of the suspensoid directly. Null-balance instrumentation might increase the sensitivity and accuracy of the determinations.

The use of a vertical radiation beam worked well in this preliminary study of the apparatus, for it made adjustment of the radiation beam path possible without necessitating the construction of a watertight cell with movable walls. The major disadvantage of this arrangement seems to be the time and labor required for calibration, which consisted of sampling the suspension at different time intervals and relating the concentration of the suspension at any given time to the intensity of the radiation beam which passed through it. An apparatus which utilized a horizontal beam might be calibrated with samples of the same suspension in different concentrations, and thereby eliminate the need of waiting for the suspension to settle.

Salts of heavy metals were chosen purposely for suspensions and solutions used in this study, for this method will have its greatest application in the evaluation of preparations containing these materials. Obviously the change in the concentration of the suspensoid will become more and more difficult to detect as the atomic number and density of the suspensoid approach those of the vehicle. To optimize the detection of small changes in suspensoid concentration, the absorption of X-radiation might be made selective for some element in the suspensoid by constructing a characteristic radiation source (through choice of a target material of the proper atomic number) which has an energy that just exceeds the critical absorption edge of the element in question. An alternative might be to use a β-emitting isotope as a source of radiation, and to determine the concentration of suspensoid by measuring the characteristic radiation emitted by one of its elemental constituents.

SUMMARY

Studies have been carried out to investigate the feasibility of a new approach to the determination of settling rates of pharmaceutical suspensions. This approach consists of passing a beam of characteristic radiation vertically through a column of suspension and measuring the attenuation of the beam by the suspension at the bottom of the column, to find the concentration of suspensoid there as it changes with time.

An apparatus has been constructed which utilizes the characteristic X-ray produced by the bombardment of lead foil with a ^{90}Sr-^{90}Y source. The concentrations of dissolved and suspended metal salts have been found with this apparatus. The relationship between concentration and intensity of radiation was studied, and the relationship was shown to be useful for studying the sedimentation of heavy metal salts. Changes in the design of the apparatus which may extend its utility further are suggested.

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Drug Standards

Spectrophotometric Assay for Potassium Guaiacolsulfonate N.F.

By RICHARD DABROWSKI and D. M. PATEL

A spectrophotometric assay method for potassium guaiacolsulfonate (KGS), which is applicable to both solid and complex liquid dosage forms, was devised. This method led to the establishment of the fact that commercial KGS is a hemihydrate. The N.F. Revision Committee has adopted this method for the new N.F. XII.

POTASSIUM guaiacolsulfonate (KGS) is determined by oxidation with hot nitric acid followed by gravimetric determination of the sulfate produced (1). Consistently low results have been obtained in this laboratory, due probably to incomplete oxidation. The ichthammol procedure (2) gave better results, but the assay is tedious and time-consuming. A simpler method is required for routine industrial control.

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Methods based on bromination in nonaqueous solvents and nonaqueous acid–base titrations failed to give satisfactory results. Literature methods for organic sulfur compounds are based on oxidation–precipitation or oxidation–titration principles, but these methods are inadequate for KGS. Since KGS shows characteristic ultraviolet absorption and since it can be obtained in high purity, a spectrophotometric method suggests itself as the easiest and most suitable method for routine analytical control if a pure reference standard can be made available. Pure KGS was prepared, and a successful spectrophotometric method was developed as described under *Experimental.*

EXPERIMENTAL

Preparation of the Reference Standard.—A working reference standard was prepared by repeated crystallization of the commercially available KGS from distilled water and absolute alcohol. A characteristic spectrum of the purified material in distilled water was obtained having two maxima, at 279.5 and 236.5 mμ, and two minima at 256 and 219.5 mμ, as shown in Fig. 1. To produce a compound which consistently gave constant absorptivities at the above wavelengths, two crystallizations were necessary. The absorptivity values of the crystals obtained from distilled water recrystallizations, although constant, were lower than those obtained from absolute alcohol recrystallization. It was found with the cooperation of Russo *et al.* (3) that the material recrystallized from distilled water is a hemihydrate. This is also true for the commercially available material. The evidence for this was established by determining the water content of the purchased material, material recrystallized from distilled water, and material recrystallized from absolute alcohol (after initial drying at 105° for 2 hr.) by Karl Fischer method. The results are summarized in Table I.

