Direct Preparation of Solid Particulates of Aminopyrine–Barbital Complex (Pyrabital) from Droplets by a Spray-Drying Technique

YOSHIAKI KAWASHIMA *x, SHAN-YANG LIN *, MASUMI UEDA *, HIDEO TAKENAKA *, and YUTAKA ANDO ‡

Received January 4, 1982, from the *Gifu College of Pharmacy, Mitahora, Gifu 502, Japan and ‡Ichimaru Co. Ltd., Matsuhora, Takatomi, Gifu 502-21, Japan. Accepted for publication May 14, 1982.

Abstract □ Aqueous slurries of aminopyrine and barbital (molecular ratio 2:1) containing various excipients such as colloidal silica, synthetic aluminum silicate, montmorillonite clay, corn starch, microcrystalline cellulose, hydroxypropylcellulose, methylcellulose, gelatin, and chitosan were spray-dried by a centrifugal wheel atomizer with various rotation speeds (10,000–40,000 rpm) at various temperatures (85–145 ± 5°). The spray-dried products were a mixture of aminopyrine–barbital complex (molecular ratio 1:1), aminopyrine, and the excipient used. The flowability and the packing property of the products were improved by compounding colloidal silica into the formulation used for spray-drying. The products with montmorillonite clay, chitosan, and a corn starch–colloidal silica mixture were compressed directly into tablets. It was found that aminopyrine in the products was oxidized during spray-drying. The oxidation products were assumed to be a trace mixture of 5-oxo-2-methyl-4-dimethylamino-1-phenyl-3-pyrazoline carboxyaldehyde and miscellaneous oxidation products. Montmorillonite clay compounded in the formulation considerably prevented the oxidation of aminopyrine during spray-drying. The present study proposes an improved method for the preparation of solid particulates of aminopyrine–barbital complex for tableting, which combines the synthesis, drying, and agglomeration processes into a single process.

Keyphrases □ Aminopyrine—complex with barbital (pyrabital), direct preparation of solid particulates from droplets by a spray-drying technique □ Barbital—complex with aminopyrine (pyrabital), direct preparation of solid particulates from droplets by a spray-drying technique □ Pyrabital—direct preparation of solid particulates of aminopyrine–barbital complex from droplets by a spray-drying technique □ Solid particulate—direct preparation of aminopyrine–barbital complex (pyrabital) from droplets by spray-drying technique

A spray-drying technique has been used widely as a preferable drying method for heat-sensitive materials (foods, drugs, *etc.*). One advantage claimed for this technique is that both drying and agglomeration or microencapsulation of the drugs can be accomplished simultaneously. Microcapsules of barbituric acid and phenobarbital were prepared (1, 2) with a tensioactive precondensate of hexamethylolmelamine type. Enteric-coated microcapsules of sulfamethoxazole for tableting also were prepared (3).

Direct preparation of solid particulates from liquid droplets by a chemical reaction is one of the recent advances in spray-drying techniques. Ammonium sulfate spheres were produced (4) by the reaction of liquid droplets of orthophosphoric acid with gaseous ammonia. Solid particulates of theophylline–ethylenediamine complex were prepared (5) directly from liquid droplets.

The objective of the present study was to prepare solid particulates of a mixture of aminopyrine–barbital complex and aminopyrine, termed pyrabital in the Japanese Pharmacopeia (JP) IX (6), employing a spray-drying technique. Several methods of preparation of the analgesic,

Table I—Formulation for Spray Drying

Excipient		Dispersing medium	
Colloidal silica	10, 20 g	Water	600 ml
Synthetic aluminum silicate	20 g	Water	600 ml
Montmorillonite clay	20 g	Water	600 ml
Microcrystalline cellulose	20 g	Water	600 ml
Colloidal silica	10 g	Water	600 ml
Corn starch	20 g		
Colloidal silica	10 g	Aqueous hydroxypropylcellulose solution (0.42%)	600 ml
Hydroxypropylcellulose	2.5 g		
Colloidal silica	10 g	Aqueous methylcellulose solution (0.83%)	600 ml
Methylcellulose	5 g		
Colloidal silica	10 g	Acetic acid solution (0.48%)	600 ml
Chitosan	2 g		
Colloidal silica	10 g	Aqueous gelatin solution (2%)	1000 ml
Gelatin	20 g		

