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Tablets of Pyrilamine Resin Adsorbate with Aspirin and Vitamin C

By SHELDON SIEGEL, ROY H. REINER, JAMES A. ZELINSKIE, and EDWARD J. HANUS

Marked changes in physical appearance manifested by dry formulations containing aspirin, an antihistamine, and vitamin C during an accelerated temperature stability study are discussed. The stabilization afforded by a resin adsorbate of a commonly used antihistamine, pyrilamine, is noted. Discrepancies in the results obtained from stability studies of these preparations have been traced to the efficiency of the closure utilized in the packaging of the product, as well as the methods employed in the pretreatment, sampling, and evaluation of test samples. The implications of these observations from a developmental standpoint are discussed.

THE AVAILABILITY of ion exchange resins suitable for oral administration has presented the formulator with a means of tailoring products in a way not heretofore possible. These materials are currently available in a wide range of types and mesh specifications and present a new means of complexation of an active ingredient which can lead to a significant enhancement in both the stability of the medicament and in the manipulation of its release pattern. It is with a variation of the former case, the reduction of an undesirable incompatibility of salts of pyrilamine in common formulations, that this paper concerns itself.

Tablet and capsule formulations for the symptomatic treatment of the common cold constitute a significant segment of the ethical and proprietary drug market. These products usually contain aspirin, an antihistamine, and vitamin C. The development of such products is complicated by interactions between the ingredients, resulting in marked changes in the physical appearance of the preparation after short storage intervals. Certain antihistamines have been shown to be incompatible in dry dosage forms containing aspirin and/or vitamin C (1, 2). This interaction is manifested by softening and darkening of tablets, surface crystal growth, and an acetous odor. Methods such as compression coating, multilayering, and pan coating, which overcome the existing problems by physical separation of the reactants, have been utilized to produce products having an acceptable shelf life. We have investigated resin adsorbates of pyrilamine for possible reduction in the degree of incompatibility in formulations of this type.

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EXPERIMENTAL

Analytical Methods

Pyrilamine Resin Adsorbate.—Accurately weigh a sample of finely ground tablets equivalent to 25 mg. of pyrilamine maleate. Disperse in 25 ml. of 2 *N* hydrochloric acid and shake vigorously for 30 minutes at room temperature. Extract with three 15-ml. portions of chloroform, discarding the chloroform layers. Add 5 ml. of 50% potassium hydroxide to the acid layer, shake well, and let stand at room temperature for 15 minutes. Extract with three 15-ml. portions of chloroform. Extract the combined chloroform extracts twice with 25 ml. of 1 *N* hydrochloric acid and measure the absorbance at 315 mμ in a suitable spectrophotometer. Use 1 *N* hydrochloric acid as the reference solution.

$$\frac{A \text{ of sample at } 315 \text{ m}\mu \times 10}{0.205 \times \text{No. of tablets}} = \text{mg. per tablet as pyrilamine maleate}$$

Ascorbic acid.—Ascorbic acid was assayed by the official U.S.P. XVI method.

Acetylsalicylic and Salicylic Acids.—A rapid spectrophotometric assay of acetylsalicylic and salicylic acids was utilized in this investigation (3). It is to be noted that the utilization of this assay procedure in preparations containing pyrilamine is somewhat inaccurate because of the interference exhibited by the absorbance of pyrilamine at the 308 mμ peak. To simplify the numerous assays involved, this interference was considered negligible; however, the values obtained should not be considered absolute.

Sample Preparation and Treatment

Pyrilamine base was adsorbed on a weakly acidic carboxylic acid ion exchange resin (XE-64)[1] in varying concentrations. The pyrilamine resin adsorbate formed (PRA) is a free flowing, off-white, essentially odorless powder. Economic and formulation considerations resulted in the utilization of a resin product containing the equivalent of from 61.2 to 64.0% pyrilamine maleate.

Hard gelatin capsules of PRA, aspirin, and vitamin C; PRA, aspirin, and sodium ascorbate; and controls containing pyrilamine maleate in place of the resin adsorbate were prepared and placed in storage at several temperature stations. The ratio of the ingredients in the formulations placed on this study is summarized in Table I.

TABLE I.—RATIO OF INGREDIENTS IN FORMULATIONS IN STUDY

	Formulation			
	1	2	3	4
Pyrilamine resin adsorbate, mg.	20.4[a]	...	20.4[a]	...
Pyrilamine maleate, mg.	...	12.5	...	12.5
Aspirin, mg.	300	300	300	300
Ascorbic acid, mg.	...	...	50	50
Sodium ascorbate, mg.	56.24[b]	56.24[b]	...	...

