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PREPARATIONS OF SOLID PARTICULATES OF AMINOPYRINE-BARBITAL COMPLEX (PYRABITAL) WITHOUT AUTOXIDATION BY A SPRAY DRYING TECHNIQUE

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ABSTRACT

Aminopyrine, barbital and colloidal silica dispersed in buffer solutions having pH 5.46 to 8.01 were spray-dried by a centrifugal wheel atomizer at 130 ± 5 °C. When the pH of the feeding liquid for spray drying was 5.70 to 7.24, the resultant product was a mixture of aminopyrine-barbital complex (pyrabital), aminopyrine and the excipient. When the pH was lower than 5.84 or higher than 7.84, barbital or sodium barbital coexisted in the above mixture products. Autoxidation of aminopyrine occurred during the spray drying was greatly prevented by introducing chelating agent, e.g. ethylenediaminetetraacetic acid and glycine, or antioxidation agent, e.g. sodium

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thiosulfate and citric acid in the feeding liquid. It was also found that reducing the pH of the feeding liquid effectively depressed the autoxidation of aminopyrine.

INTRODUCTION

Spray drying technique is a useful method for agglomeration of pharmaceutical powder as well as drying of heat sensitive food, drug and etc. The resultant agglomerates are generally spherical in shape, possess a narrow size distribution and are hollows[1]. Due to these characteristics, spray-dried agglomerates are usually free flowing, and dissolve rapidly[2].

One of the recent topics on spray drying technique, is a direct formation of solid particulates from droplets by chemical reaction during drying. Crosby and Abdul-Rahman[3] produced ammonium sulfate spheres by the reaction of liquid drops of orthophosphoric acid with gaseous ammonia. This process offered the advantages of reducing costs and easing problems of control. Takenaka et al.[4] prepared solid particulates of theophylline-ethylenediamine complex directly by spray drying ethylene diamine solution of theophylline.

In the previous study, Kawashima et al.[5] proposed a significantly improved method for the preparation of solid particulates of aminopyrine-barbital complex (pyrabital) for tableting, which combined the synthesis, the

drying and the agglomeration processes into one process. In the present study, this process was further developed for preventing autoxidation of aminopyrine occurred during spray drying. This was accomplished by formulating antioxidation substance or chelating agent in the spray drying feeding liquid and adjusting its pH properly.

MATERIALS AND METHODS

Spray drying technique

Aminopyrine and barbital used were the JP grade. Aminopyrine (34 g), barbital (13.5 g) and antioxidation substances, i.e. sodium thiosulfate and citric acid or chelating agent, i.e. ethylenediaminetetraacetic acid, glycine and sodium polyphosphate (0.1 to 0.2 W/V%) were dispersed in 600 ml of distilled water by a jet type homogenizer. Another suspension including colloidal silica and the drugs was prepared to adjust pH at 5.46, 5.84, 6.68, 7.84 or 8.01 by using a suitable buffer solution. The system was held for 20 minutes with stirring and was heated to 60 °C when necessary. The resultant uniform aqueous slurry was atomized into a drying chamber, maintained at 130 ± 5 °C. The feeding rate of the aqueous slurry into the chamber was 20-33 ml/min. The atomization of the slurry was carried out by employing a centrifugal wheel atomizer (diameter, 4 cm, Type 1051, Iwai Kikai Co. Ltd., Japan) rotated at 40000 rpm.

Measurement of physicochemical properties of the spray-dried products

The sizes of the spray-dried products were measured by a photographic counting method using a particle size analyzer (TGZ-3, Karl Zeiss Co. Ltd., West Germany). The contents of aminopyrine and barbital in the products were measured spectrophotometrically. Aminopyrine was determined with 270 nm in acidic solution at pH 1.2, composed of sodium chloride (2.0 g) and dil. hydrochloric acid (24.0 ml) made up to 1 ℓ with distilled water. Barbital was determined using a double-beam spectrophotometer (Model 556, Hitachi Manufactory Co. Ltd., Japan) at 250 nm and 269 nm in alkaline solution at pH 9.6, composed of 1/20 mol borax (44.5 ml) and 1/20 mol sodium carbonate (55.5 ml). Identification of the spray-dried products was carried out by IR spectroscopy (Model A-102, Nihon Bunko Co. Ltd., Japan) and X ray diffractometer (JDX, Nihon Denshi Co. Ltd., Japan). Autoxidation of aminopyrine in the products during spray drying was investigated by thin layer chromatography on silica gel (DC-Fertig platten Kiesel 60 F254, Merck Co.) using isopropyl alcohol-chloroform-ammonium hydroxide (28 %) (9:4.5:2) or chloroform-methanol mixture (14:1) as solvent, and by UV spectroscopy (Model 556, Hitachi Manufactory Co. Ltd., Japan).