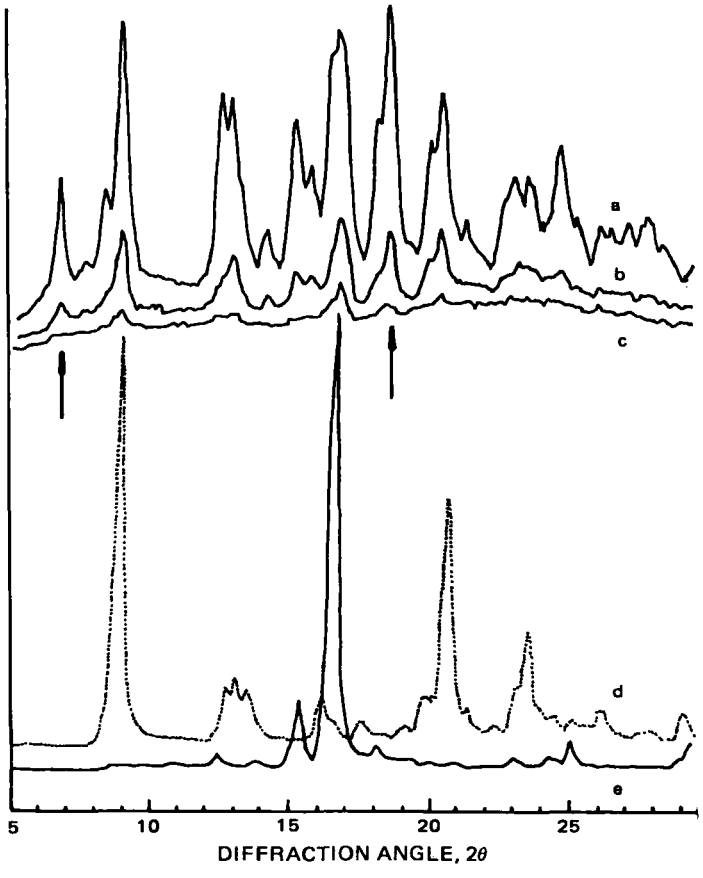

Figure 1—*X-ray diffraction patterns of the spray-dried products, pyrabital, aminopyrine, and barbital. Key: (a) pyrabital; (b) spray-dried products prepared at 85°; (c) spray-dried products prepared at 145°; (d) aminopyrine; (e) barbital.*

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Table II—Effects of Excipient Used on the Drug Contents and the Micromeritic Properties of the Spray-Dried Products [a]

Excipient	Aminopyrine content, %	Barbital content, %	Molecular content ratio of aminopyrine to barbital	Geometric mean diameter, μm	Angle of repose	Parameters in Kawakita and Ludde's (10) equation a	b
Colloidal silica (20 g)	35.45	13.30	2.1:1	12.0	45	0.22	0.082
Synthetic aluminum silicate	34.00	11.15	2.4:1	—	51	0.33	0.023
Montmorillonite clay	23.10	7.90	2.3:1	11.0	52	0.24	0.050
Microcrystalline cellulose	31.20	11.40	2.2:1	—	55	0.39	0.063
Colloidal silica + corn starch	32.60	12.70	2.0:1	11.0	47	0.23	0.062
Colloidal silica + hydroxypropylcellulose	35.35	14.80	1.9:1	16.5	54	0.27	0.044
Colloidal silica + methylcellulose	22.53	7.23	2.5:1	13.0	45	0.27	0.040
Colloidal silica + gelatin	16.53	9.20	1.4:1	8.0	47	0.33	0.032
Colloidal silica + chitosan	24.70	11.58	1.7:1	11.0	42	0.23	0.058

[a] Spray-drying conditions: drying temperature 130°; atomizer speed, 40,000 rpm.

Table III—Effects of Rotation Speed of Atomizer on the Drug Contents and the Micromeritic Properties of the Spray-Dried Products [a]

Rotation speed of atomizer, rpm	Aminopyrine content, %	Barbital content, %	Molecular content ratio of aminopyrine to barbital	Geometric mean diameter, μm	Angle of repose	Parameters in Kawakita and Ludde's (10) equation a	b
10,000	36.35	11.90	2.4:1	15.0	45	0.29	0.047
20,000	39.35	12.65	2.2:1	14.0	47	0.31	0.056
30,000	40.90	14.60	2.5:1	12.5	46	0.26	0.057
40,000	45.34	14.15	2.2:1	10.0	47	0.28	0.050

[a] Spray-drying conditions: drying temperature 130°; excipient, colloidal silica.

pyrabital, have been developed as described elsewhere (6). These methods involve several processes, such as reaction, filtration, drying, *etc.* Furthermore, the agglomeration process subsequently is required for compounding the synthesized drug into a suitable dosage form. However, the present method combines these multiple processes into one step. In addition, the resultant products are compressed directly into tablets. Also examined were the parameters affecting the micromeritic properties of the product and the autoxidation of aminopyrine in the product during spray-drying.