[a] Equivalent to 12.5 mg. pyrilamine maleate. [b] Equivalent to 50 mg. ascorbic acid.

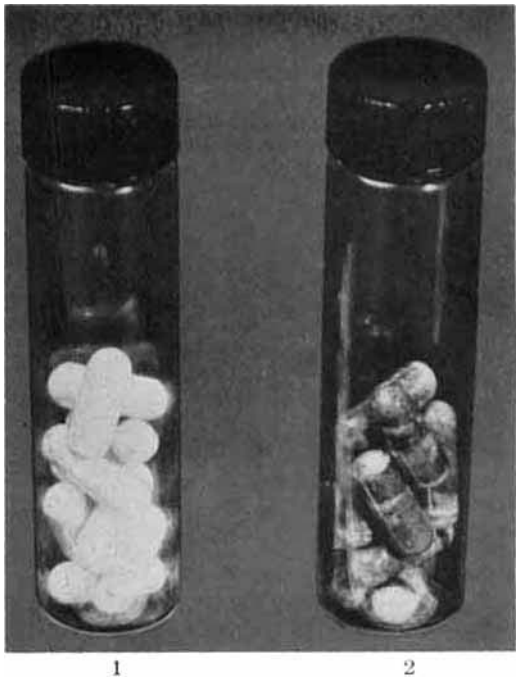
Compressed tablets containing aspirin powder, 300 mg., sodium ascorbate, 28 mg. (equivalent to 25 mg. ascorbic acid); PRA, 20.4 mg. (equivalent to 12.5 mg. pyrilamine maleate); and a control containing the maleate in place of the resin adsorbate were prepared by dry slugging methods. Corn starch, 10%; dried talcum, 5%; and Cab-O-Sil,[2] 0.5% were utilized as tableting aids. These were also placed in storage at elevated temperatures and observed periodically for gross physical changes.

As several apparent inconsistencies were disclosed in the interpretation of the observations of both the capsule and tablet formulations, a somewhat more detailed study was undertaken. The relationship of such factors as preheating of the tablets prior to packaging, the type of closure used on the container, and the frequency of inspection of the samples were investigated.

DISCUSSION

In all preparations studied under accelerated conditions, those containing the resin adsorbate of the antihistamine showed the least physical change. Figure 1 shows the difference in appearance between the capsule formulation containing PRA, aspirin, and sodium ascorbate, and that with pyrilamine maleate, aspirin, and sodium ascorbate after storage for 1 month at 45°. The enhancement of physical appearance by using the resin form is immediately apparent. It was also observed that preparations containing sodium ascorbate were far superior in this same respect to those containing ascorbic acid.

In the initial investigation, several inconsistent results were noted concerning the stability of the tablets which were not readily explainable. A significant lack of uniformity was observed between



1 2

Fig. 1.—1, Capsules of pyrilamine resin adsorbate, aspirin, and sodium ascorbate; 2, Capsules of pyrilamine maleate, aspirin, and sodium ascorbate, after 1 month of storage at 45°.

samples stored in bottles with polyethylene snap caps and those stored with Bakelite screw caps. Tablets in containers with the polyethylene closures were superior in physical appearance to those in containers sealed by screw caps. An investigation of the relationship of closure to stability was then undertaken and Fig. 2 illustrates the difference in physical stability experienced with the same formulation under different packaging conditions after storage for 2 months at 40°. Note the evidence of decomposition in the vial sealed with a nonporous cap (A), the improvement when a permeable polyethylene closure is used (C), and the absence of physical change when the containers are left open (E and F).

Although it is well known that polyethylene will allow the passage of air and other volatile material, the significance of this in common stability studies of this type has not, to our knowledge, been given sufficient recognition. Based on our accelerated studies with formulations of this type, it would then appear that the more permeable the container closure, the greater the physical stability of the contents. The following explanation is offered for this phenomenon. Under the temperature conditions imposed, this permeability would allow the escape of moisture from the formulations, thereby effectively removing the component responsible for the hydrolytic degradation of aspirin. In addition, the open container (E) and, to a lesser degree, the container with a permeable closure (polyethylene snap cap), permit the escape of the acidic gaseous degradation products resulting from aspirin hydrolysis. This would suggest that the autocatalytic degradation of aspirin is promoted by the presence of these acidic degradation products. It should also be men-

[1] Rohm and Haas Co., Philadelphia, Pa.
[2] Godfrey L. Cabot, Inc., Boston, Mass.

tioned that an acidic environment within the container would promote the desorption of the pyrilamine from the resin in the form of an acid salt, which was previously shown to be less desirable in preparations of this type.

