Drug Development and Industrial Pharmacy, 25(4), 445–452 (1999)

RESEARCH PAPER

Prevention of Small Black Spots on Sugar-Coated Tablets Containing Aluminum Acetylsalicylic Acid

Y. Tomida[1,*] and T. Makino[2]

[1] *Production Division,*
[2] *Health Care Company, Takeda Chemical Industries Ltd., 1-1*
Doshomachi, 4-Chome, Chuo-ku, Osaka 540-8645, Japan

ABSTRACT

Sugar-coated tablets containing aluminum acetylsalicylate gradually developed black spots on their surface. A factorial experiment was performed based on an L32 orthogonal array table in an attempt to halt this phenomenon. The factor responsible proved to be talc used to formulate the smooth coating layer over the subcoating layer containing aluminum acetylsalicylate. When HCl-treated talc was used as a filler for the smoothing layer, the black spots were markedly decreased. The spotting mechanism was considered to be due to hydrolysis of aluminum acetylsalicylate in the subcoating layer to salicylic acid and acetic acid, which sublimated into the pores of the smoothing layer. Then, ferrous ion substituted from magnesium ion in the talc molecule center was extracted by salicylic acid, acetic acid, and moisture. Finally, the ferrous ion was oxidized to ferric ion, and this produced an Fe^{3+} *chelate compound together with salicylic acid.*

INTRODUCTION

Formulation studies have been carried out to develop a so-called cold medicine containing acetylsalicylic acid, bucetin (3-hydroxy-*p*-butyrophenetidide), ethoxybenzamide, caffeine, potassium guaiacolsulfonate, chlorpheniramine maleate, DL-methylephedrine hydrochloride, dihydrocodeine phosphate, and sodium ascorbate. Comparatively stable aluminum acetylsalicylate was used in place of acetylsalicylic acid for these tablets. As the 60 mg of aluminum acetylsalicylate in the unit dosage form was so bulky, it was formulated as a dusting powder together with talc to the subcoating layer of a sugar-coated tablet. Other active ingredients were separated as core tablets from aluminum acetylsalicylate. On the surface of the sugar-coated tablets, many small black spots

---

[*] To whom correspondence should be addressed.

www.dekker.com

were observed during stress stability studies. This phenomenon was considered to be caused by chelation of salicylic acid generated from aluminum acetylsalicylate and ferric ion (Fe^{3+}) (1, p. 1722; 2). However, the origin of Fe^{3+} was unknown, and other factors, including enhancement effects, also needed to be considered. Accordingly, factorial experiments based on an L32 orthogonal array table (3,4) were performed on a small scale to clarify the factors causing the small black spots and to find a method for preventing their occurrence on the yellow-colored tablets. Then, the experiments to reconfirm these factors were performed from the viewpoint of production feasibility. Furthermore, the mechanism responsible for the formation of these small black spots was studied.

MATERIALS

Bucetine (Hoechst, Frankfurt, Germany), sodium ascorbate (Takeda Chemical Industries, Ltd., Osaka, Japan), calcium gluconate, citric acid, trisodium citrate (Wako Fine Chemical Ltd., Osaka, Japan), and tartrazine (San-Ei Chemical Industries Ltd., Osaka, Japan) were used in this work. Aluminum acetylsalicylate JP, ethoxybenzamide JP, caffeine JP, chlorpheniramine maleate JP, DL-methyl-ephedrine hydrochloride JP, dihydrocodeine phosphate JP, potassium guaiacolsulfonate JP, and talc JP (Haicheng, China), powdered acacia JP, hydroxypropylcellulose JP low viscosity (HPC-L), povidone K25 JP (MW 40,000), titanium dioxide JP, calcium sulfate JP, calcium phosphate JP, and sucrose JP were also used. All other chemicals were reagent grade. HCl-treated talc was prepared as follows. Talc was steeped in 5% HCl solution at 70°C for 1 hr, washed with deionized water after centrifugation, and dried in a vacuum dryer.