EXPERIMENTAL

Materials—Aminopyrine and barbital were JP grade. Pyrabital produced by the fusion method (7) was used as a reference compound for identifying the spray-dried products. The mixture of aminopyrine (0.0173 mole) and barbital (0.00865 mole) was gradually heated in a beaker until a yellow melt was obtained. The melt was cooled to room temperature resulting in a yellow compound. The physicochemical characteristics of the resultant product, such as IR spectrum and melting point (96–103°), coincided with those specified in the JP.

Spray-Drying Technique—Aminopyrine (34 g), barbital (13.5 g), and excipients such as colloidal silica[1], synthetic aluminum silicate (JP grade), montmorillonite clay[2], corn starch (JP grade), microcrystalline cellulose[3], hydroxypropylcellulose[4], methylcellulose[5], gelatin[6], and chitosan[7] were dispersed in 600 ml of distilled water by a jet-type homogenizer. The system was held for 20 min and was heated at 60° when necessary. The resultant uniform aqueous slurry was atomized into a drying chamber. The detailed formulations are in Table I. Preliminary examination showed that no products were recovered from the formulation without excipient. Therefore, the excipient contained in the formulation was necessary to obtain the products. The feeding rate of the aqueous slurry was 20–33 ml/min. The atomization of the slurry was carried out by employing a centrifugal wheel atomizer (diameter, 4 cm)[8] rotated at 10,000, 20,000, 30,000, or 40,000 rpm. The drying chamber was maintained at 85, 100, 115, 130, or 145 ± 5°. Spray-dried aminopyrine with colloidal silica was also produced at 40,000 rpm and 130°.

Measurement of Micromeritic Properties—The sizes of the spray-dried products were measured by a photographic counting method using a particle size analyzer[9]. The packing and the flow properties were

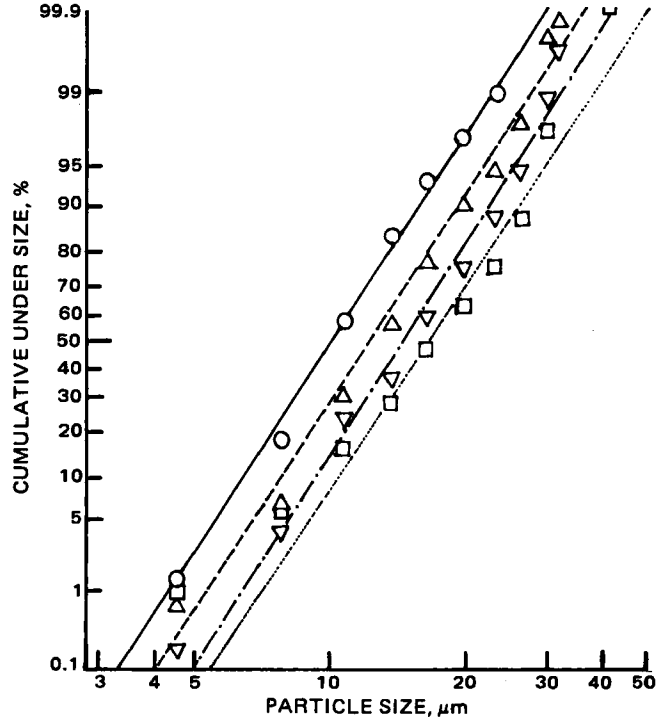

Figure 2—*Size distributions of the spray-dried products rotation speed of atomizer (rpm). Key: (▽) 10,000; (△) 30,000; (○) 40,000; (□) the products containing hydroxypropylcellulose (40,000).*

[1] Aerosil, Japan Aerosil Co. Ltd., Japan.
[2] Veegum-K, R. T. Vanderbilt Co.
[3] Avicel, Asahi Kasei Kogyo Co. Ltd., Japan.
[4] HPC-L, Shinetsu Kagaku Co. Ltd., Japan.
[5] MC (4000 cps), Wako Pure Chemical Co. Ltd., Japan.
[6] Koso Chemical Co. Ltd., Japan.
[7] Flonac, Kyowa Yushi Ind. Co. Ltd., Japan.
[8] Type 1051, Iwai Kikai Co. Ltd., Japan.
[9] TGZ-3, Karl Zeiss Co. Ltd., West Germany.

