Determination of Sorbitol and Mannitol in Pharmaceuticals by GLC of Tris-*n*-Butyldiboronate Esters

DAVID L. SONDACK

Abstract □ A rapid method for determining sorbitol or mannitol in pharmaceuticals by GLC using the tris-*n*-butyldiboronate esters is described. An internal standard unrelated to the hexitols is utilized to avoid the problems of cross-contamination introduced by the use of other hexitols.

Keyphrases □ Sorbitol—GLC determination in pharmaceuticals using tris-*n*-butyldiboronate esters □ Mannitol—GLC determination in pharmaceuticals using tris-*n*-butyldiboronate esters □ GLC—determination, sorbitol and mannitol in pharmaceuticals using tris-*n*-butyldiboronate esters

Sorbitol and mannitol have been used as artificial sweeteners in pharmaceutical preparations. The analytical procedure described in the USP (1) is tedious and cumbersome because it involves column chromatography, periodate reaction, and iodometry. Derivatization of the hexitols to their hexaacetate derivatives facilitates analysis by GLC due to increased volatility (2), but the method is still somewhat time consuming and the most suitable liquid phase found is unstable (3). The rapidity of silylation procedures does not provide a convenient assay since the common hexitols are not resolved (4).

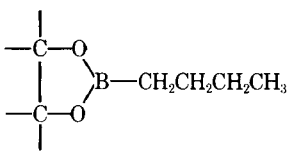
Alkane boronic acids aid in the volatilization of various organic compounds (5) and have been shown to resolve the common hexitols (6). With the method presented here, the sorbitol or mannitol content of pharmaceutical preparations may be determined by GLC utilizing the *n*-butylboronic acid derivatives (I).

EXPERIMENTAL

Equipment—A gas chromatograph[1] equipped with a flame-ionization detector was used. The detector signal was fed to a computer[2] for peak integration and to a 1-mv recorder[3] with a chart speed of 15 in./hr and a 1-sec full-scale response. Samples were injected with a 10-μl syringe[4].

Helium was used as the carrier gas, and electrolytic hydrogen and oxygen were used in the detector. The stationary phase, 2% OV-17 on 80–100-mesh Chromosorb G[5], was packed in borosilicate glass columns, 1.22 m × 0.64 cm o.d. All chemicals used were reagent grade or the best quality available.

Operating Conditions—The column was operated isothermally at 220° with the detector block and injection port at 240°. The helium flow rate was 55 ml/min with an inlet pressure of 40 psi. The



I

[1] Hewlett-Packard model 402.
[2] IBM 1800.
[3] Honeywell Electronik 16.
[4] Hamilton 701.
[5] Applied Science Laboratories, State College, Pa.

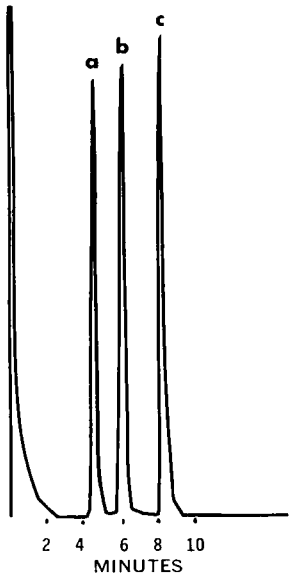


Figure 1—*Gas–liquid chromatogram of tris-*n*-butyldiboronate esters of mannitol (peak A) and sorbitol (peak B) and of* m*-diphenylbenzene, the internal standard (peak C).*

electrometer range was 100 with an attenuation of 8. Sample injections between 1 and 5 μl were made.

Internal Standard—*m*-Diphenylbenzene, 2.5 mg/ml, in pyridine was used as the internal standard.

Hexitol Analysis—Solutions (2.5 mg/ml) of reference standard sorbitol or mannitol were prepared in deionized water. Sample solutions were diluted volumetrically to provide approximately the same concentration. Aliquots of 1.00 ml were withdrawn and delivered by pipet to a screw-capped vial and placed in a vacuum desiccator over sodium hydroxide pellets or other suitable desiccant. After careful evacuation to avoid sample loss due to bubbling, the samples were allowed to stand in the desiccator overnight.

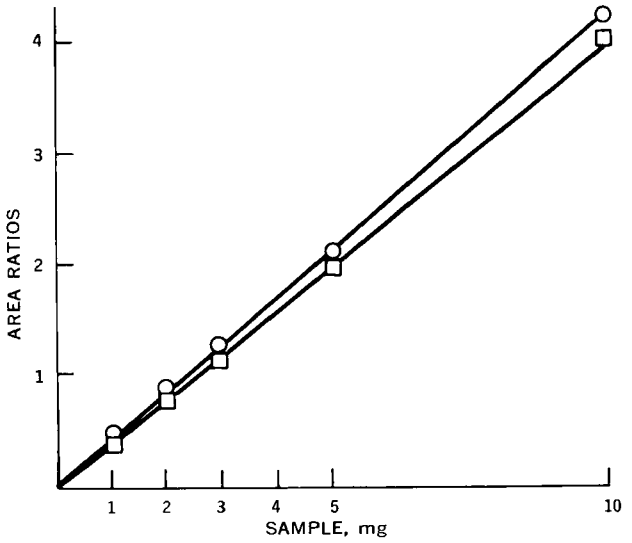


Figure 2—*Linearity of response of mannitol (○) and sorbitol (□) with concentration (conditions as in text).*

