High-Performance Liquid Chromatographic Analysis of Digoxin Formulations

BELACHEW DESTA and K. M. McERLANE ˣ

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Abstract □ A rapid, selective, and simple high-performance liquid chromatographic (HPLC) assay for digoxin formulations is described. The method utilizes a conventional octadecyl bonded phase column with detection at 220 nm. The analytical procedure has been applied for the quantitation of digoxin in tablets, elixir, and injectable formulations with a resulting relative standard deviation of 1.45, 1.70, and 1.80%, respectively. The method is sufficiently sensitive to monitor content uniformity of individual tablets. Potential impurities or degradation products are resolved from the digoxin peak in a total chromatographic time of <15 min.

Keyphrases □ High-performance liquid chromatography—analysis of digoxin formulations □ Digoxin—high-performance liquid chromatographic analysis, assay of tablet, injectable, and elixir formulations □ Formulations—high-performance liquid chromatographic analysis of digoxin formulations: tablets, elixir, and injectable

Digoxin is a cardioactive glycoside isolated from the leaves of *Digitalis lanata* and is the most frequently used drug in the treatment of congestive heart failure. Its low dosage and narrow therapeutic safety margin require assurance of potency and content uniformity of dosage forms, particularly in tablet formulations. The potential for the presence of degradation products or impurities introduces an additional requirement of assay specificity.

Previous methods for the analysis of digoxin as its drug substance and in formulations have largely been colorimetric (1–7), fluorometric (8–13), or chromatographic. The latter methods have included paper (14, 15), thin-layer (16–18), column (19, 20), gas-liquid (21–25), and high-performance liquid chromatographic (HPLC) methods (26–32). Colorimetric methods are largely nonselective and lack high sensitivity. Fluorometric methods, although more selective and certainly more sensitive, lack specificity, since the acidic fluorogenic reaction required would lead to an identical fluorescent species for digoxin and its potential impurities. GC methods require the preparation of a sufficiently volatile derivative. However, the derivitization procedures cause hydrolysis of the digitoxose sugar residues and, thus, would be inappropriate for the determination of the intact digoxin moiety in the presence of its degradation products. The utilization of HPLC for the determination of digoxin provides a distinct advantage since the digitalis glycoside does not require pretreatment to facilitate chromatographic manipulation. HPLC has been used by several investigators (30, 31) for the quantitative measurement of digoxin drug substance and its degradation products. The methods, although providing an indication of the hydrolysis rate of digoxin drug substance in aqueous media, were not applied to dosage forms.

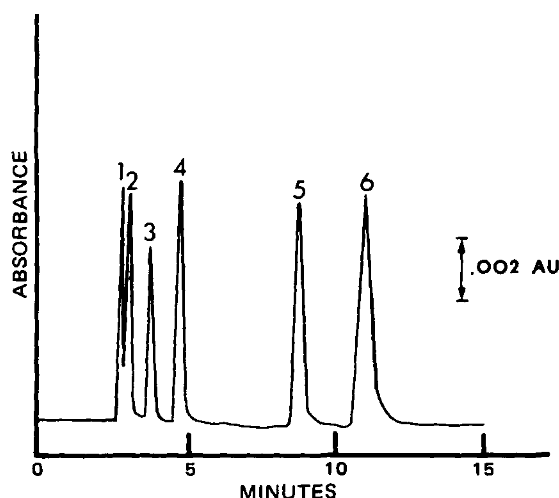

Figure 1—*HPLC of a synthetic mixture of digitalis glycosides. Sequence of elution: 1, digoxigenin; 2, digoxigenin monodigitoxoside; 3, digoxigenin bisdigitoxoside; 4, digoxin; 5, 17α-ethynylestradiol internal standard; 6, gitoxin. Mobile Phase: water–methanol–isopropanol–methylene chloride (47:40:9:4), flow rate: 1.2 ml/min.*

Therefore, it would appear that there is a need for a method of analysis of digoxin in its dosage forms that is reliable and accurate as well as sufficiently sensitive to facilitate single-tablet assay. Such a method is described in this paper.