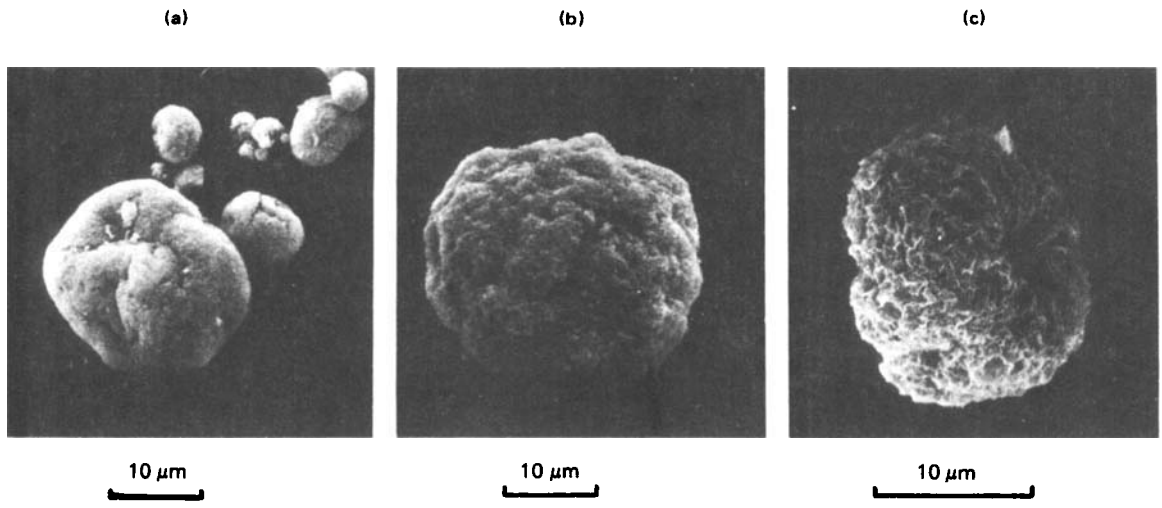

Figure 3—*Scanning electron microscopic photographs of the spray-dried products. Key: Spray-dried products containing (a) colloidal silica; (b) colloidal silica and hydroxypropylcellulose; (c) montmorillonite clay.*

investigated by using a tapping machine[10] generating a uniform force with each tap and by pouring powder on a plate (diameter, 3 cm), respectively. The direct compressibility of the spray-dried products was examined by employing a single-punch tableting machine[11]. The internal diameter of the die was 10 mm. The surface topography of the products coated with gold were investigated by a scanning electron microscope[12].

Measurement of Physicochemical Properties—The contents of aminopyrine and barbital in the products were measured with a double-beam spectrophotometer[13]: aminopyrine in acidic solution at pH 1.2[14] at 270 nm and barbital in alkaline solution at pH 9.6[15] at 250 and 269 nm. Identification of the spray-dried products was carried out by IR spectroscopy[16] and X-ray analysis[17]. Degradation of aminopyrine in the products during spray-drying was investigated by TLC on silica gel[18] using chloroform–methanol (14:1), and isopropyl alcohol–chloroform–ammonium hydroxide (28%) (9:4.5:2) as solvents and by UV spectroscopy[13]. As a reference, autoxidation of aminopyrine was carried out in an acetic acid (160 ml) and ethanol (40 ml) mixture by introducing air.

