sizes and resultant decrease in total surface area in the A-46 foam helps to explain the lower consistencies. This lack of bubble size homogeneity would seem to indicate that emulsification of A-46 propellent is more difficult. A great deal of work remains to be done on characterization of foams from flammable propellent systems.

SUMMARY AND CONCLUSIONS

(*a*) A photomicrographic technique is described for the determination of the growth of bubbles in aerosol foams which yields a reasonably good degree of reproducibility.

(*b*) Within the same formulation and propellent concentration, smaller bubbles are associated with higher consistencies.

(*c*) As a container is emptied, bubble sizes and growth slopes tend to decrease due to a higher ratio of soap to propellent and thicker interbubble films. Consistency also decreases.

(*d*) The addition of methylcellulose increases foam consistency and decreases the rate of bubble coalescence.

(*e*) Initially, propellent 114 yields larger bubbles than propellent 12. Blends yield smaller bubble sizes than either single propellent. These results are consistent with foam rheology at both 5% and 75% can emptying.

(*f*) The addition of propylene glycol tends to decrease bubble sizes and increase foam consistency except in cases of plain propellent 114 where unusual effects are noted, particularly at 75% can emptying.

(*g*) When vapor volumes are matched, flammable propellents give rise to foams of lower consistency and decreased stability. This is not always obvious when observing average bubble size alone, as bubble sizes are more disperse when A-46 propellents are used.

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Keyphrases

Aerosol foams—bubble size analysis
Bubble size—aerosol rheology
Photomicrographic technique—bubble size determination
Aging foam—bubble diameter effect
Can emptying—bubble size, density
Propellent—foam bubble size

Drug Standards

Determination of Free Salicylic Acid in Buffered Aspirin Tablets

By JOSEPH LEVINE and JOHN D. WEBER

Aspirin and free saliyclic acid are quantitatively released from buffered aspirin tablets, with a negligible degree of hydrolysis of aspirin, by briefly wetting the sample with 98–100 percent formic acid, followed by immediate dilution with chloroform. The salicylic acid is isolated and determined as previously described.

SALICYLIC ACID can be quantitatively separated from aspirin by trapping it as the complex formed with ferric ion on a partition chromatographic column, using ferric chloride (1) or ferric chloride-urea (2) solutions as the immobile phase.

In the application of this procedure to analytical samples, it is essential that the entire amount of aspirin and salicylic acid be dissolved in the mobile phase before the chromatographic treatment, and that the aspirin is not hydrolyzed during the preparation of that solution. These

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two requirements are not readily achieved in the case of buffered aspirin tablets (2). Chloroform solutions of aspirin, in the presence of basic materials such as those which comprise the buffering components of the tablets, undergo hydrolysis together with aspirin anhydride formation (1). Boric acid stabilizes the solution, at least with respect to the hydrolysis of aspirin, but does not achieve the necessary release of the aspirin and salicylic acid from the buffer components to permit their complete solution in chloroform.

A preliminary acid treatment of the buffered tablet will release the aspirin and salicylic acid. The acid may, however, concurrently hydrolyze the aspirin. In designing a valid assay procedure, the acid which is used must: (*a*) produce only minimal hydrolysis of aspirin under the conditions of the assay; (*b*) rapidly and completely release aspirin and salicylic acid from the buffer components of the tablet; (*c*) be soluble in chloroform; and (*d*) be readily removed from the chloroform, so that the ferric-salicylic acid complex will not be dissociated during the following step of the analysis.

These requirements are fulfilled by 98–100% formic acid. The common 90% reagent is not suitable because it is immiscible with chloroform. The distribution of formic acid between chloroform and inorganic acids is greatly in favor of the aqueous phase; therefore, the formic acid is removed from the chloroform solution by passage over dilute hydrochloric acid.

In the analysis the powdered sample is thoroughly wetted with the formic acid and then immediately diluted with chloroform to sharply decrease the hydrolytic action of the acid.

The extent of hydrolysis during the period of contact of the sample with the formic acid before dilution was gauged by a direct determination of the rate of the hydrolysis. Although this increase varies somewhat for various brands of buffered aspirin, it lies in the range of 0.01–0.02%/min. The procedure specifies a period of 30–45 sec. for this step; the average time of contact will be shorter since a part of this time is consumed in the wetting of the sample. The total extent of hydrolysis in this step will therefore be in the order of 0.01%.

After dilution, hydrolysis is sharply decreased to an average of only 0.03%/hr., and thus a negligible amount occurs during the 10-min. period specified for dissolving the aspirin and salicylic acid.

The degree of completeness of solution is established by direct examination of the residual solid tablet components. After vigorous treatment of the residue with hydrochloric acid, the spectrum of a chloroform extract indicated the presence of both aspirin and salicylic acid. In view of the hydrolytic effect of the acid treatment, these results indicate that perhaps the major portion of the residual acidic material is aspirin, rather than salicylic acid. In any event, the total amount of the residual material, whatever its original identity, was about 0.02%, calculated as salicylic acid.

EXPERIMENTAL

The ferric chloride-urea reagent, salicylic acid standard, and chromatographic tubes are prepared as previously described (2).

Column A—Pack a plug of cotton about 15 mm. deep in the base of the chromatographic tube to absorb any stationary phase which may bleed off column. Mix 5 Gm. of diatomaceous earth[1] with 3 ml. of 0.05 *N* hydrochloric acid to a uniform mixture, transfer, and pack the mixture in three portions, lightly enough to obtain a 12 ml./min. flow of chloroform.