RESULTS AND DISCUSSION

Physicochemical 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 30 μm and their distributions were represented by a log-normal form.

It was found that the contents of aminopyrine and barbital in the products depended on the formulation for spray drying as seen in Table I. Although the percentage of drug contents in the products varied widely, the molecular ratio of aminopyrine to barbital was fairly constant, i.e. 2.2 ± 0.4, when the pH values of the feeding liquid for spray drying were 5.70 to 7.24, irrespective of the type of the additive used as shown in Table I. With increasing pH of the feeding liquid for spray drying without antioxidation and chelating agents, the molecular ratio of aminopyrine to barbital in the products decreased. This finding might be interpreted in terms of increased solubility of barbital and decreased solubility of aminopyrine with an increase in pH of the feeding liquid for spray drying as seen in Table II. Undissolved aminopyrine particles might be separated easily from the droplet due to the inertia force exerted to them during atomizing.

Identification of the spray-dried products

Infrared spectra of the spray-dried products showed a broad peak of colloidal silica contained in the product

TABLE I

Drug Contents in the Spray-dried Products with the Additive

Additives	Aminopyrine content (%)	Barbital content (%)	Molecular content ratio of aminopyrine to barbital
ethylenediaminetetraacetic acid	36.90	12.80	2.3 : 1
glycine	36.40	15.20	2.0 : 1
sodium thiosulfate	49.50	16.13	2.3 : 1
citric acid	24.81	7.74	2.6 : 1
sodium polyphosphate	26.13	10.81	1.9 : 1

TABLE II

Effects of pH on Drug Contents in the Spray-dried Products and Drug Solubilities

*Solubilities at 30 °C

pH of the feeding liquid	Aminopyrine content (%)	Barbital content (%)	Molecular content ratio of aminopyrine to barbital	Solubility of aminopyrine (mg/ml)*	Solubility of barbital (mg/ml)*
5.46	34.75	13.15	2.1 : 1	60.0	10.2
5.84	23.77	11.52	1.6 : 1	58.5	10.1
6.68	18.52	11.29	1.3 : 1	57.0	10.0
7.84	13.18	19.87	0.5 : 1	56.5	11.2
8.01	11.23	23.29	0.4 : 1	56.0	11.5

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} in the spectra of the spray-dried products prepared from the slurries controlled at pH 5.46 to 8.01. None of these characteristic peaks appeared in the IR spectra of aminopyrine, barbital and their physical mixture. The IR spectra of the products prepared from the feeding liquid with pH values less than 5.84 differed from that of pyrabital, which suggested that the products were almost physical mixture of aminopyrine and barbital. It was found that the products prepared from the feeding liquid with pH values larger than 7.84 contained sodium barbital, which was identified by their IR spectra as shown in Fig. 1.

X-ray diffraction patterns of the spray-dried products are seen in Fig. 2. Although the intensities of the diffraction peaks of the products were weaker than those of pyrabital, aminopyrine and barbital, the characteristic peak of pyrabital at 6.6 and 18.5 ° in diffraction angle 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. In the pattern of the product prepared from the feeding liquid with lower pH than 5.84, characteristic diffraction peaks of aminopyrine and