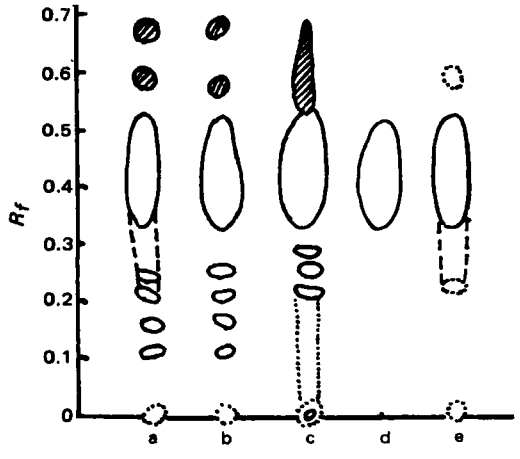

Figure 4—*Thin-layer chromatogram of the spray-dried products and the reference compounds developed with chloroform and methanol (14:1). Key: (a) spray-dried products with colloidal silica; (b) spray-dried aminopyrine; (c) oxidized aminopyrine; (d) aminopyrine; (e) pyrabital. Dotted drawing illustrates a trace spot or tailing. Shaded area indicates yellow spot or band.*

[10] Apparent specific volume meter PHK type, Konishi Manufactory Co. Ltd., Japan.
[11] Type KUI, Erweka GmbH, West Germany.
[12] JMS-SI, Nihon Denshi Co. Ltd., Japan.
[13] Model 556, Hitachi Manufactory Co. Ltd., Japan.
[14] Sodium chloride (2.0 g) and dilute hydrochloric acid (24.0 ml) made up to 1 liter with distilled water.
[15] 0.05 mole borax (44.5 ml) and 0.05 mole sodium carbonate (55.5 ml).
[16] A-102, Nihon Bunko Co. Ltd., Japan.
[17] JDX, Nihon Denshi Co. Ltd., Japan.
[18] DC-Fertig platten Kiesel 60 F_{254}, Merck Co.

RESULTS AND DISCUSSION

Identification of the Spray-Dried Products—It was found that the contents of aminopyrine and barbital in the products depended on the formulation for spray-drying and on the operating conditions as seen in Tables II–IV. The drug contents varied with the type of excipients used. The drug content in the product containing colloidal silica and gelatin was the lowest compared with the other excipients used in the present study (Table II). For the spray-drying condition, the drying temperature and the rotation speed of the atomizer were the main factors affecting the drug content in the products (Tables III and IV). With increasing rotation speed or decreasing drying temperature, the drug content increased. The inertia force exerted on the excipient was stronger than on the drugs in the droplet due to the fact that the density of the excipient was greater than that of the drug. Therefore, the excipient was separated more easily from the droplet than the drugs by increasing the rotation speed of the atomizer, which resulted in increasing the drug content in the spray-dried products. The effect of temperature on decreasing the drug content in the product was more significant than that of the rotation speed of the atomizer. An explanation for this finding is not clear at present. Although the percentage of drug content in the products varied widely, the molecular ratio of aminopyrine to barbital was fairly constant (2.2 ± 0.2 as shown in Tables II–IV).

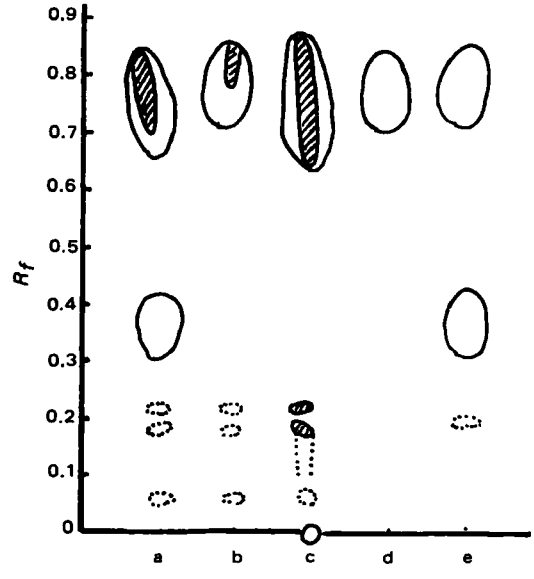

Figure 5—*TLC of the spray-dried products and the reference compounds developed with isopropyl alcohol–chloroform–ammonium hydroxide (9:4.5:2). Key: (a) spray-dried products with colloidal silica; (b) spray-dried aminopyrine; (c) oxidized aminopyrine; (d) aminopyrine; (e) pyrabital.*

Table IV—Effects of Drying Temperature of the Chamber on the Drug Contents and the Micromeritic Properties of the Spray-Dried Products [a]

Drying temperature of chamber	Aminopyrine content, %	Barbital content, %	Molecular content ratio of aminopyrine to barbital	Geometric mean diameter, μm	Angle of repose	Parameters on Kawakita and Ludde's (10) equation	
						a	*b*
85 ± 5	56.00	18.20	2.4:1	12.0	51	0.35	0.053
100 ± 5	54.75	18.20	2.4:1	8.9	55	0.29	0.068
115 ± 5	46.45	15.15	2.5:1	9.2	46	0.28	0.080
130 ± 5	45.34	14.15	2.2:1	10.0	47	0.28	0.050
145 ± 5	36.20	11.75	2.4:1	9.5	46	0.28	0.051

[a] Spray-drying conditions: atomizer speed, 40,000 rpm; excipient, colloidal silica.