Several other very practical considerations which may be explained on the above basis were observed during this investigation. Filled containers appeared to exhibit greater instability than partially filled ones (see Fig. 2). This indicates that this difference is due to the entrapment of significantly more volatile decomposition products, hence increasing the rate of degradation. Further corroboration of this postulate is taken from the observation that samples which had been opened frequently to check stability appeared more stable than counterparts which had remained unopened.

It was reasoned that if the foregoing explanation for the marked stability differences was valid, preheating the tablets prior to packaging should result in a significant enhancement of stability. Figure 3 illustrates the result of heating tablets for 20 and 40 hours at 50° before packaging and subsequent storage at 45° for 1 month. The unheated sample (G) underwent considerable physical degradation, evidenced by darkening of the tablets and appearance of a large number of crystals, shown by infrared spectroscopy to be salicylic acid. The heated samples (H and I) show no change in physical appearance. It thus appears that this preheating procedure resulted in the expulsion of both moisture and aspirin degradation products and, in this way, exerted a stabilizing influence on the formulation in addition to that achieved by the use of the resin adsorbate of pyrilamine. The chemical stability of this formulation is summarized in Table II. It is clear from the analytical data that the gross physical appearance of the preparation served as a valid indicator for the actual decomposition of the formulation.

It is felt that the observations reported here have strong implications from the developmental standpoint. The type of container closure and degree of fill are obviously of prime importance in evaluation of these products by accelerated temperature studies. It is interesting that formulations of this type appear to reverse the well documented belief that, to a large extent, stability is dependent upon the ability of the container to isolate the ingredients from the environment. It can be seen that a stability study that does not take into consideration factors of this type is quite likely to lead to fallacious extrapolations.

SUMMARY

Formulations containing pyrilamine resin adsorbate, aspirin, and vitamin C were found to be less subject to physical change in accelerated stability studies than control formulations containing the maleate salt of pyrilamine. An apparent lack of uniformity in the stability of such formulations has been related to the selection of container closures, container fill,

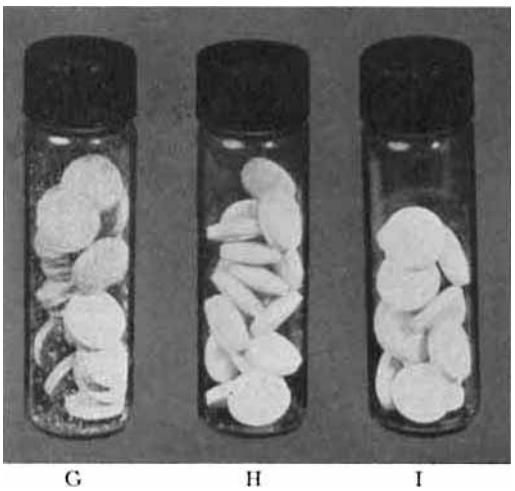


Fig. 3.—Effect of preheating on the stability of tablets containing pyrilamine resin adsorbate, aspirin, and sodium ascorbate after 1 month storage at 45°.