EXPERIMENTAL

Apparatus—A high-performance liquid chromatograph[1] equipped with dual pumps[2], a 20-μl injector[3], and a dynamically stirred mixing chamber[4] were used throughout with a variable wavelength detector[5] and an electronic data processor[6]. All analyses were performed on a 4.6 mm × 250-mm column[7] packed with 5-μm bonded octadecylsilane (C_{18} phase).

Materials—Water, methanol, isopropanol, and methylene chloride were of HPLC grade[8]. Digoxin[9] and 17α-ethynylestradiol[10] were used without further purification.

Preparation of Internal Standard Solutions—An accurately weighed quantity, equivalent to 100 mg of 17α-ethynylestradiol, was dissolved in 100 ml of methanol.

Preparation of Standard Solutions of Digoxin—A stock solution was prepared by dissolving an accurately weighed quantity, equivalent to 20 mg of digoxin, in 80 ml of boiling methanol, cooling the flask to room temperature, and bringing the final volume to 100 ml with methanol. Six aliquots equivalent to 0.1, 0.2, 0.4, 1.0, 2.0, and 2.5 mg of digoxin were added to 100-ml volumetric flasks. A 2.5-ml aliquot of the internal standard was added to each flask, followed by an amount of methanol required to bring the volume to 35 ml. The flasks were then brought to volume with distilled water and thoroughly mixed. Three injections of each of the six standard solutions containing digoxin and 17α-ethynylestradiol were used to establish linearity and response ratios.

Sample Preparation—Not less than 30 tablets were weighed and

[1] Model 322, Beckman Instruments, Inc. Toronto, Ontario, Canada.
[2] Model 100A, Beckman Instruments, Inc.
[3] Model 210, Beckman Instruments, Inc.
[4] Model 400, Beckman Instruments, Inc.
[5] Model 100-10, Hitachi Ltd., Tokyo, Japan.
[6] Model C-RIA, Shimadzu Corp., Kyoto, Japan.
[7] Ultrasphere, Beckman Instruments, Inc.
[8] Fisher Scientific, Vancouver, B.C., Canada.
[9] Boehringer Mannheim Corp., Mannheim, G.F.R.
[10] Sigma Chemical Co., St. Louis, Mo.

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Table I—Results of the Analysis of Composite Samples of Digoxin Tablets by HPLC and the USP Method

	Percent of Label Claim							
	Brand A				Brand B		Brand C	
	0.125 mg		0.25 mg		0.25 mg		0.25 mg	
Number	HPLC Method	USP Method	HPLC Method	USP Method	HPLC Method	USP Method	HPLC Method	USP Method
1	98.0	103.0	94.0	105.6	98.8	101.4	101.6	97.7
2	101.2	96.1	96.8	96.2	97.2	98.8	100.0	102.7
3	99.2	94.9	95.2	98.4	98.0	103.0	104.8	103.2
4	101.2	—	95.2	—	97.6	—	98.4	—
Mean	99.9	98.0	95.3	100.1	97.9	101.0	101.2	101.2

triturated to a fine powder. An accurately weighed quantity, equivalent to 1.25 mg of digoxin, was transferred to a 100-ml volumetric flask. Ten milliliters of distilled water was added and the flask was swirled for 2–3 min. Exactly 32.5 ml of methanol was added and the mixture was mechanically shaken for 15 min. The suspension was filtered using filter paper[11], and the residue was washed with three 5-ml portions of distilled water. The combined filtrate and washings were collected in a 100-ml volumetric flask containing a 2.5-ml aliquot of the internal standard solution, and the flask was brought to volume with distilled water and thoroughly mixed. A 20-μl sample, containing 12.5 ng/μl of digoxin and 25 ng/μl of the internal standard, was injected into the liquid chromatograph.

Single Tablet Assay—One tablet was placed in a 100-ml volumetric flask and treated in the same manner as the tablet composite assay.