IR spectra of the spray-dried products, pyrabital, and the mixture of aminopyrine and barbital (2:1) showed a broad peak of colloidal silica contained in the product at 1000–1200 cm^{-1} that partly impaired the identification of the spray-dried products. The characteristic bands of pyrabital appeared at 1703, 1656, and 1584 cm^{-1}, strongly suggesting the existence of pyrabital in the products. None of these characteristic peaks appeared in the IR spectra of aminopyrine, barbital, and a mixture of the two.

X-ray diffraction patterns of the spray-dried products, pyrabital, aminopyrine, and barbital are seen in Fig. 1. Although the intensities of the diffraction peaks of the products were weaker than those of pyrabital, aminopyrine, and barbital, the characteristic peaks of pyrabital at a diffraction angle of 6.6 and 18.5° were detected. The reduced intensities of the product peaks indicated that some crystals in the product converted to a disordered form due to rapid crystallization during spray-drying. The more reduced intensities of the products prepared at 145° instead of 85° also indicated that the amorphism occurred because of the rapid crystallization.

It was reported (8) that pyrabital was a mixture consisting of a molecular compound of aminopyrine and barbital (molecular ratio 1:1) and an additional molecule of aminopyrine. Recalling that the molecular ratio of aminopyrine to barbital contained in the products was >2 (Tables II–IV), it appears that the present product was a mixture of pyrabital, aminopyrine, and the excipient used.

Micromeritic Properties of the Spray-Dried Products—The spray-dried products were observed to be fairly spherical particles under an optical microscope. Their sizes varied from 4 to 40 μm, and their distributions were described by a logarithmic plot shown in Fig. 2. As suggested from a previous study (9), the geometric mean diameter of the products increased with a decrease in the rotational speed of the atomizer.

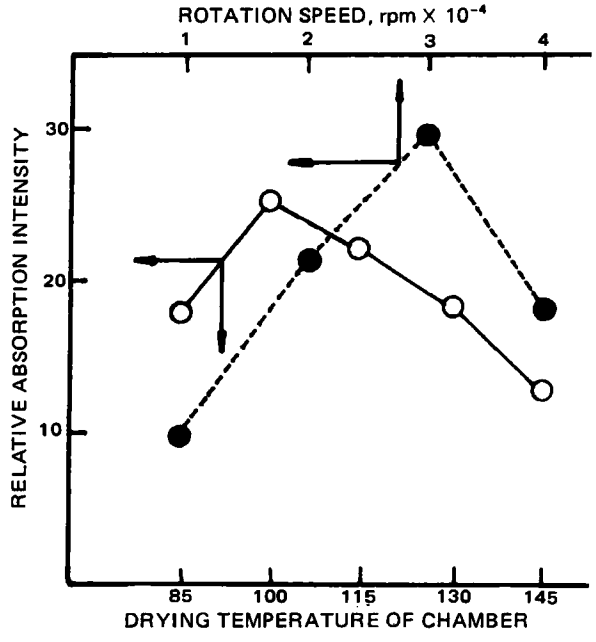

Figure 6—*The relative absorption intensities at 385 nm of the spray-dried products to pyrabital as a function of atomizer speed and drying temperature of the chamber.*

Hydroxypropylcellulose contained in the formulation also acted to increase the product size as seen in Fig. 2 and Table II.

Surface topography of the products depended mainly on the type of the excipient used. The products with colloidal silica and binder (hydroxypropylcellulose) revealed a fairly smooth surface, whereas the surface of the products with montmorillonite clay were pitted as shown in Fig. 3.