Table I.—Absorptivity Values and Water of Crystallization of Various Grades of KGS

Grade KGS	Absorptivity Values in Distilled Water 279.5 mμ	236.5 mμ	% Water of Crystallization by Karl Fischer
Recrystallized from absolute alcohol	122.5	357.5	0.08
Recrystallized from distilled water	118.3	344.7	3.60
Purchased material	...	...	3.42

Theoretical water content of KGS hemihydrate = 3.59%

Results of Table I satisfactorily account for the constant differences in absorptivity values of material recrystallized from distilled water and absolute alcohol. Either material can be used as a reference standard provided that water of crystallization is taken into consideration.

pH Effect on the Spectrum.—During the initial stages of this work, all the spectrophotometric measurements were made in distilled water. No shift in absorption maxima was noticed. However, differences in pH values between the solutions of material recrystallized from distilled water (5% solution had a pH value of 5.10) and commercially available material (5% solution has a pH value of 7.51) were observed. In view of this, the effect of pH on the spectrum was investigated. At pH 3 in 0.2 *M* potassium chloride–0.2 *M* hydrochloric acid buffer, and at pH 7 in 0.2 *M* potassium phosphate monobasic–0.2 *M* sodium hydroxide buffer the absorption spectra were identical. A different but characteristic spectrum at pH 9.5 in 0.2 *M* boric acid, potassium chloride, 0.2 *M* sodium hydroxide was obtained having a maximum at 259.5 mμ and a minimum at 230 mμ. (See Fig. 2.) No further change in spectrum was observed in 0.1 *N* sodium hydroxide. Measurement at 279.5 mμ in pH 7 phosphate buffer system was selected for the proposed assay method.

Establishment of Absorptivities in pH 7 Phosphate Buffer.—Absorptivity values of material recrystallized from distilled water and absolute alcohol at 279.5 and 236.5 mμ at pH 7 in 0.2 *M* phosphate buffer were established. The average value of each is presented in Table I. Also, material recrystallized from distilled water and absolute alcohol adheres to

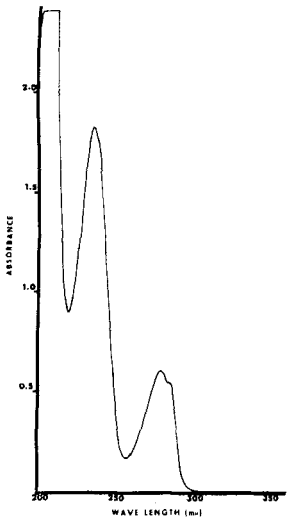

Fig. 1.—Spectrum of KGS recrystallized from absolute alcohol in distilled water

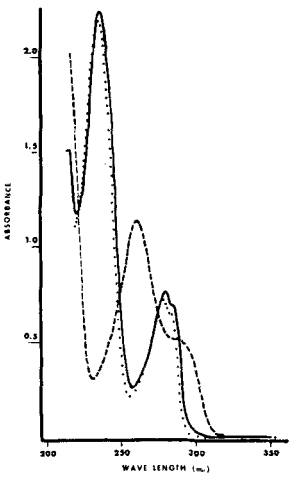

Fig. 2.—Spectrum of KGS at various pH values. Key: ——, pH 7 phosphate buffer; . . . ., pH 3 hydrochloric acid–potassium chloride buffer; – – – –, pH 9.5 borate buffer.