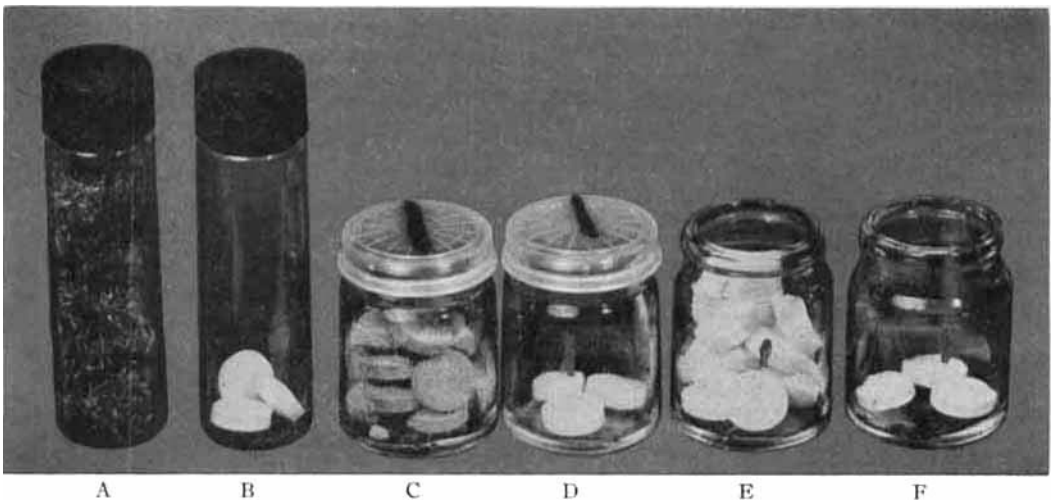


Fig. 2.—Comparative stability of a formulation containing pyrilamine resin adsorbate, aspirin, and sodium ascorbate under different packaging conditions after 2 months storage at 40°.

TABLE II.—CHEMICAL STABILITY OF FORMULATIONS[a]

Formula G	Initial Assay	60°C. 1 wk.	45°C. 1 wk.	45°C. 4 wk.	45°C. 8 wk.	45°C. 10 wk.	45°C. 12 wk.
Acetylsalicylic acid	319	271	314	297	273	267	252
Salicylic acid	7.0	76	10.5	18.7	58.0	77.0	82.0
Pyrilamine resin adsorbate (expressed as pyrilamine maleate)	12.7	...	12.7	...	11.8	...	11.0
Sodium ascorbate (expressed as ascorbic acid)	24.6	...	23.4	...	13.8	...	1.2
Formula H							
Acetylsalicylic acid	317	317	308	304	321	322	310
Salicylic acid	7.4	16	10.3	7.9	9.2	8.7	9.4
Pyrilamine resin adsorbate (expressed as pyrilamine maleate)	12.8	...	12.7	...	12.2	...	12.2
Sodium ascorbate (expressed as ascorbic acid)	25.6	...	23.8	...	24.8	...	24.7
Formula I							
Acetylsalicylic acid	324	298	316	305	317	314	314
Salicylic acid	7.6	16	9.6	8.7	7.6	8.6	8.8
Pyrilamine resin adsorbate (expressed as pyrilamine maleate)	12.7	...	12.6	...	12.7	...	12.4
Sodium ascorbate (expressed as ascorbic acid)	25.1	...	23.4	...	24.2	...	23.8

[a] Assay results reported as milligrams per tablet.

and sample handling techniques. The heat treatment of tablets prior to packaging has been shown to enhance further the stability of such products when stored at elevated temperatures.

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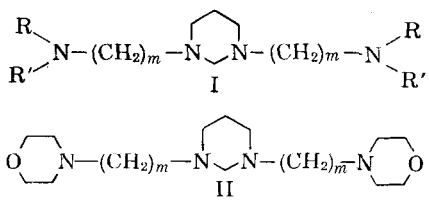
Hexahydropyrimidines I. Preparation of 2-Substituted-1,3-bis(*p*-dimethylaminobenzyl)-hexahydropyrimidines

By JOHN H. BILLMAN and LINNEAUS C. DORMAN†

A number of 2-substituted-1,3-bis(*p*-dimethylaminobenzyl)hexahydropyrimidines have been prepared by allowing various aldehydes to react with 1,3-bis(*p*-dimethylamino)propane. The latter diamine was prepared by the catalytic reduction of the di-Schiff base 1,3-bis(*p*-dimethylaminobenzylideneamino)propane. It was felt that *these compounds might possess antifungal, antibiotic, and antiviral activity.*

ALTHOUGH the synthesis of hexahydropyrimidines from 1,3-diamines and carbonyl compounds has been described for some time by a number of workers (1–7), a review of the literature reveals that relatively few hexahydropyrimidines have been prepared and examined for medicinal activity. Two particularly interesting publications by Van Hook and Craig report that 1,3-bis(dialkylaminoalkyl)- (I) (8) and 1,3-bis(heterocyclicaminoalkyl)hexahydropyrimidines (II)(9) possess antifungal, antibacterial and



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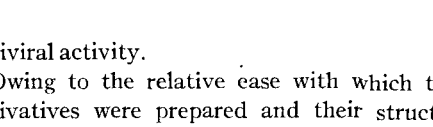

II

antiviral activity.

Owing to the relative ease with which these derivatives were prepared and their structural significance, it was of interest to determine if hexahydropyrimidines substituted in the 1-,2-, and 3-positions might also display similar, if not superior, pharmacological activity to the 1,3-di-

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