Column B—Pack a plug of glass wool[2] in the base of the chromatographic tube for support. To prepare the lower state, mix 1 Gm. of diatomaceous earth with 0.5 ml. of 30% phosphoric acid to retain any ferric chloride which may be removed during the elution of larger quantities of salicylic acid (3), as are often found in buffered tablets. Transfer the mixture to the tube and tamp to a uniform mass. For the upper stage, mix 3 Gm. of diatomaceous earth with 2 ml. of ferric chloride-urea solution, transfer to the column directly above the phosphoric acid layer, and tamp. Cover with a pad of cotton about 20 mm. thick to insure uniform distribution of the solvent over the column cross section. Mount column A above column B.

Procedure—(Use water-saturated solvents throughout.) Determine the average weight of a representative number of tablets. Grind to a fine powder rapidly, and immediately weigh an amount equivalent to about 500 mg. of aspirin. Transfer to a 100-ml. volumetric flask and immediately add 5 ml. of 98–100% formic acid. Agitate to wet the sample thoroughly; then within 30–45 sec. add 75 ml. of chloroform. Shake for 10 min., and adjust to volume with chloroform. Filter through a loose plug of glass wool. Pass 20.0 ml. of the sample over the columns, and then wash with three 25-ml. portions of chloroform, allowing each portion to pass through both columns before the successive addition. Discard the eluate and column A, and rinse the tip of column B with a stream of chloroform.

Place as receiver under column B a 100-ml. volumetric flask containing 10 ml. of methanol and 2 drops of hydrochloric acid. Pass a solution of 1 ml. of glacial acetic acid in 10 ml. of ether through the column and follow with 1% acetic acid-chloroform (v/v) to volume.

Concomitantly determine the absorbance of this solution and of the standard at the maximum at about 306 mμ.

[1] Celite, acid-washed, Johns-Manville Corp., New York, N. Y.

[2] Pyrex Filtering Fiber, Corning Glass Co., catalogue No. 3950.

TABLE I—SALICYLIC ACID CONTENT OF COMMERCIAL BUFFERED ASPIRIN TABLETS

Brand	% Salicylic Acid Found
A	0.53
	0.56
	0.57[a]
A[b]	0.51
	0.50
B	1.85
	1.86
C	0.69
	0.70[a]
	0.76[c]
	0.78[c]
D	1.41
	1.45
E	2.66
F	2.82
	2.91
G	0.86
	0.83

[a] Analysis by extrapolation of hydrolysis rate curve. [b] Separate bottle of same brand. [c] Analyzed 1 mo. after bottle was opened.

Determination of Rate of Hydrolysis—Weigh portions of sample equivalent to about 100 mg. of aspirin into individual 150-ml. beakers. Add 1 ml. of 98–100% formic acid to each beaker and agitate to wet the sample thoroughly. Immediately add 2 Gm. of diatomaceous earth to one beaker, mix thoroughly, transfer to column A, and tamp. Pass 25 ml. of chloroform through the columns, recording the interval between the addition of the formic acid and the addition of the chloroform as the period of contact. Continue the analysis as described above. Add the diatomaceous earth to the other samples at proper intervals to provide contact periods of 5, 10, 20, and 30 min.

RESULTS AND DISCUSSION

A number of commercial samples of buffered aspirin tablets purchased from local retailers were analyzed for their salicylic acid content. Results are shown in Table I.

The total extent of hydrolysis of aspirin during an actual assay is shown in the values obtained in the analysis of pure aspirin by the original procedure (2) and by the proposed procedure, using formic acid. The original procedure gave a salicylic acid value of 0.025% and the current procedure 0.036%, an increase of only 0.011%. Although a slightly larger increase may result during the analysis of buffered tablets, since the rate of hydrolysis of aspirin in these tablets is somewhat greater than that for pure aspirin (Fig. 1), it remains at a level close to the precision of the determinative steps (2), and therefore does not constitute a significant source of error. This is substantiated by the fact that the values obtained by extrapolation of the hydrolytic rate series to zero time agreed well with those obtained by the method as proposed.

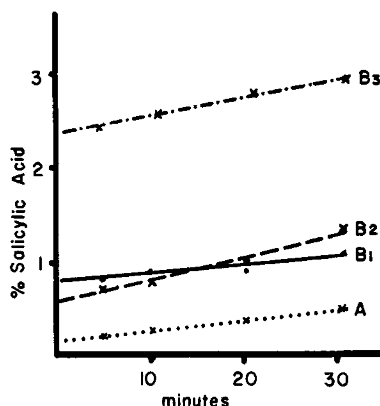

Fig. 1—Rate of hydrolysis of (A) aspirin tablets and (B 1–3) buffered tablets.

Atmospheric humidity can cause an appreciable degree of hydrolysis before the analysis. A freshly opened bottle of buffered tablets gave a value of 0.70% salicylic acid. One month later the salicylic acid content had increased to 0.77%. For this reason, the procedure requires assay immediately after the sample is ground.

The very small amount of salicylic acid found on analysis of residual tablet material demonstrates the effectiveness of the procedure in completely releasing aspirin and salicylic acid from the buffering materials. It has not been resolved whether the free salicylic acid is present as such adsorbed on the buffering components or has been converted to its metallic salts. The formic acid treatment readily recovers salicylic acid from its calcium or magnesium salt, but the aluminum salt is quite refractory to the treatment. Hence, if a metallic salicylate is formed, it must be other than aluminum salicylate.

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Keyphrases

Salicylic acid, free—analysis
Aspirin tablets, buffered—free salicylic acid
Formic acid—preanalysis sample wetting
Chloroform diluent
Hydrolysis rate—aspirin
Column chromatography—separation
UV spectrophotometry—identity