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Modified USP Assay of Calcium Gluceptate

Keyphrases □ Calcium gluceptate—modified USP assay □ USP assay—modification for calcium gluceptate

To the Editor:

The USP assay procedure for calcium gluceptate consists of the complexometric estimation of calcium with ethylenediaminetetraacetic acid (1). To an accurately weighed amount of calcium gluceptate (~800 mg), 150 ml of water containing 2 ml of 3 *N* HCl is added. While stirring, ~25 ml of 0.05 *M* ethylenediaminetetraacetate disodium is added from a buret. Then 15 ml of 1 *N* NaOH and 300 mg of hydroxy naphthol blue indicator are added, and the titration is continued to a blue end-point.

A similar procedure is described for the assay of precipitated calcium carbonate, calcium chloride, calcium gluconate, calcium hydroxide, calcium lactate, and calcium levulinate and for the calcium content analysis of calcium pantothenate and racemic calcium pantothenate. Although each assay calls for the addition of hydrochloric acid, this step is only necessary where the calcium salt has a limited aqueous solubility (2, 3). Since calcium gluceptate is freely soluble in water (4), we suggest that the addition of hydrochloric acid should be omitted. Table I shows that assay results are not affected by the presence or absence of hydrochloric acid.

Table I—Assay of Calcium Gluceptate in the Presence and Absence of Hydrochloric Acid

Calcium Gluceptate	Assay Value, %[a]	
	USP Method	Modified USP Method
Source A[b]	96.80 ± 0.42 (96.55–97.43)	96.82 ± 0.32 (96.54–97.10)
Source B[c]	97.02 ± 0.39 (96.51–97.42)	97.16 ± 0.21 (96.97–97.41)
Source C[d]	101.15 ± 0.08 (101.04–101.24)	100.86 ± 0.49 (100.14–101.17)

[a] Mean ± *SD*, $n = 4$; range is given in parentheses. [b] Pfanstiehl. [c] Givaudan. [d] Italsintex.

The sodium hydroxide solution and the hydroxy naphthol blue indicator can be added to the calcium gluceptate solution at the beginning of the assay; thus, it is unnecessary to interrupt titration to make these additions. The estimation of calcium with ethylenediaminetetraacetic acid using hydroxy naphthol blue as the indicator is carried out at pH 12–13 (5). The addition of 15 ml of 1 *N* NaOH solution in the official assay brings the pH to this range. In the absence of hydrochloric acid, ~10 ml of 1 *N* NaOH solution would be sufficient to bring the pH to the required range. Thus, omitting the hydrochloric acid both simplifies the procedure and enables the amount of sodium hydroxide to be reduced.

We suggest that hydrochloric acid might be omitted in the assay of other freely soluble calcium salts.

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Observed Artifacts due to Pellet Preparation in IR Spectrometry

Keyphrases □ IR spectrometry—observed artifacts due to pellet preparation □ Pellets—observed artifacts due to preparation, IR spectrometry

To the Editor:

IR spectrometry is required for identifying organic substances by most pharmacopeia and official compendia such as the USP XIX and the NF XIV (1, 2). The USP recommends: "Chemically identical substances of differing polymorphic forms often exhibit different infrared spectra when examined in the solid state. If a difference appears in the spectra, dissolve portions of both the sample and the reference standard in a suitable solvent, evaporate the solution to dryness, and repeat the test on the residues" (1). Differences resulting from polymorphism are considered to be the major reason for errors.

Certain secondary and tertiary amine derivatives such as bupivacaine, cinnarizine, and many butyrophenones have the same spectrum, in part or in whole, for their hydrochloride, hydrobromide, and free base forms when they are dissolved in methanol, ethanol, or isopropanol and if grinding with potassium bromide is prolonged.

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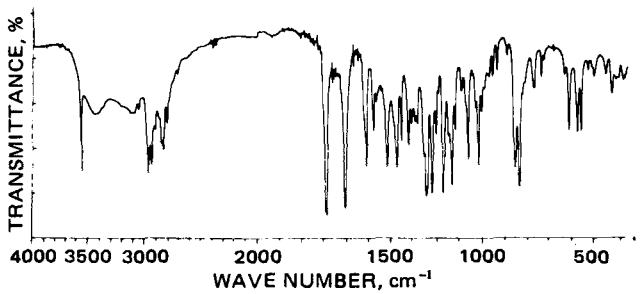

Figure 1—*Spectrum of moperone base; grinding with potassium bromide without any solvent.*