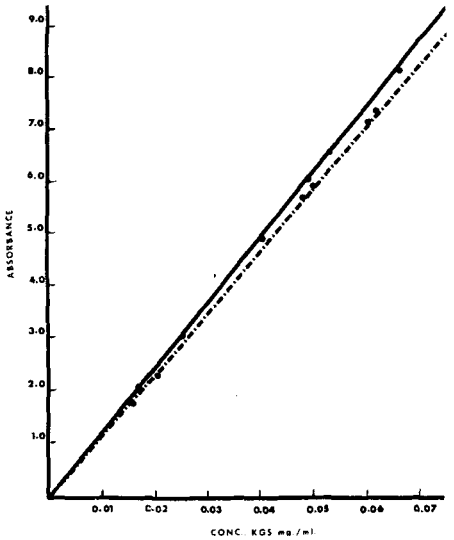

Fig. 3.—Relationship of absorbance and concentration for various grades of KGS. Key: ——, recrystallized from absolute ethanol; –·–·, recrystallized from water.

Beer's law over a wide range of concentration. (See Fig. 3.)

Assay Method Proposed to N.F. XII for KGS.—Transfer about 250 mg. of KGS, accurately weighed, to a 500-ml. volumetric flask, dissolve in 400 ml. of water, dilute to volume, and mix. Dilute 10 ml. of this solution to 100.0 ml. with pH 7.0, 0.2 *M* phosphate buffer, and mix. Concomitantly determine the absorbance of this solution and a solution of N.F. KGS reference standard similarly prepared at a concentration of about 50 mcg./ml., in 1-cm. cells, at the maximum at about 279.5 mμ with a suitable spectrophotometer, using a mixture of water and pH 7.0 phosphate buffer (1 in 10) as the blank. Calculate the quantity, in mg., of $C_7H_7KO_5S$ in the KGS taken by the formula $5C \times (A_U/A_S)$, in which C is the exact concentration of the reference standard, in mcg./ml., calculated on the anhydrous basis, A_U is the absorbance of the sample solution, and A_S is the absorbance of the reference standard solution.

Application of the Spectrophotometric Method to Liquid Dosage Form.—The spectrophotometric principle can be extended to liquid cough preparations containing KGS in the presence of antihistamines and narcotics after isolation of KGS from other drugs *via* solvent extraction. The liquid preparation[1] selected for this study contains bromdiphenhydramine hydrochloride, diphenhydramine hydrochloride,[2] codeine sulfate, and KGS as active ingredients. Bromdiphenhydramine hydrochloride and diphenhydramine hydrochloride are first removed from the syrup at pH 1 by multiextraction using chloroform. The aqueous portion containing KGS and codeine sulfate is now made alkaline (pH 9–9.5) and the liberated codeine base is removed through chloroform extraction. The remaining aqueous phase is diluted appropriately with pH 7, 0.2 *M* phosphate buffer and the absorption of KGS measured at 279.5 mμ on a spectrophotometer. Some of the coloring matter present in the syrup remains in the aqueous phase after chloroform extraction from both acidic and basic media. However, no interference in the determination of KGS was noticed from either the color, bromdiphenhydramine hydrochloride, diphenhydramine hydrochloride, or codeine sulfate. Results are summarized in Table II.

TABLE II.—RECOVERY OF KGS FROM COUGH SYRUP

Batch No.	Recovery of Label Claim, %
1	97.2
2	98.2
3	96.3
4	98.5
5	96.7

DISCUSSION

Commercially available KGS is a hemihydrate which was confirmed through Karl Fischer titrimetric determination of water. Spectrophotometric reference standard of KGS can be prepared by two crystallizations of commercial KGS from distilled water or absolute alcohol. Crystals obtained by two crystallizations from distilled water contained one-half mole of water of crystallization; this material can be used as a reference standard after correcting for water content by Karl Fischer method. The spectrum of KGS at pH 9.5 is different from the spectra at pH 7 and pH 3. The shift in absorption maximum in going from lower to higher pH is typical of phenolic compounds. The pH of the solvent must be controlled for measurements. The spectrophotometric method was extended to complex liquid dosage forms containing drugs having absorption in the U.V. region. The interfering drugs were separated from KGS by liquid–liquid extractions after series of pH changes in the aqueous phase.

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[1] Marketed as Ambenyl Expectorant by Parke, Davis & Co.

[2] Marketed as Ambodryl Hydrochloride and Benadryl Hydrochloride, respectively, by Parke, Davis & Co.