The angle of repose of the products with colloidal silica and chitosan was fairly low compared with the other products, as shown in Table II. The packing property of the products was evaluated by the parameter *a* from a previously described equation (10), which describes the packing process of powders by tapping into a measuring cylinder:

$$\frac{N}{C} = \frac{N}{a} + \frac{1}{ab} \quad \text{(Eq. 1)}$$

$$C = (V_0 - V_N)/V_N \quad \text{(Eq. 2)}$$

where *b* is a constant, *C* is the compaction ratio, *N* is the number of taps, V_0 is the volume of powder in a measuring cylinder at the loosest packing, and V_N is the volume after the *N*th tapping. The parameter *a* corresponds to the proportion of consolidation at the closest packing attained; therefore, the smaller *a* indicates easier packing. The parameter *a* of the products with colloidal silica was the smallest among the products, indicating that they were the most easily packed.

It was found that the products with chitosan, montmorillonite clay, and a mixture of corn starch and colloidal silica were directly compressible

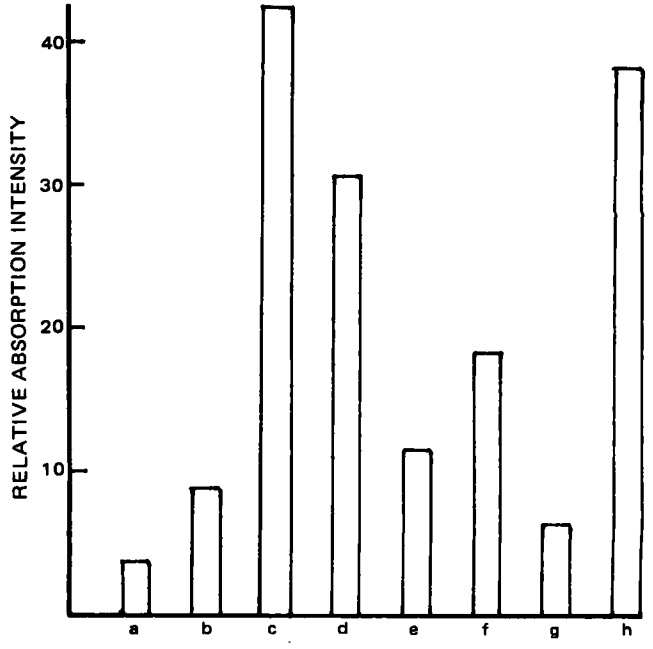

Figure 7—*The effects of excipient used on the relative absorption intensities at 385 nm of the spray-dried products to pyrabital. Excipient contained in the spray-dried products: (a) montmorillonite clay; (b) colloidal silica and gelatin; (c) microcrystalline cellulose; (d) colloidal silica and methylcellulose; (e) colloidal silica and chitosan; (f) colloidal silica and corn starch; (g) synthetic aluminum silicate; (h) colloidal silica and hydroxypropylcellulose.*

into tablets. The hardness[19] values of the resultant tablets were 4–4.5 kg. The weight variation tests of the tablets with <324 mg average weight were within the tolerances specified in the USP and the JP. For the other products, it was necessary to compound some microcrystalline cellulose (>50% w/w) in the formulations for tableting to obtain satisfactory tablets.

Degradation of Aminopyrine During Spray-Drying—Extracts of the spray-dried products exhibited absorbance at 385 nm, where aminopyrine does not absorb. The intensity of the peak depended on the excipient used and on the operating conditions (drying temperature and the rotation speed of the atomizer).

Thin-layer chromatograms of the spray-dried products containing colloidal silica developed with chloroform–methanol (14:1) coincided with that of spray-dried aminopyrine as seen in Fig. 4. As a reference, TLC of the autoxidized aminopyrine in the acetic acid–ethanol solution was also conducted as shown in Fig. 4. No separated yellow spots appeared at R_f 0.60 and 0.68, but a long yellow band appeared in the chromatogram of the autoxidized aminopyrine (Fig. 4c). The main spot at R_f 0.44 in the chromatograms was identified as aminopyrine (Fig. 4). The chromatograms developed with isopropyl alcohol–chloroform–ammonium hydroxide (9:4.5:2) are shown in Fig. 5. Two major spots at R_f 0.36 and 0.75 appeared in the spray-dried products. The spot at R_f 0.36 was identified as barbital by referring to the chromatograms of barbital and pyrabital in Fig. 5. The yellow band appearing at R_f 0.75 is characteristic of spray-dried products and oxidized and spray-dried aminopyrine.