Injectable Formulation Assay—The contents of 20 ampules were bulked and a 2-ml aliquot was transferred to a 10-ml volumetric flask (in the case of the 0.05 mg/ml injection) or to a 50-ml volumetric flask (in the case of the 0.25 mg/ml injection). Aliquots of 0.25 ml and 1.25 ml of internal standard solution were added to the 10- and 50-ml volumetric flasks, respectively. A volume of 0.25 ml (0.25 mg) of the internal standard solution was added to the 10-ml volumetric flask, and 1.25 ml (1.25 mg) of the internal standard solution was added to the 50-ml volumetric flask. A volume of methanol equivalent to 2.8 and 14.0 ml, was added to the 10- and 50-ml volumetric flasks, respectively. The theoretical final concentration of digoxin and the internal standard were 10 and 25 ng/μl, respectively.

Elixir—A 20-ml aliquot of the elixir was transferred to a 100-ml volumetric flask, followed by 2.5 ml of the internal standard solution and 20 ml of methanol. The flask was brought to volume with distilled water and thoroughly mixed. The theoretical final concentration of digoxin and the internal standard were 10 and 25 ng/μl, respectively.

Precision of Tablet Assay—A total of 40 digoxin tablets were weighed and triturated to a fine powder. Six aliquots, equivalent to 1.25 mg of digoxin, were weighed into six volumetric flasks and treated as described under tablet assay. Three injections were made for each sample.

Recovery of Digoxin from Tablets—Six aliquots of digoxin tablets were prepared as described previously. To each aliquot an accurately weighed[12] quantity of digoxin reference standard[9], equivalent to 0.625 mg, was added, and the samples were treated as described under tablet assay. Three injections were made for each sample.

HPLC Conditions for Tablet and Injectable Formulation Assays—The mobile phase consisted of water–methanol–isopropanol–methylene chloride (47:40:9:4) and was pumped at a flow rate of 1.2 ml/min. The UV detector was set at 220 nm.

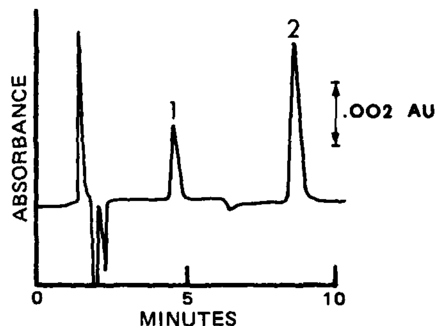

Figure 2—*HPLC of a digoxin tablet formulation. Sequence of elution: 1, digoxin; 2, 17α-ethynyl estradiol. Mobile Phase: refer to Fig. 1.*

[11] Number 1, Whatman Paper, W. and R. Balston Ltd., Eng.
[12] Cahn Electrobalance, Ventron Instruments Corp., Paramount, Calif.

HPLC Conditions for Elixir Formulation Assay—The mobile phase consisted of water–methanol–isopropanol–methylene chloride (51:42:5:2). All other conditions were identical to those described for tablet and injectable formulation assay.

RESULTS AND DISCUSSION

A chromatogram of a standard mixture of digoxin and its potential degradation products, digoxigenin, digoxigenin monodigitoxoside, digoxigenin bisdigitoxoside, as well as a common impurity, gitoxin, and the internal standard, ethynylestradiol, is given in Fig. 1. From this chromatogram it can be ascertained that the common potential impurities would not interfere with the assay of digoxin (Peak 4). In addition, common tablet excipients such as starch, lactose, methylcellulose, and stearate lubricants were subjected to the extraction procedure for the tablet assay and were found to be noninterfering.

The presence of a relatively small amount of methylene chloride in the mobile phase contributes to absorption of radiant energy at 220 nm and therefore raises the baseline. However, the presence of a considerably large amount of water minimizes the absorbance effect of methylene chloride. The problem of miscibility of the two solvents is resolved by the presence of methanol and isopropanol. Moreover, since there is sufficient differential absorbance contributed by digoxin, it has been consistently shown that no problem arises from the presence of methylene chloride. A description of the evolution of the mobile phase has been given (33) where the HPLC separation of a number of cardiac glycosides has been reported using different proportions of the four solvents (water–methanol–isopropanol–methylene chloride).

