Quantitative Determination of Salicylic Acid and Benzoic Acid in Ointments

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Abstract □ Simple, precise, and accurate methods for the analysis of salicylic acid (I) and benzoic acid (II) in ointments are reported. Compound I is determined by extracting its sodium salt with hot water, reacting it with ferric nitrate, and measuring colorimetrically. The total acidity is determined with sodium hydroxide, and then II can be calculated by difference.

Keyphrases □ Salicylic acid–benzoic acid ointments—colorimetric analysis □ Benzoic acid–salicylic acid ointments—colorimetric analysis □ Ointments, benzoic and salicylic acids—colorimetric analysis □ Colorimetry—analysis, salicylic acid–benzoic acid ointments

Many physicians are using ointments containing salicylic acid and benzoic acid. One ointment of this type was official in USP XVI (1). Depending upon the source, the ratio of the active ingredients and the nature of base may vary. Among the most commonly used bases are polyethylene glycols (A), petrolatum (B), cold cream USP or modified (C), and vanishing cream (D). The procedures for the determination of salicylic acid (I) and benzoic acid (II) in ointments were reported by Weber (2) and Blake (3). Weber's method requires a time-consuming separation of I and II by column chromatography. Blake's method requires the use of nonaqueous titration and plotting of the data. This method is also time consuming and extremely sensitive to carbon dioxide in the air. Garratt (4) recommended the determination of total acidity and a separate assay on I using a complicated extraction and bromination procedure.

The purpose of this paper is to report simple and accurate methods for the analysis of I and II when mixed with various ointment bases.

Table I—Assay Results for Salicylic Acid and Benzoic Acid Using the Proposed Procedures

Ointment Base	Sample Number	Assay Results (Percent Recovery) on I (Salicylic Acid)	II[a] (Benzoic Acid)
A	1	100.5	99.8
	2	100.2	99.8
	3	99.8	99.2
	4	100.3	99.6
	Average	100.2	99.6
	SD	±0.2	±0.2
B	1	100.2	99.9
	2	100.3	99.7
	3	99.7	99.8
	4	99.8	100.2
	Average	100.0	99.9
	SD	±0.25	±0.15
C	1	99.9	99.8
	2	100.3	99.9
	3	99.9	100.1
	4	100.3	100.6
	Average	100.1	100.1
	SD	±0.2	±0.25
D	1	100.0	99.6
	2	100.4	99.1
	3	100.5	99.5
	4	99.7	99.0
	Average	100.2	99.3
	SD	±0.25	±0.25

[a] Only vanishing cream base had slight blank value.

EXPERIMENTAL

Chemicals and Reagents—All of the chemicals and reagents used were USP, NF, or ACS grade and were used without further purification.

Preparation of Solutions—A 0.1 *N* solution of sodium hydroxide was prepared according to directions in USP XVI (1). A 1% solution of ferric nitrate in 1% nitric acid was prepared using a simple solution method.

Preparation of Ointments—With four different bases, ointments containing I (3%) and II (6%) were prepared using a simple trituration process. A portion of the melted base was used as the wetting agent. The following bases were used in these investigations: A, (water soluble) as recommended by USP XVI (1); B, white; C[1], containing the following ingredients: white wax USP, spermaceti USP, cetyl alcohol NF, tegin, mineral oil USP, sodium lauryl sulfate USP, distilled water, and perfume; and D[2], containing the following ingredients: polyhydric alcohol esters, propylene glycol, liquid petrolatum, and preservatives.

Analysis of Salicylic Acid—The assay method for I is based on its reaction with ferric nitrate to form ferric salicylate (violet color) which can be measured colorimetrically. This reaction was recommended by Pankratz and Bandelin (5) and was modified to assay I in ointments.

