml): Water, 183 Acid solution,1519 Alkaline solution, 339

a) Correlation Coefficient between solubility in water and degree of crystallinity: -0.550 (significant at the 10 % level)

bed in the above, the I.R. spectra of the spray-dried products coincided with the original sulfisomidine. This indicated that polymer complexes of spray-dried sulfisomidine with binders were not formed through the spray drying process. It was concluded from these results that the net decrease in the degree of crystallinity was due to the amorphous effect alone, which was probably produced by drastic evaporation of ammonia during spray-drying.

Solubilities of Spray-dried Sulfisomidine

Solubilities of the spray-dried sulfisomidine bound with various kinds of binder at 37 °C in three kinds of solvents are listed in Table 3. The solubilities of mixtures comprising the original sulfisomidine and the spray-dried binders, whose compositions corresponded with those of the spray-dried products, were also measured under the same conditions as in the solubility study of the spray-dried products.

Solubilities of sulfisomidine increased by 1.05 to 1.9 times those of the original sulfisomidine after spray drying treatment. The products prepared from ammonium solutions showed an increased solubility over those from aqueous slurries. The R test showed that the proportion of the increase in solubility of spray-dried sulfisomidine in water had a negative correlation with the degree of crystallinity at the 10 % significance

level. However, the solubility increases may not be accounted for by the crystalline amorphous effect alone. This was suggested by the fact that the addition of binder to the solvent affected also the solubility of sulfisomidine as seen in Table 3. The interaction effects between sulfisomidine and binder molecules in the solutions may lead to such phenomena. However, this problem was still unsolved in this study and further studies must be awaited.

CONCLUSIONS

Sulfisomidine was agglomerated or encapsulated by the spray drying of aqueous slurries or ammonium solutions containing various kinds of binder and sulfisomidine. Although the spray-dried particles were microspheres, their micromeritic properties did not improve as expected. Spray-dried products prepared from aqueous slurries were coated with a smooth surface film, while the products from ammonium solutions were agglomerates with characteristic agglomerating crusts. The spray-dried sulfisomidine from the ammonium solutions was in the non-salt form which contained a large amount of disordered crystals leading improved solubility.

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