Calibration curves were constructed, and the relative response ratios of digoxin to the internal standard, 17α-ethynylestradiol, was found to be 1.426 for the analysis of digoxin tablets and injection, and 1.386 for the analysis of digoxin elixir. The relative standard deviation was 2% ($n = 6$) in both cases. Calibrations were performed for each batch of solvent systems prepared on a daily basis.

The chromatogram depicted in Fig. 2 is representative of a composite assay of a tablet containing 0.25 mg of digoxin. The initial baseline disturbance and the small negative peak at ~6.5 min are due to a solvent effect from the sample injection.

The recovery data for the extraction of digoxin from tablets (0.25 mg) was determined by adding an amount of digoxin reference standard equivalent to half of the amount of digoxin contained in the tablet sample. Analysis of six such samples resulted in recovery values of 99.7, 101.3, 96.8, 102.6, 95.2, and 103.4% of the total quantity expected. The mean and relative standard deviation were found to be 99.8 and 3.2%, respectively, with a 95% confidence limit of (±) 3.4. The precision of the assay was

Table II—Results of HPLC Single-Tablet Assay of Digoxin Tablets

	Percent of Label Claim[a]	
Number	0.125 mg	0.25 mg
1	90.0	92.8
2	91.4	96.4
3	105.8	92.6
4	102.4	106.0
5	93.9	102.0
6	96.8	94.8
7	94.6	98.6
8	96.8	96.9
9	101.2	93.2
10	98.4	92.8
Mean ($\bar{x}$)	97.1	96.6
RSD[b], %	5.1	4.6

[a] Brand A. [b] Relative standard deviation.

Table III—Results of the Analysis of Digoxin Injection and Elixir Formulations by HPLC and the USP Method

	Percent of Label Claim					
	Injection				Elixir	
	0.05 mg/ml		0.25 mg/ml		0.05 mg/ml	
Number	HPLC Method	USP Method	HPLC Method	USP Method	HPLC Method	USP Method
1	102.5	103.2	98.4	101.2	100.5	101.6
2	98.5	101.2	102.4	101.9	98.6	97.4
3	97.5	99.6	99.2	102.7	97.4	98.2
4	99.0	—	98.9	—	101.2	—
5	100.0	—	97.6	—	—	—
6	99.0	—	98.4	—	—	—
Mean ($\bar{x}$)	99.4	101.3	99.1	101.9	99.4	99.1
RSD[a], %	1.7	1.8	1.6	0.8	1.8	2.2

[a] Relative standard deviation.

independently determined on six aliquots of the same tablet lot. The values for the percentage of label claim were: 98.0, 99.4, 98.2, 98.0, 101.4, and 100.5% with a mean value of 99.2% and a relative standard deviation of 1.45%. Therefore, it can be observed from the above data that the assay has satisfactory accuracy and precision.

The application of the HPLC assay to three commercial sources of digoxin tablet formulations provided the data given in Table I. Four aliquots of each of the four tablet lots were independently assayed, and it can be observed that all lots were well within the USP limits of 92–108% (7). The same four lots were assayed by the USP colorimetric method for digoxin tablets and the results are also given in Table I. The respective mean assay values for the four lots compare favorably; however, a significant time benefit of the HPLC assay was noted. The time taken for the total assay of four aliquots of a single tablet lot using the USP method was ~4.5 hr, while the HPLC assay required only 45 min.

The USP monograph for content uniformity of tablets is a long colorimetric procedure requiring repetition of the tablet assay for each of 10 tablets. Consequently, the HPLC procedure developed was applied to a single-tablet assay of 10 randomly selected tablets from two tablet strengths obtained from the same manufacturer. As shown in Table II, the individual assay results for a 0.125-mg tablet fell within 90.0–105.8% and for a 0.25-mg tablet, 92.6–106.0%. The general requirement for content uniformity of tablets in the USP specifies that the potency of all 10 tablets must fall within 85–115% of the label claim. Hence the tablets selected in this determination met the pharmacopeial requirements. The assay time for the HPLC method was significantly shorter.