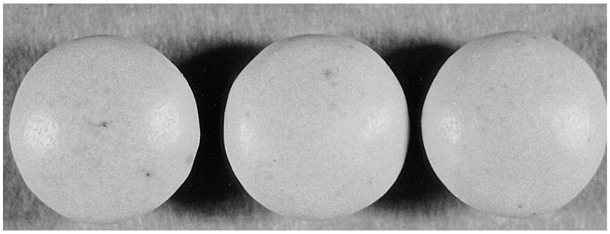

Figure 1. Small black spots on sugar-coated tablets stored at 40°C at 82% RH for 8 days.

METHODS

Tablet Preparation

For preparation of a cold medicine, ascorbic acid and other active ingredients except aluminum acetylsalicylate were separately granulated according to the conventional wet granulation method and compressed into core tablets (diameter 8.0 mm, thickness 3.75 mm, R diameter 7.0 mm, weight 190 mg). Lactose tablets of the same size as the cold medicine were made conventionally. Sugar-coating operations were also performed conventionally.

Method for Black Spot Evaluation

On the surface of the tablets stored at 40°C at 82% relative humidity (RH) for 8 days, small black spots were observed (Fig. 1). Accordingly, the small black spots on 20 coated tablets were examined with the naked eye, and scores were given separately based on the size and number of spots (Table 1). The degree of black spots on each group of 20 tablets was calculated using Eq. 1:

Table 1

Scores for Expressing the Degree of Small Black Spot Generation

a. Size of Small Black Spots

Rank	1	2	3	4	5
Size	None	Very small	Visible	A little larger	Very large
Score	0	1	2	4	8

b. Number of Small Black Spots

Rank	A	B	C
Number	Few or negligible	Medium	A lot
Score 1	1	5	10
Score 2	1	10	20
Score 3	1	2	3

$$S = \sum_{i=1}^{20} (score\ a)_i \cdot (score\ b)_i \qquad (1)$$

where scores *a* and *b* are spot size and number, respectively. Analysis of variance in factorial experiments was then performed.

Three evaluations were performed using three sorts of score sets, as shown in Table 1. As the conclusion of the evaluation did not vary regardless of which score set was used, the score set 1 : 5 : 10 was adopted.

RESULTS AND DISCUSSION

First Factorial Experiment

For the coating process for aluminum acetylsalicylate, nine factors (A to I) with two through four levels were selected and allocated to an L32 orthogonal array (Table 2). On a small scale at random along the array, 32 batches were prepared.

For the dusting method, a mixture of aluminum acetylsalicylate (56 parts) and talc or HCl-treated talc (20 parts) and acacia (4 parts) as a dusting powder, acacia syrup (sucrose 10, water 5, acacia 1.2 parts), a suspension of talc, HCl-treated talc, calcium sulfate or calcium phosphate (6.7 parts) (binding suspensions) were used for the subcoating layer (180 mg), respectively. These binding suspensions were also used for the smoothing layer (50 mg). For the suspension method, aluminum acetylsalicylate(1 part) was suspended in 5% polyvinylpyrrolidone (PVP) or HPC-L ethyl alcohol solution (1 part), and 65 mg of aluminum acetylsalicylate layer was coated on the core tablets without dusting powder. Calcium gluconate (5), reported as a stabilizer, or citric acid, as a chelating reagent to prevent coloration of salicylic acid and Fe, and tartrazine were dissolved in each suspension. Stabilizers

Table 2

Factors and Their Levels Investigated, Improvement of Small Black Spots, and Results of Analysis

Factors	Row	Level	Score[a]
A Core tablets	2	A1 Cold medicine	221
		A2 Lactose tablet	152
B Blowers of coating machine	8	B1 Nontreated	163
		B2 Cleaned	209
C Water for binding suspension	16	C1 City water	160
		C2 Distilled water	212
D Al-acetylsalicylate coating method	1,5,4	D1 With talc	158
		D2 With HCl-treated talc	143
		D3 Suspension in PVP solution	84
		D4 Suspension in HPC solution	359
E Stabilizers for Al-acetylsalicylate	15,22,25	E1 None	151
		E2 Ca-gluconate	85
		E3 Citric acid + tri-Na citrate	358
F Layers coated directly on Al-acetylsalicylate layer	11,28,23	F1 None	161
		F2 Film layer	358
		F3 Sugar-coated layer	83
		F4 TiO_2 sugar-coated layer	144
G Fillers in binding suspension	14,29,19	G1 Talc	714[b]
		G2 HCl-treated talc	13[b]
		G3 Calcium sulfate	11[b]
		G4 Calcium phosphate	7[b]
H Binders for binding suspension	21	H1 Gumi arabic	166
		H2 PVP	206
I Color (Tartrazine)	12	I1 Used	221
		I2 Nontreated	151

[a] Storage condition: 40°C at 82% RH for 8 days.