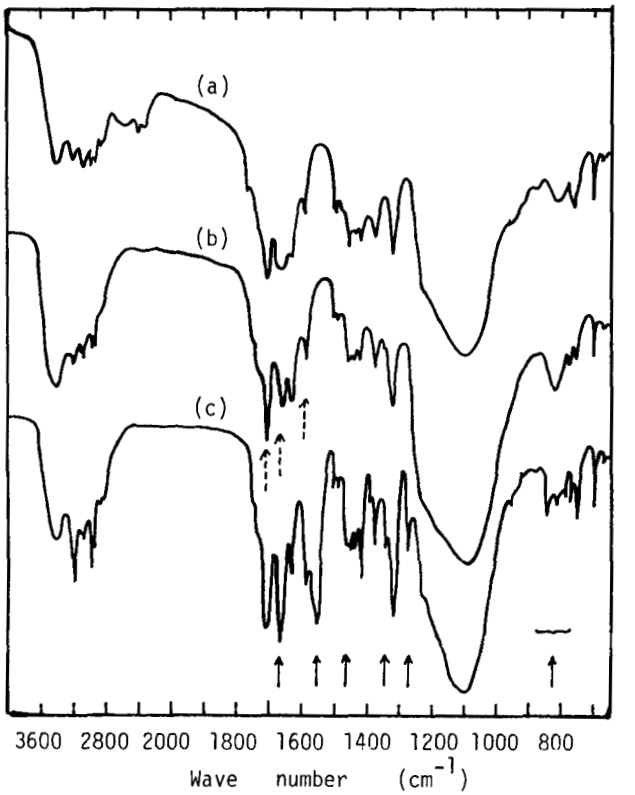

FIGURE 1

IR Spectra of the Spray-dried Products

pH of the feeding liquid for spray drying:
(a) 5.46 to 5.84 (b) 6.68 (c) 7.84 to 8.01
↑ and ↑ represent characteristic absorption bands of pyrabital and sodium barbital respectively.

barbital appeared. When pH of the feeding liquid was higher than 7.84, the resultant product revealed characteristic peaks of sodium barbital at 10.8 °, 17.0 ° and 26.8 °.

Pfeiffer[6] reported that pyrabital was a mixture consisting of a molecular compound of aminopyrine and barbital (molecular ratio 1:1) and an additional molecule

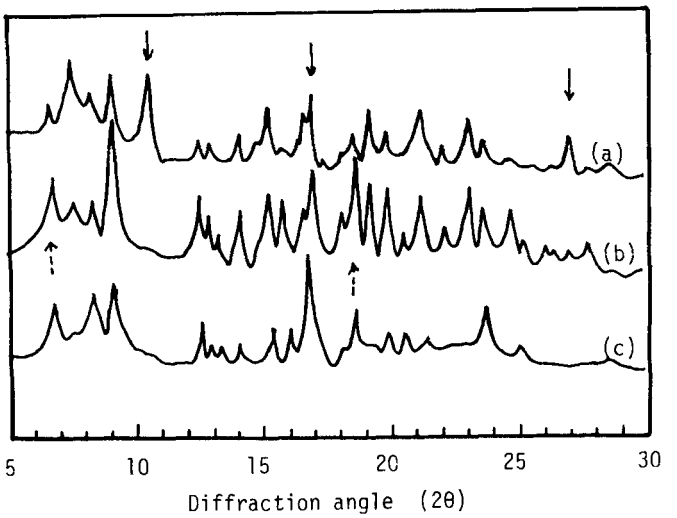

FIGURE 2

X-ray Diffraction Patterns of the Spray-dried Products

pH of the feeding liquid for spray drying:
(a) 7.84 to 8.01 (b) 6.68 (c) 5.46 to 5.84
↑ and ↓ represent characteristic diffraction peaks of pyrabital and sodium barbital

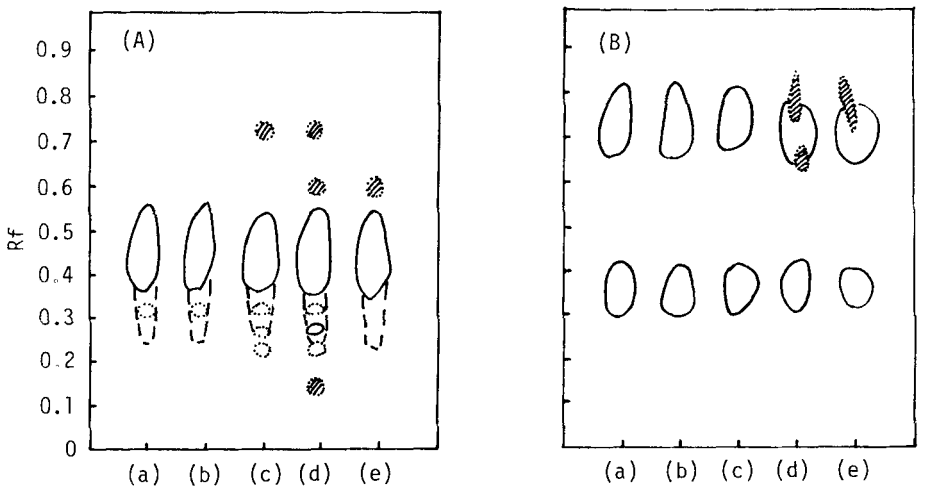

FIGURE 3

TLC of the Spray-dried Products with the Additives

(A) Developed with chloroform and methanol (14:1)
(B) Developed with isopropyl alcohol, chloroform and ammonium hydroxide (9:4.5:2)