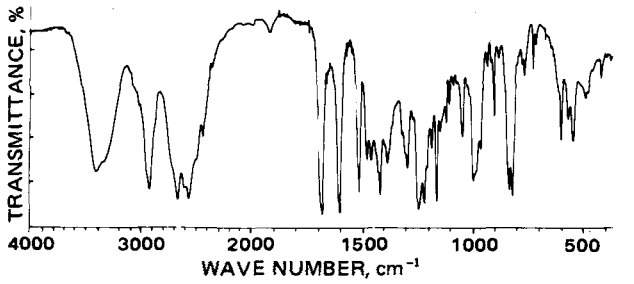

Figure 2—*Spectrum of moperone hydrochloride; grinding with potassium bromide without any solvent.*

In the case of amine hydrochloride, the exchange of chlorine ions with bromine ions was reported (3, 4). However, this explanation is unsatisfactory for the free base form. The presence of very intense absorption bands between 2650 and 2500 cm^{-1}, indicating nitrogen protonation, was confirmed (Figs. 1–3). In the case of moperone, the hydrobromide reextracted from the potassium bromide pellet by a minimum volume of methanol shows a final melting temperature of 184°, determined by thermomicroscopy, even though melting temperatures of the hydrobromide, hydrochloride, and free base forms are 186, 222, and 123°, respectively. It was reported (5) that amine salts having a protonated nitrogen atom of the NH_3^+, NH_2^+, or NH^+ type possess characteristic frequencies of 4000–2000 cm^{-1}.

The hydrobromide form of moperone (reextracted from potassium bromide pellets) was confirmed using X-ray diffraction. The spectra present the characteristic moperone hydrobromide pattern, including intense bands corresponding to *d* values of 0.64, 5.29, 5.16, 4.89, 4.78, 4.25, 3.68, and 3.61 Å. Identical results were obtained with pharmaceutical organic raw materials such as bupivacaine, cinnarizine, diethylpropion, diisopromine, fenfluramine, fluanisone, haloperidol, homatropine, and moperone.

The hydrobromide formation may be attributed to atmospheric carbon dioxide combined with the entropy of the system since the potassium bromide effect persists when sodium redistilled methanol or pyridine and potassium bromide solutions (pH 10) are used. Thus, it is important not to attribute the spectral consequences of this potassium bromide effect to the existence of a new polymorphic form.

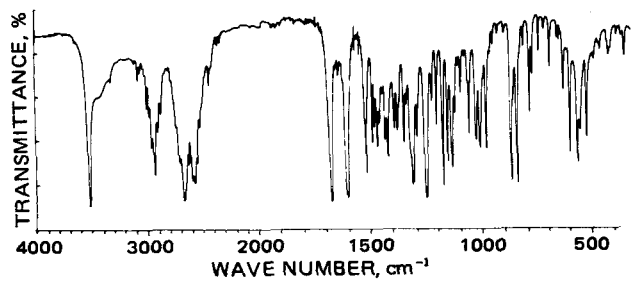

Figure 3—*Spectrum of moperone base or hydrochloride; grinding with potassium bromide and solvent.*

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First-Pass Clearance of Lidocaine in Healthy Volunteers and Epileptic Patients: Influence of Effective Liver Volume

Keyphrases □ Lidocaine—first-pass clearance in healthy volunteers and epileptic patients compared □ Bioavailability—lidocaine, compared in healthy volunteers and epileptic patients, influence of effective liver volume □ Hepatic retention—effect on first-pass clearance of lidocaine, healthy volunteers and epileptic patients compared

To the Editor:

Recent reports (1, 2) compared the absolute oral bioavailability of lidocaine in epileptic patients receiving chronic anticonvulsant drug therapy to that in normal healthy volunteers not receiving enzyme-inducing drugs. The authors of these reports concluded that the greater than twofold reduction in absolute availability observed in the epileptic patients was the result of increased hepatic first-pass metabolism caused by the chronic administration of anticonvulsant drugs.

The present study considers the possible impact of increased hepatic retention, rather than increased metabolic activity, on reduced bioavailability using the first-pass perfusion model presented in Scheme I. The model was used to simulate the effect of increased hepatoportal retention of lidocaine that could result from the induction of nonenzyme-related protein synthesis in the eliminating organ. The product of the liver volume (V_H) and liver retention (R_H) is the effective liver volume (3). Therefore, by definition, an increase in liver mass or hepatic tissue binding is reflected as an increase in hepatic organ clear-

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