The findings from spectrophotometric and TLC analysis (Figs. 4 and 5) suggested that the absorbance peak at 385 nm and the yellow spots on the chromatograms of the spray-dried products were attributed to the oxidation products of aminopyrine produced during spray-drying. The yellow substance in the spray-dried products detected by TLC in Figs. 4 and 5 could not be separated because of its low yield. A yellow substance was obtained previously (7) as an oxidation byproduct in the preparation by fusion of a molecular compound of aminopyrine and barbital. It was found that this substance was 5-oxo-2-methyl-4-dimethylamino-1-phenyl-3-pyrazoline carboxyaldehyde (I), which exhibits a strong absorbance band at 389 nm. The coexistence of other miscellaneous oxidation products of aminopyrine that caused shifting of the band at 389 nm from I toward the shorter wavelength region was reported (11), and it was suggested that the yellow substance in the spray-dried products might be a mixture of I and miscellaneous oxidation products.

The relative absorbance intensities at 385 nm of the spray-dried products to that of pyrabital (A_s/A_p) are plotted in Fig. 6, as a function of the operating conditions (the rotation speed of the atomizer and the drying temperature). The relative absorbance intensities increased with increasing atomizer speed up to a maximum at 30,000 rpm. Above this point, the relative intensity decreased as shown for 40,000 rpm in Fig. 6. With increasing rotation speed of the atomizer, the diameters of atomized droplets may decrease resulting in an increase in the total air-exposed surface area of the droplets. Therefore, autoxidation of aminopyrine in the droplets could be enhanced with increasing rotation speed of the atomizer up to 30,000 rpm. The increased rotation speed of the atomizer also accelerates the drying speed of the resultant smaller droplets. Once the droplets are solidified, the oxidation of aminopyrine in the solid state may be reduced compared with that in the liquid state. At a 40,000-rpm rotation speed of the atomizer, the rapid solidification of droplets might prevent further oxidation of aminopyrine that appears above 20,000 rpm (Fig. 6).

By increasing the drying temperature, the oxidation rate of aminopyrine in the droplets increases. At the same time, the evaporation rate of droplets increases. The rapid solidification of the droplets by increasing the drying temperature may reduce the oxidation of aminopyrine which is similar to that found at the 40,000-rpm rotation speed of the atomizer. The relative absorbance intensity was the highest at 100°. At temperatures >100°, aminopyrine autoxidation was reduced with increasing temperature because of the more rapid solidification of aminopyrine. The oxidation of aminopyrine during spray-drying also depended on the excipient contained in the products, as seen in Fig. 7. The absorbances of the product with hydroxypropylcellulose and microcrystalline cellulose are distinguishable from the other products. The products with montmorillonite clay exhibited the lowest absorbances, indicating that the oxidation of aminopyrine during spray-drying largely was prevented. The products with synthetic aluminum silicate, similar to montmorillonite clay, showed the next lowest absorbance at 385 nm. At present, no physicochemical explanation for this finding is apparent.

[19] A moving platen-type hardness tester, Kyowa Seiko Co. Ltd., Japan.

REFERENCES

(1) P. Speiser, H. P. Merkle, and L. Schibler, *Ger. Offen.*, **2**, 233, 428 (1973).

(2) C. Voellmy, P. Speiser, and M. Soliva, *J. Pharm. Sci.*, **66**, 631 (1977).

(3) H. Takenaka, Y. Kawashima, and Shan-Yang Lin, *ibid.*, **69**, 1387 (1980).

(4) Y. A. K. Abdul-Rahman and E. J. Crosby, *Chem. Eng. Sci.*, **28**, 1273 (1973).

(5) H. Takenaka, Y. Kawashima, S.-Y. Lin, and Y. Ando, *J. Pharm. Sci.*, **71**, 914 (1982).

(6) Instruction of JP IX, Hirokawa Shoten, Tokyo, 1976, pp. C-1112.

(7) T. Kametani, K. Kigasawa, N. Ikari, T. Iwata, M. Saito, and H. Yagi, *Chem. Pharm. Bull.*, **15**, 1305 (1967).

(8) P. Pfeiffer and R. Seydel, *Z. Physiol. Chem.*, **176**, 1 (1928).

(9) H. Takenaka, Y. Kawashima, T. Yoneyama, and K. Matsuda, *Chem. Pharm. Bull.*, **19**, 1234 (1971).

(10) K. Kawakita and K. H. Ludde, *Powder Technol.*, **4**, 61 (1970/71).

(11) K. Kigasawa, N. Ikari, M. Saito, T. Iwata, and R. Shoji, *YAKUZAIGAKU*, **33**, 31 (1973).

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