Dotted drawing illustrates a trace spot or tailing.
Shaded spot or band indicates yellow one.
Additives: (a) ethylenediaminetetraacetic acid (b) glycine (c) sodium thiosulfate (d) sodium polyphosphate (e) citric acid

of aminopyrine. Referring to the larger molecular ratio of aminopyrine to barbital contained in the products prepared with the additive at pH 5.70 to 7.24, they were assumed to be a mixture of pyrabital, aminopyrine and the additive used. The products prepared at the lower pH than 5.84 were a mixture of pyrabital, aminopyrine and barbital. At the higher pH than 7.84, the resultant products were a mixture of pyrabital, sodium barbital and aminopyrine.

Autoxidation of aminopyrine during spray drying and a method for prevention of it

Thin-layer chromatograms of the spray-dried products developed with chloroform and methanol (14:1) and with isopropyl alcohol, chloroform and ammonium hydroxide (9:4.5:2) are shown in Figs. 3 and 4. The main spots of Rf 0.48 and Rf 0.45 in the chromatograms developed with chloroform-methanol and isopropyl alcohol-chloroform-ammonium hydroxide mixture were identified with aminopyrine and barbital respectively in the previous study[5]. The yellow bands at Rf 0.82 and the other miscellaneous bands in the chromatograms were characteristic of the spray-dried products. It was suggested in the previous paper[5] that this yellow spot was attributed to the oxidation products of aminopyrine produced during spray drying. It was also found that the oxidation products caused to absorbing at 385 nm, where aminopyrine did not absorb as seen in Fig. 5 (A).

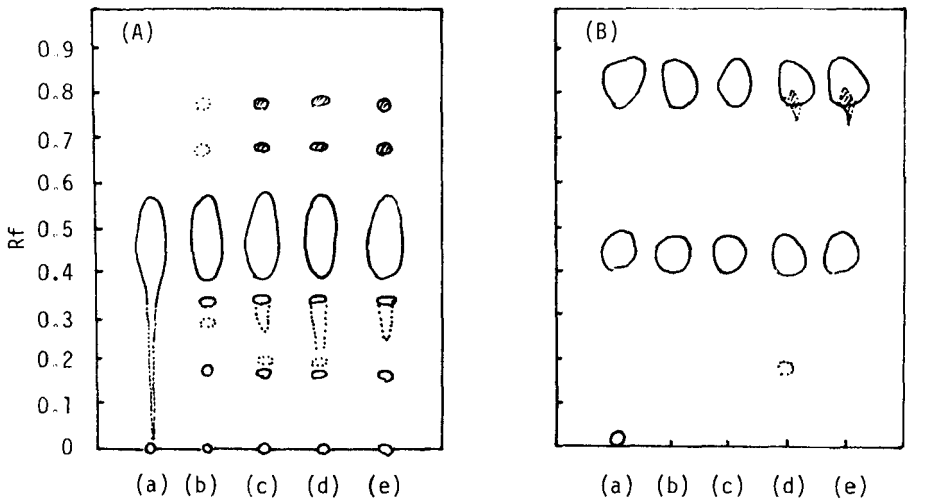

FIGURE 4

TLC of the Spray-dried Products Prepared from the Various pH Feeding Liquid

pH: (a) 5.46 (b) 5.84 (c) 6.68 (d) 7.84 (e) 8.01

Based on the above results, improved formulations for preventing the autoxidation of aminopyrine in the spray-dried products were searched by means of spectrophotometric and TLC analyses. When the pH of the feeding liquid for spray drying was low, e.g. 5.46, the main spot at Rf 0.48 for aminopyrine in the chromatogram of the resultant product tailed a little, but no miscellaneous spots were found in Fig. 4. When ethylenediaminetetraacetic acid or glycine was formulated in the feeding liquid, the main spot and a trace spot appeared in the chromatogram as shown in Fig. 3. The products prepared at pH 5.46 and with ethylenediaminetetraacetic acid or glycine revealed no absorption peak at 385 nm as seen in