[b] Statistically significant difference (alpha = .05).

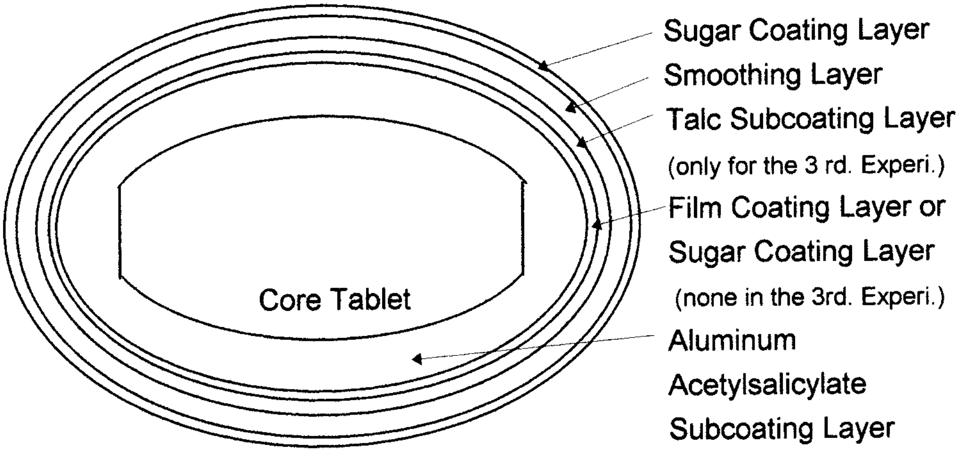

Figure 2. Cross-section of sugar-coated tablet prepared in the first and second factorial experiments and the large-scale experiments.

(1 part) were added to aluminum salicylate (100 parts). Tartrazine (0.6% w/v) was added to the binding solution and syrup. The sugar-coated tablets were prepared as shown Fig. 2. The weight of sugar coating or HPC-L film layer coated directly on the aluminum acetylsalicylate layer was 20 mg.

Analysis of variance revealed the following. Factor G, a filler in binding suspension, had the greatest effects of all the factors, and level G1 (raw talc in the fillers) significantly increased the generation of black spots, while level G2 (HCl-treated talc), level G3 (calcium sulfate) and level G4 (calcium phosphate) did not. Second, level D3 (the suspension-in-PVP-solution method for aluminum acetylsalicylate), level F3 (sugar coating layers coated directly on the aluminum acetyl-salicylate layer, as shown in Fig. 2), and level E2 (calcium gluconate) seemed to suppress the development of black spots slightly. The other factors, A, B, C, H, and I, were statistically negligible.

Second Factorial Experiments

To reconfirm the above experimental results, second factorial experiments of the coating process were performed on a small scale according to a three-way layout method taking the feasibility of commercial production into consideration. Based on the previous experiments, first raw talc and HCl-treated talc were selected as levels 1 and 2, respectively (the additives for the dusting powder and the binding suspension for the aluminum acetylsalicylate subcoating layer, respectively) of factor A,. Second, the sugar-coating layer and none were selected as levels 1 and 2, respectively, of factor B, the sugar-coating layer on the aluminum acetylsalicylate. Third, talc, HCl-treated talc, and calcium phosphate (1 part) plus HCl-treated talc (1 part) were selected as levels 1, 2, and 3 (the fillers for the smoothing layer), respectively, of factor C. Lactose tablets were used as the core tablets. The formulations for the dusting powder of aluminum salicylate, binding solution, and syrup were the same as those used for the first factorial experiments. Table 3 shows the scores for small black spots that appeared on the surface of the sugar-coated tablets that were stored at 40°C at 82% RH for 8 days.

