Assay for Iodochlorhydroxyquin in Iodochlorhydroxyquin Ointment

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The U.S.P. assay for iodochlorhydroxyquin in iodochlorhydroxyquin ointment was found, in our laboratories, to be unworkable with either hydrocarbon or hydrophilic ointment bases. A colorimetric method was developed which is rapid, reproducible, accurate, and applicable to various ointment formulations. It is believed that this procedure is superior to the official assay presently in use.

THE U.S.P. XVI (1) assay for iodochlorhydroxyquin in ointment formulations involves the precipitation of iodochlorhydroxyquin as a copper chelate from an acetone extract of the ointment and subsequent gravimetric determination by weighing the precipitate.

Attempts were made without success to utilize this assay method in the determination of iodochlorhydroxyquin in two ointment formulations —one an oil-in-water emulsion and the other a hydrocarbon base. The ointment base ingredients do not remain in solution during precipitation of the iodochlorhydroxyquin complex thus seriously contaminating the precipitate on the filter.

Therefore, a method was sought for the assay of iodochlorhydroxyquin in ointment formulations which would circumvent these difficulties and, at the same time, find application to a variety of different types of ointment bases. A colorimetric assay based on the reaction described by Haskins and Luttermoser (2) was developed and found to be applicable to both of the formulations studied. The method depends upon the formation of a colored complex between iodochlorhydroxyquin and ferric ion at a pH between 1.0 and 2.0. Table I demonstrates the application of the method to quantitatively prepared standard samples.

TABLE I.—RECOVERIES OF IODOCHLORHYDROXYQUIN FROM STANDARDS

Hydrophilic Base, %	Hydrocarbon Base, %
100.0	99.4
98.5	99.1
101.5	98.8
101.0	101.0

EXPERIMENTAL

Apparatus and Reagents.—A Beckman DU spectrophotometer with tungsten light source and 1-cm. cells; acetone, reagent grade; methyl cellosolve, reagent grade; and iron reagent (prepare by adding 1 Gm. of ferric chloride, reagent grade, and 1 ml. concentrated hydrochloric acid to a 1-L. volumetric flask and diluting to volume with water) were utilized in this study.

Procedure.—Using a hypodermic syringe with a needle large enough to easily accommodate the ointment, add approximately 3 Gm. of ointment to a tared 100-ml. volumetric flask and weigh to determine the sample weight. Add 50 ml. of acetone to the contents of the flask and heat the mixture on a steam bath with occasional swirling until the ointment melts. Stopper the flask, shake vigorously for a short while, and allow to cool to room temperature. Dilute to volume with acetone and mix thoroughly. Add a 3-ml. aliquot to a 25-ml. volumetric flask, using a pipet with a cotton pledget over the tip. Evaporate the acetone from the flask on a steam bath and chill the residue briefly in an ice bath until it solidifies. To the residue add 20 ml. of methyl cellosolve and swirl to disperse the solid material (do not shake vigorously). Add 2 ml. of iron reagent, dilute to volume with methyl cellosolve, and mix thoroughly. Prepare a reagent blank solution by diluting 2 ml. of iron reagent to 25 ml. with methyl cellosolve. Insert a cotton swab on the end of a glass rod into the solution in the neck of the flask and withdraw it to remove most of the oil globules from the surface of the solution. Fill a 1-cm. Pyrex cell using a 4-ml. pipet with a cotton pledget over its tip. The solution at this point must be clear. Determine the absorbance of the solution against the reagent blank at 650 mμ on the spectrophotometer.

Calculations.—Calculate the amount of iodochlorhydroxyquin in the sample by

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mg. iodochlorhydroxyquin per Gm.

$$\text{of ointment} = \frac{A}{K \times \text{Gm. of sample}}$$

where A = absorbance at 650 mμ, and K = absorbance index in terms of mg. of drug per 100 ml. of sample solution.

Absorbance Index.—Prepare three standard solutions of iodochlorhydroxyquin reference standard in methyl cellosolve to contain approximately 30, 50, and 70 mg. per 100 ml. Develop the color for each standard as follows. Add a 3-ml. aliquot to a 25-ml. volumetric flask and add 17 ml. of methyl cellosolve. Add 2 ml. of the iron reagent, dilute to volume with methyl cellosolve, and mix thoroughly. Prepare a reagent blank by diluting 2 ml. of the iron reagent to 25 ml. with methyl cellosolve. Determine the absorbance at 650 mμ using the 1-cm. cells and the reagent blank solution in the reference cell. Calculate the absorbance index K by the equation $K = A/c$, where c is the concentration of standard in mg. per 100 ml. and A is the observed absorbance for the corresponding colored solution. Table II shows the results for three such standards using the Beckman DU spectrophotometer.

TABLE II.—DETERMINATION OF ABSORBANCE INDEX ($K = A/c$)

Concn. c, mg. per 100 ml.	Absorbance A	Absorbance Index K
34.8	0.218	0.00626
52.0	0.320	0.00615
69.5	0.427	0.00614

CONCLUSIONS

The U.S.P. method for iodochlorhydroxyquin in ointment preparations presents many difficulties. It is practically impossible to obtain a precipitate free of ointment base materials from an acetone extract of most ointment preparations.

The method described in this paper offers several advantages over the official method in that it is simple, rapid, reproducible, and accurate. The color formed by the reaction of ferric ion and iodochlorhydroxyquin in methyl cellosolve has been shown to be stable over a period of at least 1.5 hours. The application of the assay to two different types of ointment bases was demonstrated.

REFERENCES

(1) "United States Pharmacopeia," 16th rev., Mack Publishing Co., Easton, Pa., 1960, p. 357.
(2) Haskins, W. T., and Luttermoser, G. W., *Anal. Chem.* **23**, 456(1951).

Technical Articles

Preparation of Parenteral Dispersions

By THOMAS J. MACEK

Parenteral dispersions of medicinal products may take the form of parenteral colloids, parenteral emulsions, or parenteral suspensions. The paper defines these categories and discusses problems of manufacture and stability and illustrates with practical examples.

THE TERM "dispersion" is very general and may have several meanings. A simple solution of a salt or sugar in water can be considered an aqueous dispersion. As such, it occupies a position at one end of a scale describing various states of matter. Heterogeneous admixtures of a liquid and relatively large fragments of another immiscible liquid or solid, on the other hand, are described as emulsions or suspensions and occupy a place at the opposite end of that scale. The state of matter between these two extremes, and more particularly when the dispersed phase consists of particles between 1 and 100 mμ in size is that intermediate range called the "colloidal state." This region frequently is subdivided further by the term "colloidal solution" or "sol" as in the case of a solution of gelatin or of silver iodide, and colloidal dispersions, as in the case of colloidal gold having solids suspended in the submicron form. The term "hydrosol" is employed when the solvent is water, and the term "aerosol" refers to a colloidal dispersion in air or another gas.

Actually, the line of demarcation between a true solution and the colloidal state is not really very sharp. Solids dissolve in a liquid such as water when there is complete or near complete intermingling of solute and solvent molecules or ions. The ionic bonds of salts such as exist between Na^+ and Cl^- must be fractured in the process of dissolving, the energy being derived from the polarity of the solvent. At best, solute to solute and solvent to solvent bonds have to be broken and new solute to solvent bonds formed. If the forces—such as

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