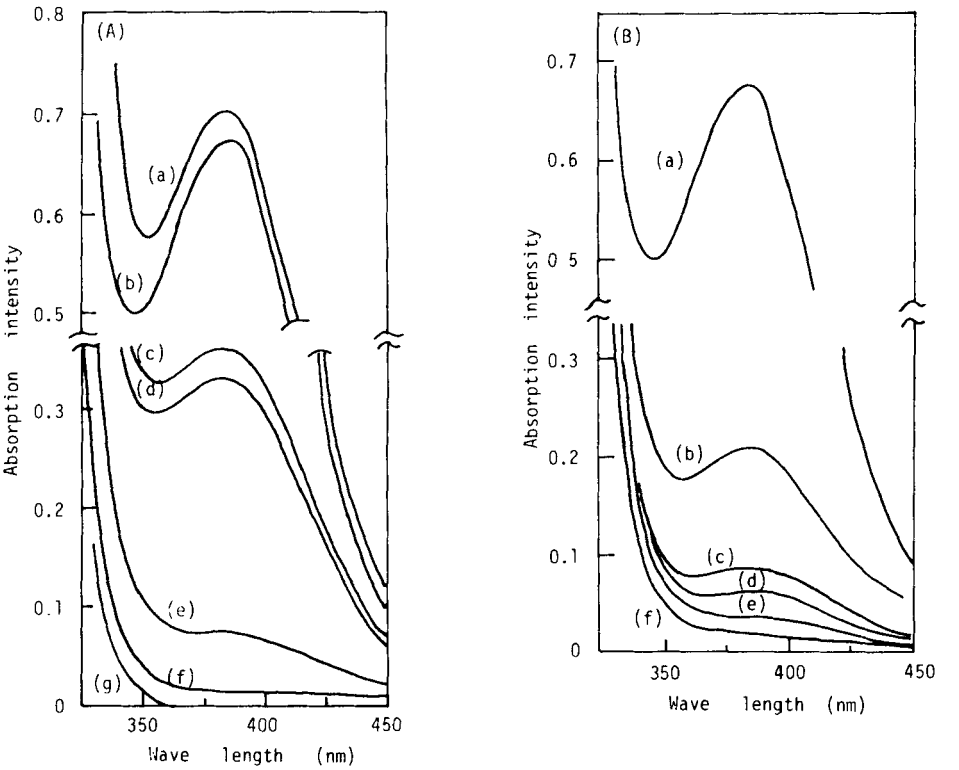

FIGURE 5

UV Spectra of the Spray-dried Products

Parameters: (A) pH of the feeding liquid
(b) 8.01 (c) 7.84 (d) 6.68
(e) 5.84 (f) 5.46
(B) Type of the additives
(b) sodium polyphosphate (c) citric acid (d) sodium thiosulfate
(e) glycine (f) ethylenediamine-tetraacetic acid
(a) the product prepared from aqueous solution without additive
(g) original aminopyrine

Fig. 5. At pH 5.84, two small spots and three small traces appeared in the chromatogram developed with chloroform-methanol. When the pH was higher than 7.84, yellow spots at Rf 0.68 and 0.78 and miscellaneous spots at Rf

0.18 and 0.33 appeared in the chromatograms developed with chloroform-methanol. A small tailing at Rf 8.0 appeared in the chromatogram developed with isopropyl alcohol-chloroform-ammonium hydroxide mixture. The product with citric acid revealed additional small spots and a faint band to the main spots in the chormatograms. In the chromatogram of the product with polyphosphoric acid, several small spots and bands appeared as shown in Fig. 3. At 385 nm a weak absorption peak appeared for the product with citric acid. Among the additives used in the present test, the absorption strength of the polyphosphoric acid product was fairly strong. But the actual autoxidation level described in the above was extremely low compared with that of a reference spray-dried product without additives as seen in Fig. 5.(B).

To describe the degradation of aminopyrine during spray drying quantitatively, the relative absorption intensities at 385 nm of the spray-dried products to that of pyrabital (As/Ap) as a reference standard are plotted in Fig. 6. The relative absorption intensity increased almost linearly with increasing the pH of the feeding liquid for spray drying as shown in Fig. 6. The present finding contradicted the finding by Kigasawa[7], that aminopyrine was more susceptible to oxidation in the acidic solution than in the alkaline solution. It was confirmed that the coexistence of barbital and colloidal