Through analysis of variance, as shown in Table 4, it was reconfirmed that factor C greatly influenced the generation of the small black spots, which was drastically decreased on replacement of raw talc by HCl-treated talc or calcium phosphate plus HCl-treated talc as the filler for the smoothing layer. On the other hand, as factor A shows, the type of talc in the aluminum acetylsalicylate layer did not affect the spot generation. Factor B, the sugar layer directly coated on the aluminum acetylsalicylate layer, was not effective in preventing the spots.

Methods for Hydrochloric Acid Treatment of Talc

As a manufacturing procedure to prevent the formation of small black spots on sugar-coated tablets without changing the formulation, it was determined that raw talc should be replaced by acid-treated talc in the smoothing layer coated on the aluminum acetylsalicylate layer, except for raw talc in the other layers. Accordingly, the talc treatment conditions were studied. As the degree of spot generation did not differ between the HCl treatment times

Table 3

Factors, Their Levels for Reconfirmation Experiments on Small Black Spots, and the Results

Factor A, Talc for Aluminum Salicylate Layer	Factor B, Sugar Layer on Aluminum Salicylate Layer	Factor C, Filler for Smoothing Layer	Score, 40°C at 82% RH for 8 days
Raw	None	Raw talc	928
		Treated talc	37
		Treated talc + Ca-phosphate	15
	Prepared	Raw talc	320
		Treated talc	4
		Treated talc + Ca-phosphate	12
HCl-treated	None	Raw talc	1080
		Treated talc	25
		Treated talc + Ca-phosphate	5
	Prepared	Raw talc	1320
		Treated talc	24
		Treated talc + Ca-phosphate	22

(30 and 60 min) at 70°C, 30 min was selected, and the effectiveness of the HCl concentration (1%, 2%, 4%, 6%) and the HCl treatment temperature (room temperature, 70°C) were compared by examination of the spot generation of each sugar-coated tablet with a smoothing layer prepared using each HCl-treated talc. Each raw talc (25 parts) was steeped in each HCl solution (35 parts). Based on the results, shown in Table 5, the concentration of HCl, the treatment temperature, and the treatment time were set at 5%, 70°C, and 30 min, respectively.

Large-Scale Experiments

Three lots of sugar-coated tablets, shown in Table 6, were prepared using the HCl-treated talc (5% HCl, 70°C, 30 min) and a conventional coating pan 101.6 cm diameter, and the samples were stored at 40°C at 82% RH for 8 days. Long-term stability studies were also performed. As indicated in Table 6, the results showed that the change from raw to HCl-treated talc for the talc subcoating layer on the aluminum acetylsalicylate layer and the smoothing layer on the talc subcoating layer solved the problem of black spot generation. The talc subcoating layer was prepared to prevent the smoothing layer from being contaminated with raw talc adhering to the inner surface of the coating pan.

The three lots hardly differed from each other in strength, disintegration, loss on drying, moisture, physical shock, falling-down tests, and each active ingredient stability study.

Table 4

Results of Analysis of Variance

Factor	SS	DF	MS	Fo
A. Talc for aluminum acetylsalicylate layer	112,326	1	112,326	1.99
B. Sugar layer on aluminum acetylsalicylate	12,610	1	12,610	0.22
C. Filler for smoothing layer	2,630,863	2	1,065,426	18.895[a]
A * B	67,350	2	67,350	1.194
A * C	219,465	2	109,732	1.946
B * C	21,577	2	10,788	0.191
Error	112,772	2	56,386	

SS, sum of square; DF, degree of freedom; MS, mean square; Fo, unbiased variance ratio

[a] $F(2, 2, 0.05) = 19.0$.

Table 5

Small-Spot Generation on Sugar-Coated Tablets Prepared Using Talc Treated with Each Concentration of HCl at Each Temperature

	Concentration of HCl			
	1%	2%	4%	6%
HCl treating temperature				
RT	51	45	47	42
70°C	35	30	18	21

Physicochemical Properties of Talc and HCl-Treated Talc

The physicochemical properties of raw talc and the HCl-treated talc (5% HCl, 70°C, 30 min) were then compared. As shown in Table 7, hardly any difference between raw talc and the HCl-treated talc was evident except for the quantity of iron extracted with 5% acetic acid at 40°C at 30 min and the pH of the suspension. This was considered to indicate that the surface layers of the two talcs were different. The quantity of iron was determined by atomic absorption analysis. Hydrofluoric acid was used to determine the whole content of iron in the talc.