Table I—Determination of Sorbitol and Mannitol in Various Samples

Sample	Milligrams Taken	Sorbitol Found, mg	Mannitol Found, mg
Sorbitol			
1	34.2	30.6	3.7
2	33.7	30.2	3.6
3	31.6	28.3	3.3
4	29.9	26.8	3.2
5	30.8	27.6	3.4
6	30.4	27.2	3.3
Mannitol			
1	36.5	3.6	32.7
2	36.0	3.5	32.2
3	33.4	3.3	39.9
4	32.6	3.1	29.2

Approximately 10 mg of *n*-butylboronic acid[6] and exactly 1.00 ml of internal standard solution were added to the dried samples. The reaction was completed almost immediately, and 1-μl portions were injected onto the column.

RESULTS AND DISCUSSION

The chromatogram shown in Fig. 1 is of the tris-*n*-butyldiboronate esters (6) of mannitol and sorbitol under the described conditions. No mannitol or sorbitol samples obtained were free of mutual contamination. It is advisable to observe the precaution offered by Eisenberg (6), *i.e.*, to ascertain the purity of the *n*-butylboronic acid reagent by GLC of a pyridine solution on the OV-17 column at 92°. It follows, then, that excess reagent elutes with the solvent front during hexitol analysis. The reagent used here was essentially free of any impurities.

The response of the analytical system was linear to a concentration four times that described in Fig. 2. The residual standard deviations calculated for five replicate samples of mannitol and sorbitol, analyzed separately, were both ±1.2% (Table I). These values compare favorably with those using the method of Manius *et al.* (3). The advantages of this method are the ease of derivatization, the shorter analysis time, and the greater thermal stability of the liquid phase.

[6] Pierce Chemical Co.

REFERENCES

(1) "The United States Pharmacopeia," 18th rev., Mack Publishing Co., Easton, Pa., 1970, pp. 678–680.

(2) J. A. Hause, J. A. Hubicki, and G. G. Hazen, *Anal. Chem.*, **34**, 1567(1962).

(3) G. Manius, F. P. Mahn, V. S. Venturella, and B. Z. Senkowski, *J. Pharm. Sci.*, **61**, 1831(1972).

(4) F. Loewus, *Carbohyd. Res.*, **3**, 130(1966).

(5) C. J. W. Brooks and I. MacLean, *J. Chromatogr. Sci.*, **9**, 18(1971).

(6) F. Eisenberg, *Carbohyd. Res.*, **19**, 135(1971).

ACKNOWLEDGMENTS AND ADDRESSES

Received March 4, 1974, from *Eli Lilly and Company, Indianapolis, IN 46206*

Accepted for publication July 19, 1974.

Chemistry of Nonaqueous Titration of Chlorpromazine

SOBHI A. SOLIMAN ˣ, HASSAN ABDINE, and NASHAAT A. ZAKHARI

Abstract □ The chemistry of the red color formed during perchloric acid titration of chlorpromazine hydrochloride in acetic acid in the presence of mercuric acetate is discussed. Addition of ascorbic acid prevents the color formation and allows titration using a crystal violet end-point. Ascorbic acid addition also sharpens the potentiometric end-point. Ascorbic acid and its oxidation product, dehydroascorbic acid, being neutral to perchloric acid, do not interfere with the titration.

Keyphrases □ Chlorpromazine hydrochloride—chemistry of nonaqueous titration, method proposed, compared to official methods □ Nonaqueous titration—chlorpromazine hydrochloride, chemistry □ Titration, nonaqueous—chlorpromazine hydrochloride, chemistry

Chlorpromazine hydrochloride, a phenothiazine derivative, is extensively used as a psychopharmacological agent in various dosage forms. Chlorpromazine hydrochloride is official in the USP XVIII (1), the BP 1963 (2), and the BP 1968 (3) as a pure compound and as injection and tablet dosage forms.

The pure compound is titrated potentiometrically in glacial acetic acid medium, according to the USP XVIII and the BP 1963, and in acetone using methyl orange indicator according to the BP 1968. The injection is assayed spectrophotometrically in the three compendia. In the BP 1968 and the BP 1963 methods, the injection solution is diluted with 0.1 *N* hydrochloric acid solution to a suitable concentration and then the absorbance is measured directly. In the USP XVIII method, several extraction processes are carried out before measurement.

Tablets are determined spectrophotometrically according to the USP XVIII and the BP 1968. The BP 1963, however, recommends the titration of chlorpromazine hydrochloride content of tablets against standard ceric ammonium sulfate solution.

DISCUSSION

Several methods of analysis have been proposed for chlorpromazine hydrochloride involving gravimetry, titrimetry, spectroscopy, colorimetry, and chromatography. Spectrophotometric and colorimetric methods include the estimation of chlorpromazine in biological fluids (4) by measuring the red color produced by concentrated sulfuric acid. Colorimetric determination of chlorpromazine in tablets containing methampyrone [sodium (antipyrinylmethylamino)methanesulfonate] was reported (5).

A method using acid indicator dyes was suggested (6) for the de-