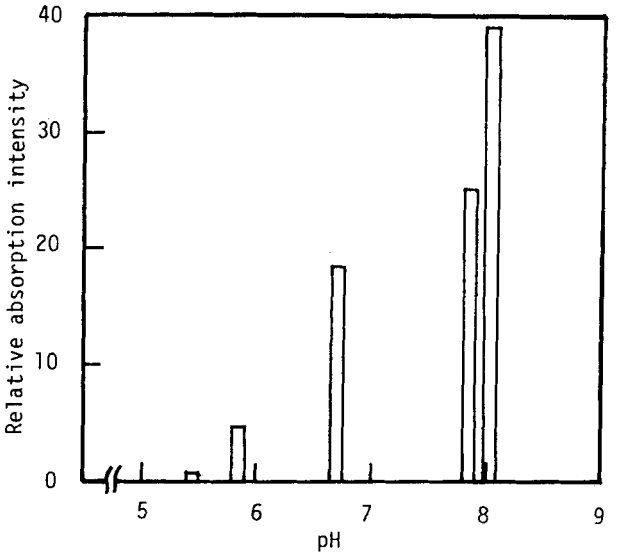

FIGURE 6

The Effects of pH on the Relative UV Absorption Intensities

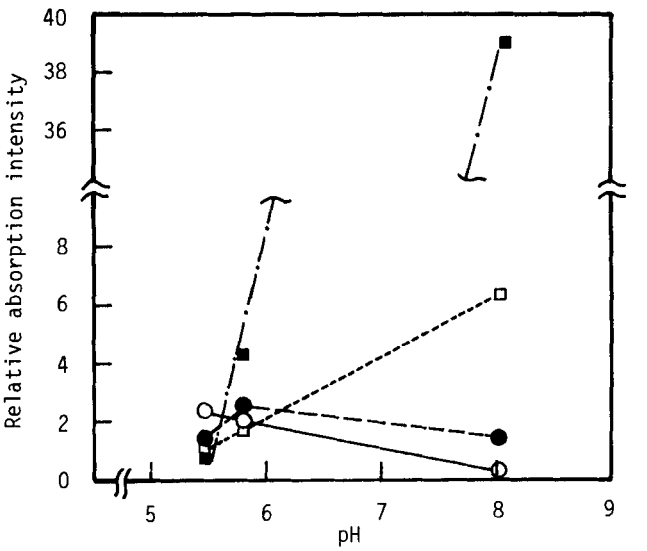

FIGURE 7

The Effects of pH and Addition of Barbital and Colloidal Silica on the Autoxidation of Aminopyrine

○ , original aminopyrine and aminopyrine + colloidal silica ● , aminopyrine + barbital □ , aminopyrine + barbital + colloidal silica ■ , spray-dried products containing aminopyrine, barbital and colloidal silica

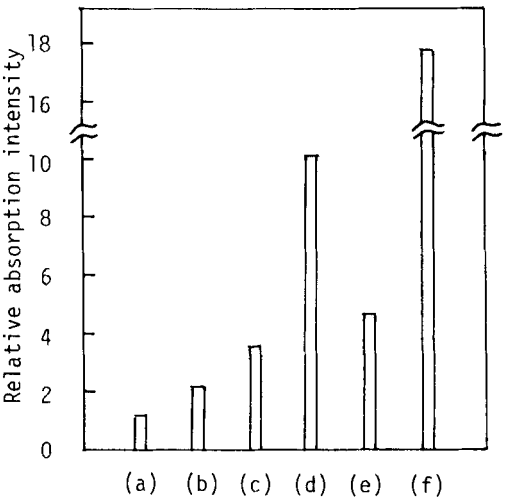

FIGURE 8

The Effects of the Additives on the Relative UV Absorption Intensities

Type of additive: (a) ethylenediamenetetraacetic acid (b) glycine (c) sodium thiosulfate (d) sodium polyphosphate (e) citric acid (f) without addition of the additive

silica in the formulation was responsible for the above characteristic finding by the following reference test. The test was conducted by introducing air into the solution adjusted to various pH containing aminopyrine alone or aminopyrine, barbital and colloidal silica as shown in Fig. 7. The pH dependency of aminopyrine oxidation was not affected by colloidal silica alone. Barbital was also almost inactive to changing the pH dependency. When the feeding liquid for spray drying was used as the air-oxidation test solution, the autoxidation of aminopyrine in the solution increased with increasing pH, contrasted

to the other tests. This trend was greatly enhanced by spray drying. The explanation for this characteristic finding was not found at present.

Ethylenediaminetetraacetic acid and glycine were the most effective additives for preventing the autoxidation of aminopyrine. It was assumed that they reacted easily with a trace metal in the feeding liquid which acted as a catalyst for the autoxidation of aminopyrine. Polyphosphoric acid is also a chelating agent, but the alkalinity of the solution 7.24 might decrease the effect of preventing the autoxidation of aminopyrine. Reduction agent such as sodium thiosulfate and citric acid fairly reduced autoxidation of aminopyrine as expected as shown in Fig. 8.

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