The quantities of inorganic atoms extracted from raw talc into water or 10% HCl were also determined by atomic absorption analysis. None of the atoms likely to be related to the spot generation, except iron, were found, as shown in Table 8.

Iron in talc is water insoluble, and iron extracted into

Table 6

Large-Scale Preparation of Sugar-Coated Tablets Containing Aluminum Acetylsalicylate

	Lot No.		
	101	102	103
Talc			
Aluminum acetylsalicylate layer (180 mg)	Raw	Raw	Raw
Talc subcoating layer (45 mg)	Raw	Raw	HCl treated
Smoothing layer (50 mg)	Raw	HCl treated	HCl treated
Sugar-coating layer (35 mg)	—	—	—
40°C, 82% RH, 8 days	1120	90	20
25°C, 65% RH, 12 months	20	1	1

	Lot No.		
	101	102	103
Physical properties			
Diameter (mm)	10.4	10.4	10.4
Thickness (mm)	6.2	6.1	6.1
Weight (mg)	509.5	497.4	498.6
Strength (kg)	16.7	16	16.6
Disintegration time (min)	49	48	55
Loss on drying (60°C, 4mmHg, 5hr)	2.09	2.26	2.14
Falling test (1.5 m, 50-ml glass bottle, 20 tablets)			
Chipped	14	21	17
Cracked	64	55	38
Bubblelike damaged	16	22	34
Undamaged	6	2	11

Table 7

Physicochemical Properties of Talc and HCl-Treated Talc

Density:	Lot No.	Bulk Density	Tapped Density
Talc	A714	2.4 ml/g	1.7 ml/g
	17520	2.4	1.5
HCl-treated talc	17521	2.2	1.2
	17523	2.4	1.5
Sedimentation speed: HCl-treated talc is slightly faster			
X-ray diffraction: not different			
IR spectroscopy: not different			
Differential thermal analysis: not different			
Surface acidity: not different			
pH of suspension (5 g/20 ml water, shaking for 45 min):			
	Lot No.	pH	
Talc	1447	9.03	
	1881	9.08	
HCl-treated talc	17521	6.87	
	17523	6.61	
		Iron	
Extracted iron (ppm):	Lot No.	5% HAc	HF
Talc	1447	20	600
HCl-treated talc	17521	0.5	600
Smoothing effect (sugar coating): not different			

5% acetic acid was colored with *o*-phenanthroline. As this result showed that the extracted talc contained Fe^{2+}, the quantities of Fe^{2+} and Fe^{3+} were colored separately with *o*-phenanthroline (6) and potassium thiocyanate (1, p. 1728) reagents, and their absorbances were determined by a spectrophotometer at 509.6 nm and 479.6 nm, respectively. The extraction with 5% acetic acid was performed anaerobically to prevent the ferrous ion from being oxidized by oxygen in the head space of the vessel and in 5% acetic acid. Table 9 shows that all the iron ions were Fe^{2+}, which does not color with salicylic acid.

Mechanism of Small Black Spot Generation

The small black spots were considered actually to be deep purple spots of a chelation compound of Fe^{3+} with salicylic acid, a hydrolysis product from aluminum acetylsalicylate, and blended with the color of the tablets. Accordingly, Fe^{+2} extracted from raw talc, as shown in Table 9, needs to be oxidized to Fe^{3+}. In fact, the tablets prepared with raw talc were stored in a 100% RH desiccator with oxygen replaced with nitrogen gas at 40°C for 8 days, and it was found that the black spots did not ap-

Table 8

Inorganic Atoms Extracted from Talc with Water and 5% HCl (ppm)

		Al	Si	Ca	Mg	Fe
Distilled water	RT/60 min	—	10.1	20.1	8.7	—
5% HCl	RT/60 min	1.7	16.3	356.7	808.3	22
Distilled water	70°C/30 min	—	73.6	176.1	18.4	—
5% HCl	70°C/30 min	5.6	155.2	256.0	2120	39.5

Talc lot no. 1440.