The analysis of digoxin injection indicated that the peaks due to digoxin and the internal standard are free from interference from formulation excipients. The chromatogram was essentially identical to that

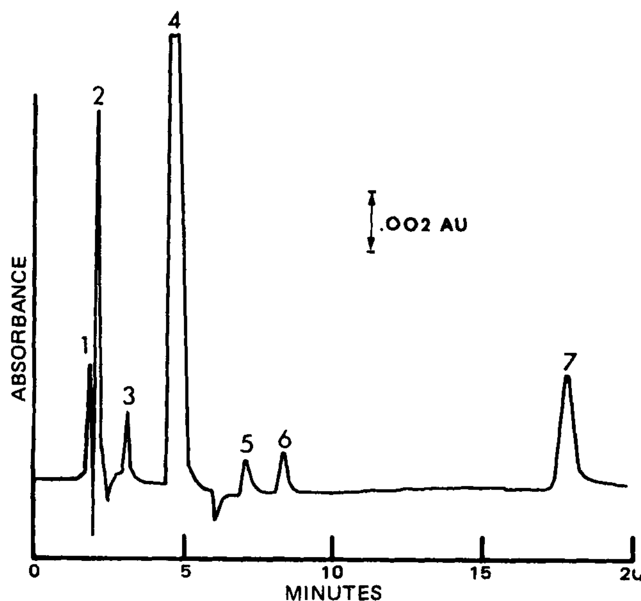

Figure 3—*HPLC of a digoxin elixir formulation. Sequence of elution: 1–3, unknown; 4, methylparaben; 5, digoxin; 6, unknown; 7, 17 α-ethynylestradiol. Mobile Phase: Water–methanol–isopropanol–methylene chloride (51:42:5:2) flow rate: 1.2 ml/min.*

shown for a tablet formulation (Fig. 2). The assay results (Table III) for two strengths of injectable formulation obtained from the same manufacturer provided a mean potency of 99.4 and 99.1% with a respective relative standard deviation of 1.7 and 1.6%. The mean potency of the HPLC assay compares favorably with that obtained for the same formulations using the USP assay (Table II).

Due to the presence of excipients in the elixir formulation, the relative composition of mobile phase for this assay was modified slightly. The chromatogram depicted in Fig. 3 is representative of the analysis of a single elixir formulation. Peaks 1–4 and 6 were due to pharmaceutical excipients. Peak 4 was determined to be methylparaben, the remaining excipients, however, were not identified. The assay results obtained from 4 aliquots of this formulation are given in Table III and indicate a mean potency of 99.4%, with a relative standard deviation of 1.8%. The assay results for the elixir formulation as obtained by the USP method (Table III) compare favorably with those obtained from the HPLC assay method. It is significant that the analysis of both the injectable and elixir formulations was achieved by simple dilution of the formulation. The USP, on the other hand, requires a prior solvent extraction for the analysis of the elixir.

In comparison with the long, labor-intensive requirements for the assay of tablet, injectable,and elixir formulations as outlined in the USP, the HPLC method described herein provides a significant advantage in terms of selectivity, simplicity, convenience, and time of analysis.