Weigh accurately 1 g. of the ointment and transfer it to a 250-ml. beaker. Add to it about 100 ml. of hot (75°) distilled water and 2 drops of phenolphthalein T.S. Then add enough 0.1 *N* sodium hydroxide solution (about 7 ml.) so that the mixture is light pink in color. Heat the mixture to 85°, and add more sodium hydroxide solution, if necessary, until the mixture is light pink in color. Let the mixture cool to room temperature, transfer it to a 250-ml. volumetric flask, and bring to volume with distilled water. Filter, reject the first few milliliters of the filtrate, and then transfer 16.0 ml. of the filtrate to a 50-ml. volumetric flask. Add 5 ml. of ferric nitrate solution and bring to volume with distilled water. Measure the absorbance of the solution at 525 nm. against the reagent blank[3].

[1] The Upjohn Co., Kalamazoo, MI 49001
[2] Burroughs Wellcome & Co. Inc., Research Triangle Park, NC 27709
[3] A DK_2 spectrophotometer was used in these investigations.

Similarly, determine the absorbance of a standard solution of salicylic acid (total I 1.920 mg. in a 50-ml. volumetric flask) and calculate the number of milligrams of I contained per gram of the ointment. Since Beer's law is followed (5):

$$\frac{A_{sample}}{A_{standard}} \times 30 = \text{mg. I/g. ointment} \qquad \text{(Eq. 1)}$$

The results are presented in Table I.

Effect of Ointment Bases and Benzoic Acid on Assay Results of Salicylic Acid—Separate batches of the ointments containing only II (6%) were prepared using the procedure already described. These ointments were assayed using the procedure for the analysis of salicylic acid. The results are presented in Table II.

Assay Procedure for Benzoic Acid—Weigh accurately about 2 g. of the ointment and determine the total acidity using the procedure previously reported (6) for salicylic acid ointments. Also weigh accurately an equivalent quantity (in grams) of the ointment base and determine the total acidity using exactly the same procedure (6). By difference, determine the volume of sodium hydroxide used against both acids. The volume of sodium hydroxide solution used × normality equals milliequivalents of the total acids present in the ointment. Calculate the milliequivalents of I using Eq. 2 and subtract it from the total milliequivalents to obtain the number of milliequivalents of II contained in the portion of the ointment weighed:

$$\text{meq. I} = \frac{\text{mg. I (determined in Eq. 1)} \times \text{g. ointment weighed}}{138.1} \qquad \text{(Eq. 2)}$$

Using Eq. 3, calculate the number of milligrams of II contained per gram ointment:

$$\frac{\text{meq.}^4 \times 122 \text{ mg./meq.}}{\text{g. ointment}} = \text{mg. II/g. ointment} \qquad \text{(Eq. 3)}$$

The results for the various ointments are presented in Table I.

DISCUSSION AND CONCLUSIONS

The results indicate that the ointments containing salicylic acid and benzoic acid can be assayed accurately using the proposed method (Table I). The ointment bases tested do not interfere[5] in the assay procedures. Since there are many different types of bases in use and the manufacturers may change the formulas of their bases without notice, it is recommended that the analyst determine whether there is any interference from the components of the ointment base. Interferences can be easily determined by assaying the base without the active ingredients, as explained in the procedures.

The extraction of salicylic acid with hot water appeared to be complete, since water was in large excess as compared with the base, and the sodium salt of salicylic acid is very soluble in water. The reasons for using hot water and heating the mixture to 85° were already explained (6). The chance of error in the determination of benzoic acid by difference is negligible, since the assay procedure for salicylic acid is precise and accurate. With the proposed methods, an average analyst can test 8–10 samples per day.

[4] Milliequivalents of benzoic acid found by difference as explained above.

[5] Except vanishing cream which interferes slightly in the determination of total acidity.

Table II—Effect of Ointment Bases and Benzoic Acid on Assay Results of Salicylic Acid

Ointment Base[a]	Results of Assay for Salicylic Acid
A	0.0
B	0.0
C	0.0
D	0.0

[a] Containing 6% of benzoic acid.

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