Table 9

Quantity of Ferrous and Ferric Ions Extracted at 40°C for 24 hr from Talc Lot No. 1447

Solution for Extraction	Fe^{2+}	Fe^{3+}	Fe
5% Acetic acid solution	21.0 ppm	ND	20 ppm
0.2% Salicylic acid solution	ND	ND	ND

pear under the anoxic conditions, with oxygen being necessary for their generation. Water or glacial acetic acid could not extract Fe^{+2} from the talc. Therefore, the mechanism of small black spot generation was speculated to be as shown in Fig. 3.

First, aluminum acetylsalicylate is hydrolyzed to salicylic acid and acetic acid with moisture in the aluminum acetylsalicylate layer. Second, some of the molecules of salicylic acid and acetic acid migrate into the smoothing layer through small pores in the aluminum acetylsalicylate layer. Third, these molecules, with water, extract ferrous ions from the surface of the talc in the smoothing layer. Fourth, extracted Fe^{2+} is oxidized to Fe^{3+}, and this chelates with salicylic acid to generate the small spots, which can be seen through the considerably transparent yellow-colored sugar coating.

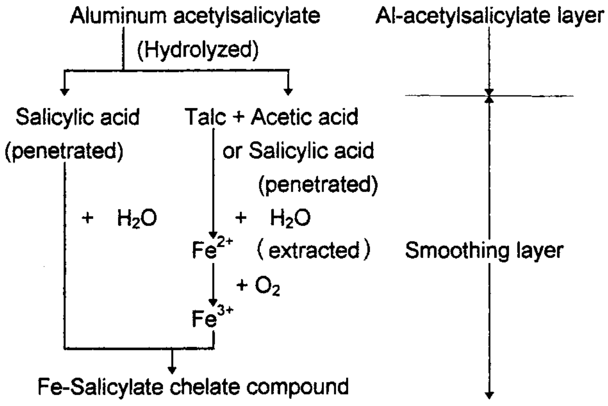

Figure 3. Mechanism of generation of small black spots in talc smoothing layer of the sugar-coated tablets containing aluminum acetylsalicylate in the subcoating layer.

These pores are considered to be the cause of the spot, but not the whole coloration. Tablets comprising a mixture of talc and salicylic acid were colored when stored at 40°C at 82% RH for 8 days, although nearly saturated 0.2% salicylic acid solution hardly extracted iron from talc. This means that salicylic acid can extract Fe^{2+} from talc. In the case of the sugar-coated tablets with the HCl-treated talc subcoating layer and HCl-treated talc in the smoothing layer, the spots generate in the same manner in the aluminum acetylsalicylate layer, and the some parts of molecules of salicylic acid and acetic acid migrate through the pores in the aluminum acetylsalicylate layer and the HCl-treated talc subcoating layer and reach the HCl-treated talc smoothing layer. However, the spots are not generated due to lack of the Fe^{2+} ion in the surface of the talc in the talc subcoating and smoothing layers, and the spots in the aluminum acetylsalicylate layer cannot be seen through these layers. Iron is considered to be one of the atoms with which a very small amount of magnesium in the talc molecule is replaced (7). The small black spots, but not the whole coloration, are considered to stem from the pores located in the smoothing layer.

REFERENCES

1. U.S. Pharmacopeial Convention, *The United States Pharmacopeia*, 23rd ed., Author, Rockville, MD, 1995.
2. G. Wallrabe and H. Schartner, Talcum D.A.-B. VI. Apoth. Ztg., 48, 571–572, 27CA, 3287 (1933).
3. G. Taguchi, *Tables of Orthogonal Arrays and Linear Graphs*, Marzen, Tokyo, Japan, 1962.
4. K. Ishikawa, T. Fujimori, and H. Kume, *Jikken Keikaku Hoh* (*Experimental Design*) (Joh, Ge), Tokyo Kagaku Dojin, Tokyo, Japan, 1967.
5. I. Grabowska, Attempts to stabilize acetylsalicylic acid in solid mixtures, 15678, 30 CA, 1964.
6. *The Merck Index*, 12th ed., Merck and Company, White House Station, NJ, 1996, p. 7356.
7. Japan Clay Academy, *Nendo* (*Clay*) *Handbook*, Gihohdo, Tokyo, Japan, 1967, p. 79.