REFERENCES

(1) Ph. Lafon, *C. R., Hebd. Seances Acad. Sci.*, **100,** 1463 (1885).
(2) H. Beljet, *Schweiz. Apoth. Ztg.*, **56,** 71, 84 (1918).
(3) M. Pesez, *Ann. Pharm. Fr.*, **10,** 104 (1952).
(4) D. H. E. Tattje, *J. Pharm. Pharmacol.*, **9,** 29 (1957).
(5) P. Mesnard and G. Devaux, *C. R. Hebd. Seances Acad. Sci.*, **253,** 497 (1961).
(6) J. W. Myrick, *J. Pharm. Sci.*, **58,** 1018 (1969).
(7) "United States Pharmacopeia," 20th rev., U.S. Pharmacopeial Convention, Rockville, Md., 1980.
(8) K. B. Jensen, *Acta. Pharmacol. Toxicol.*, **9,** 66 (1953).
(9) D. Wells, B. Katzung, and F. H. Meyers, *J. Pharm. Pharmacol.*, **13,** 389 (1961).
(10) I. M. Jakovljevic, *Anal. Chem.*, **35,** 1513 (1963).
(11) A. J. Khoury, in "Automation in Analytical Chemistry," Technicon Symposium, 1966, Vol. I, Technicon Symposia Medad, Inc., White Plains, N.Y., 1967, pp. 192–195.
(12) L. F. Cullen, D. L. Packman, and G. J. Papariello, *J. Pharm. Sci.*, **59,** 697 (1970).
(13) L. Nyberg, K. E. Andersson, and A. Bertler, *Pharm. Suecica*, **11,** 459 (1974).
(14) H. Pötter, *Pharmazie.*, **18,** 554 (1963).
(15) G. Rabitzsch and S. Jungling, *J. Chromatogr.*, **41,** 96 (1969).
(16) W. Hauser, Th. Kartnig, and G. Verdino, *Scientia Pharm.*, **36,** 237 (1968).
(17) H. Pötter and H. Bärisch, *Pharmazie*, **27,** 315 (1972).
(18) F. J. Evans, P. A. Flemons, C. F. Duignan, and P. S. Cowley, *J. Chromatogr.*, **88,** 341 (1974).
(19) A. Stoll, E. Angliker, F. Barfuss, W. Kussmaul, and J. Renz, *Helv. Chim. Acta.*, **34,** 1460 (1951).
(20) F. Kaiser, *Arch. der Pharmazie.*, **299,** 263 (1966).
(21) R. W. Jelliffe and D. H. Blankenhorn, *J. Chromatogr.*, **12,** 268 (1963).

(22) L. Tan, *ibid.*, **45**, 68 (1969).
(23) E. Watson, P. Tramell, and S. M. Kalman, *ibid.*, **69**, 157 (1972).
(24) W. E. Wilson, S. A. Johnson, W. H. Perkins, and J. E. Ripley, *Anal. Chem.*, **39**, 40 (1967).
(25) A. H. Kibbe and O. E. Araujo, *J. Pharm. Sci.*, **62**, 1703 (1973).
(26) M. C. Castle, *J. Chromatogr.*, **115**, 437 (1975).
(27) W. Lindner and R. W. Frei, *ibid.*, **117**, 81 (1976).
(28) F. Nachtmann, H. Spitzy, and R. W. Frei, *ibid.*, **122**, 293 (1976).
(29) F. Erni and R. W. Frei, *ibid.*, **130**, 169 (1977).
(30) L. A. Sternson and R. D. Shaffer, *J. Pharm. Sci.*, **67**, 327 (1978).
(31) T. Sonobe, S. Hasumi, T. Yoshino, Y. Kobayashi, H. Kawata, and T. Nagai, *ibid.*, **69**, 410 (1980).
(32) Y. Fujii, H. Fukuda, Y. Saito, and M. Yamazaki, *J. Chromatogr.*, **202**, 139 (1980).
(33) B. Desta and K. M. McErlane, *J. Chromatogr.*, in press.

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Formation of Hydrotalcite in Mixtures of Aluminum Hydroxycarbonate and Magnesium Hydroxide Gels

ROGER K. VANDERLAAN *, JOE L. WHITE ‡, and STANLEY L. HEM *x

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Abstract □ IR and X-ray analysis demonstrate that hydrotalcite forms during the aging of aluminum hydroxycarbonate gel and magnesium hydroxide gel mixtures. The formation of hydrotalcite produces a change in the pH-stat titrigram and a sharp increase in the pH of the mixture. Hydrotalcite was noted earlier in mixtures having a high molar ratio of magnesium to aluminum, a high total gel concentration, a high initial pH, or in mixtures stored at elevated temperatures. The addition of sorbitol to the mixtures substantially delayed the appearance of hydrotalcite. Nonacid-reactive hydrotalcite formed when mixtures of chloride-containing aluminum hydroxide gel and magnesium hydroxide gel were aged.

Keyphrases □ Hydrotalcite—formation, mixtures of aluminum hydroxycarbonate and magnesium hydroxide gels, IR and X-ray analysis □ Mixtures—formation of hydrotalcite in mixtures of aluminum hydroxycarbonate and magnesium hydroxide gels □ Gels—aluminum hydroxycarbonate and magnesium hydroxide gels, mixtures, formation of hydrotalcite

It has been reported recently that amorphous aluminum hydroxycarbonate gel forms a coating on magnesium hydroxide particles due to electrostatic attraction (1). This interaction was detected because the rate of acid neutralization of mixtures of aluminum hydroxycarbonate gel and magnesium hydroxide gel was slower than expected, based on individual rates of acid neutralization. The interaction occurred immediately and an additive rate of acid neutralization only occurred when the gels were separately added to the reaction vessel. As the mixtures aged, the rate of acid neutralization decreased further, suggesting that the amorphous aluminum hydroxycarbonate coating was becoming more ordered as the amorphous to crystalline phase transition occurred.

It was noticed, however, that the rate of acid neutralization in some aged mixtures was greater than the initial rate of acid neutralization. Thus, a further reaction appeared to be occurring during the aging of mixtures of aluminum hydroxycarbonate and magnesium hydroxide gels. This interaction is the focus of this study.

EXPERIMENTAL

Magnesium hydroxide gel[1] was obtained commercially as a paste containing the equivalent of 21% (w/w) MgO. Aluminum hydroxycarbonate gel was prepared as described previously (2) by the addition of 0.47 M $AlCl_3 \cdot 6H_2O$ to 0.53 M $NaHCO_3$ and 0.23 M Na_2CO_3 to a final pH of 6.5. Chloride-containing aluminum hydroxide gel was prepared as described previously (2) by the addition of 13% (v/v) strong ammonia solution to 0.29 M $AlCl_3 \cdot 6H_2O$ to a final pH of 7.0.

Aluminum and magnesium content were determined by chelatometric titration (3).

Mixtures of aluminum hydroxycarbonate gel or chloride-containing aluminum hydroxide gel and magnesium hydroxide gel were prepared on a weight basis. For example, a 200-g mixture containing a total of 0.6 mmole of metal/g in a magnesium–aluminum molar ratio of 5:1 was prepared by weighing magnesium hydroxide gel and aluminum hydroxycarbonate gel or chloride-containing aluminum hydroxide gel containing 100 mmoles of magnesium and 20 mmoles of aluminum, respectively. A solution containing an excipient was added when necessary. The final weight was adjusted to 200 g with double-distilled water and the mixture was stirred mechanically until uniform. The mixtures were aged in widemouth polyethylene bottles.

The acid neutralization reaction was monitored by an automated[2] pH-stat titrator at pH 3.0, 25° using a sample size which would theoretically neutralize 2.25 mEq (4).

X-ray diffractograms were obtained using air-dried samples in McCreery mounts (5). Diffractograms were recorded from 6 to 40° (2θ) under the following conditions[3]: CuK_α radiation, 30 kV, 28 mamp, 2°/min.

IR[4] spectra were recorded using potassium bromide disks containing 0.8–2.0 mg of air-dried sample and 300 mg of KBr.

RESULTS AND DISCUSSION

The rate of acid neutralization of a mixture of aluminum hydroxycarbonate gel and magnesium hydroxide containing 0.6 mmole of metal/g in a magnesium–aluminum molar ratio of 5:1 decreased during the first 31 days of aging at 25° (Fig. 1A). A slight decrease in the total acid reac-

[1] HydroMagma, Merck & Co., Rahway, N.J.
[2] PHM 26, TTT II, ABU 12 (2.5 ml), TTA 3, SBR 2, Radiometer, Copenhagen, Denmark.
[3] Siemens AG Kristalloflex 4 generator, Type F diffractometer, Karlsrule, West Germany.
[4] Model 180, Perkin-Elmer Co., Norwalk, Conn.

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